UNIVERSITY OF LEICESTER

STATISTICAL ANALYSIS PLAN

A Randomised Controlled Trial of Mepolizumab Initiated During Admission to Hospital for a Severe Exacerbation of Eosinophilic COPD

Mepolizumab for COPD Hospital Eosinophilic admissions Pragmatic trial

(COPD-HELP)

SAP Version: 3.0 Final
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Revision History

Version	Date	Author(s) and Role	Summary of Changes/Comments
0.1	21/11/2019	Ana Suazo Di Paola, Trial Statistician	Initial version
0.2	10/12/2019	Ana Suazo Di Paola, Trial Statistician	**Exploratory Samples for future research** Inclusion of section addressing definition and analysis of outcomes.
0.3	15/04/2020	Ana Suazo Di Paola, Trial Statistician	**Primary and Secondary Outcomes** Improvement of definition. **Inclusion of other variables to be summarised** **Protocol Deviations** Inclusion of additional major protocol deviations. **Inclusion of Derived/Computed variables**
0.4	27/07/2020	Ana Suazo Di Paola, Trial Statistician	**Introduction** Improvement of wording **Subgroup Objectives** Improvement of wording **Visit Schedule table** Improvement of formatting **Other variables to be summarised** Removed detailed list of variables as shown in CRF booklet **General Issues for Statistical Analysis** Improvement of wording
0.5	13/03/2023	Ghazala Waheed Trial Statistician	**Removal of COVID-19 omitted procedures** Removed COVID-19 omitted procedures: Post-BD (FEV1/FVC) Spirometry, Oscillometry, Induced

			sputum samples, Throat swab (viral PCR) **Truncated follow-up for patients' recruitment from April 2023** Update to study timelines (total study duration) in line with truncated follow-up
0.6	12/12/2023	Ghazala Waheed Trial Statistician	**Review of SAP;** Updated Protocol following review by principal statistician (PS), added details to the specification of outcome measures, analysis populations, analysis methods. Added comments for discussion with CI
0.7	24/01/2024	Ghazala Waheed Trial Statistician	**Review of SAP;** Changes and amendments following review by CI and PS.
0.8	01/02/2024	Ghazala Waheed Trial Statistician	**Review of SAP;** Changes and amendments following review by TMG.
0.9	03/07/2024	Ghazala Waheed Trial Statistician	**Review of SAP;** Changes and amendments following review by TMG.
0.10	09/07/2024	Ghazala Waheed Trial Statistician	Minor changes and amendments following review by Chris and Neil.
1.0	01/08/2024	Ghazala Waheed Trial Statistician	**Final version**
2.0	01/10/2024	Ghazala Waheed Trial Statistician	Clarification of definition of per protocol population. Clarification of imputation rules for sensitivity analyses. Inclusion of analysis in the intention-to-treat population for the outcomes of number of hospital readmission and number of moderate exacerbations.

			Clarification of minimum follow-up period for the truncated follow-up participants.
3.0	05/02/2025	Cassey Brookes Principal Statistician	Clarification of the definition of the secondary outcome; moderate exacerbations, to exclude events that led to hospitalisation thus making moderate and severe exacerbation events mutually exclusive.

SAP approval for finalised version:

Trial Statistician	***Ghazala Waheed***	
		
		05/02/2025
	Signature	**Date**
Chief Investigator	***Professor Chris Brightling***	
	chris brightling	**10/02/2025**
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	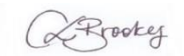	**13/02/2025**
	Signature	**Date**

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
APR	Annual progress report
AR	Adverse Reaction
BNP	Brain natriuretic peptide
BRC	Biomedical Research Centre
CA	Competent Authority
CAT	COPD Assessment Tool
CDMS	Clinical data management system
CDU	Clinical Decisions Unit
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
CXR	Chest X-Ray
DNA	Deoxyribonucleic Acid
DSMC	Data Safety Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
eMRC	Extended MRC dyspnoea score
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FBC	Full Blood Count
FEV1	Forced Expiratory Volume in 1 second
FEVC	Forced Vital Capacity
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
HR	Hazard Ratio
HTA	Human Tissue Act
IB	Investigator Brochure
ICF	Informed Consent Form

ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LCADL	London Chest Activities of Daily Living
LCTU	Leicester Clinical Trials Unit
MA	Marketing Authorisation
MACE	Major Adverse Cardiac Events
MedDRA	Medical Dictionary for Regulatory Authorities
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
NYHA	New York Heart Association
PCR	polymerase chain reaction
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Public and Patient Involvement
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
RNA	ribonucleic acid
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SC	Subcutaneous
SDV	Source Data Verification
SGRQ	St. George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPPB	Short Physical Performance Battery
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group

Trop I	Troponin I
TSC	Trial Steering Committee
VOC	Breath Volatile Organic Compounds
WOCBP	Women of child-bearing potential

Contents

1 Introduction

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the "**Mepolizumab for COPD Hospital Eosinophilic admission Pragmatic trial (COPD-HELP)**". The reader of this SAP is encouraged also to read the clinical trial protocol.

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

Throughout the document: Any verbatim text from the protocol is provided inside a box:

Text from the protocol

1.1 Study Objectives

1.1.1 Primary Objectives

The primary objective is to evaluate the efficacy of mepolizumab initiated during hospitalisation on future hospital readmission or death (all cause) compared with placebo in severe exacerbations of eosinophilic COPD.

1.1.2 Secondary Objectives

To assess the effects of mepolizumab on health status, well-being, exercise capacity, frailty, moderate exacerbations, healthcare usage, and death, compared with placebo in patients admitted to hospital with an eosinophilic exacerbation of COPD.

1.1.3 Subgroup Objectives

To evaluate if the efficacy, in terms of the primary outcome, is different between grouped baseline stratification factors of 1) MRC dyspnoea score ((≤3, >3) and 2) past hospitalisation in the previous 12 months ((0, ≥1) and WHO clinical progression score at baseline (4, 5, 6).

2 Study Design

This will be a single-centre, double-blinded, randomised, placebo-controlled trial comparing mepolizumab 100mg versus placebo in patients with eosinophilic COPD, started during their index admission to hospital. 238 participants will be recruited over a 3-year period.

Participants will be dosed every 4 weeks for 48 weeks and be followed up for 12 months with the exception of those randomised during the truncated follow-up period.

2.1 Truncated follow-up

Patients randomised from July 2023 to December 2023 will be consented to a truncated follow-up model, whereby the timing of the last patient last visit will remain on the same timeline as originally planned; this will result in participants consented in July to have up to the 44-week follow-up, those in August will have up to the 40-week follow-up, and so on. Patients will be dosed for a minimum of 20 weeks, with secondary outcomes measured as per original timelines (baseline, 4 weeks, 8 weeks, etc.) however final outcome measures normally measured at 48 weeks will occur at 4 weeks ± 7 days post final dosing visit.

2.2 Overview

2.2.1 Participants

Adults aged 40 years old and above with symptoms typical of COPD when stable (baseline eMRC dyspnoea grade 2 or more) and whose Serum Eosinophil count is ≥ 300 cells/µL either at time of admission or at any one time in the preceding 12 months will be deemed as eligible participants. However, COPD adults without eosinophilia (defined as persistently < 300 cells/µL within the last 12 months) and who have other conditions that may be the cause of eosinophilia would make any potential participant ineligible to take part in the Study.

2.2.2 Treatment groups

Participants will be randomised in a 1:1 ratio to mepolizumab or placebo.

2.2.2.1 Mepolizumab group

The Investigational Medicinal Product (IMP) for this trial is mepolizumab 100mg powder for solution for injection.

Dosing will be undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab or placebo, administered subcutaneously. Participants are required to complete the scheduled clinic visits within the specified time windows in order to maintain sufficient intervals between

doses. Trial medication can only be administered at the Respiratory BRC. The participant will return on an outpatient basis following their initial hospitalisation every four weeks to receive their scheduled dose and undertake trial assessments. For participants who do not receive dosing during their index hospitalisation, the first injection must occur within seven days of discharge. The participant's time in the trial begins at randomisation.

Scheduled doses can be delayed by up to four weeks. The exception will be if dosing is delayed due to an exacerbation resulting in hospitalisation, where there will be no limit on the length of delay, and the next dose will be administered at the next due date or as soon as possible afterwards to allow the participant to recover. A delay will then be carried through to all their subsequent study visits. If the participant misses a dose it will be recorded in the medical notes and the next scheduled dose will be administered. Participants will be allowed to miss one dose of the study drug only, or they will be discontinued from the trial treatment. Dosing completed outside of the seven day window will be recorded as a protocol deviation.

Participants consented to the truncated follow-up phase of the study will follow the dosing regimen of one dose every 4 weeks (± 7 days) for at least 20 weeks (minimum of 6 doses); however the number of doses will be dependent on when they consented to the study i.e. patients consented earlier will receive more. The method of dosage and blinding procedures will remain the same.

2.2.2.2 Placebo group

Dosing will be undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab or placebo, administered subcutaneously. Participants are required to complete the scheduled clinic visits within the specified time windows in order to maintain sufficient intervals between doses. Trial medication can only be administered at the Respiratory BRC. The participant will return on an outpatient basis following their initial hospitalisation every four weeks to receive their scheduled dose and undertake trial assessments. For participants who do not receive dosing during their index hospitalisation, the first injection must occur within seven days of discharge. The participant's time in the trial begins at randomisation.

Scheduled doses can be delayed by up to four weeks. The exception will be if dosing is delayed due to an exacerbation resulting in hospitalisation, where there will be no limit on the length of delay, and the next dose will be administered at the next due date or as soon as possible afterwards to allow the participant to recover. A delay will then be carried through to all their subsequent study visits. If the participant misses a dose it will be recorded in the medical notes and the next scheduled dose will be administered. Participants will be allowed to miss one dose of the study drug

only, or they will be discontinued from the trial treatment. Dosing completed outside of the seven day window will be recorded as a protocol deviation.

Participants consented to the truncated follow-up phase of the study will follow the dosing regimen of one dose every 4 weeks (± 7 days) for at least 20 weeks (minimum of 6 doses); however the number of doses will be dependent on when they consented to the study i.e. patients consented earlier will receive more. The method of dosage and blinding procedures will remain the same.

2.2.3 Sample size

Readmission rates at 6, 9 and 12 months were 51%, 59% and 64% respectively for patients admitted with a diagnosis of COPD (ICD code: J44) in Leicestershire in 2015. This is in line with national data from the HQIP RCP National COPD audit (2014) which had a readmission rate of 43% at 3 months. In addition, 6% of patients discharged from hospital with an exacerbation of COPD died in the 12 months following admission without hospital readmission.

National UK data from the HQIP funded RCP/BTS National COPD audit (2014; data unpublished) showed 24.9% patients had an eosinophil count of ≥ 300 cells/µL on admission. In patients with an eosinophil of ≥ 300 cells/µL on admission (n=1,587), 46.1% of patients were readmitted within 3 months of initial hospitalisation, similar to the non-eosinophilic COPD population.

Assuming 65% of patients receiving usual care will have an event by 48 weeks (composite endpoint: hospitalisation or death) and those treated with mepolizumab have a hazard ratio of 0.6, then 226 patients (113 per group) would be required to show a statistical difference power 0.8, alpha=0.05). We have also assumed 5% drop-out (recruited but not receiving first dose) and therefore the final recruitment target of 238 patients.

2.2.4 Randomisation and blinding

The LCTU will supply a web based randomisation system from a third party (Sealed Envelope Ltd.). Participants will be randomised in a 1:1 ratio to mepolizumab or placebo. The trial team and participants will be blinded to treatment assignment. Randomisation will be stratified on baseline eMRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1).

Each participant will be given a unique trial ID number at randomisation. Randomisation results will be printed out and signed as confirmation by the unblinded trial personnel performing the randomisation and a copy will be stored securely with the unblinded documentation and presented to pharmacy alongside the prescription.

[…..]

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial will remain blind to the randomised treatment assignments until after final analysis is complete. The exception(s) to this are as follows;

- The trial statistician will have access to the web based randomisation database of all randomised participants in order to prepare the unblinded DMC to make safety decisions and complete end of trial analyses.
- The Pharmacy team will be unblinded and have responsibility for storing and dispensing IMP and placebo.
- Unblinded trial personnel from the Respiratory BRC will have responsibility for reconstituting the IMP/placebo and dosing the participants.

[…..]

The treatment allocation will remain blinded to all other trial team members until after database lock.

2.2.5 Emergency Unblinding

[……]

Unblinding will only occur in the case of a medical emergency when the identity of the allocated treatment must be known in order to provide appropriate medical treatment. It is not anticipated that unblinding will be required in this trial as there is no recovery treatment.

[……]

Unblinding of all participants will be undertaken by the trial statistician after the last participant has completed their final visit, and the database has been locked.

2.3 Visit schedule

Trial assessment	Randomised treatment (visit window +/- 7 days)												
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V 10**	**V 11**	**V 12**	**V 13/Final follow up**
	Wk0	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	**Wk28**	**Wk32**	**Wk36**	**Wk40**	**Wk44**	**Wk48**
Consent	x												
Review Inclusion & Exclusion	x												
Randomisation	x												
Dosing	x	x	x	x	x	x	x	x	x	x	x	x	
Demographics, medical history & physical exam	x												
Concomitant Med	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood serum pregnancy test (if applicable)	x												
Urine Pregnancy test (if applicable)		x	x	x	x	x	x	x	x	x	x	x	x
Electrocardiogram (ECG[£]),Chest X-ray (CXR[$]), Arterial blood gas (ABG) (part of standard care), spirometry^ (FEV1, FVC, FEV1 % predicted)	x												
WHO Clinical Progression Score	x												
Extended MRC dyspnoea score (eMRC)*	X*	x	x	x			x			x			x
St George's Respiratory Questionnaire (SGRQ)	x	x	x	x			x			x			x
COPD Assessment Tool (CAT)	x	x	x	x			x			x			x

Warwick-Edinburgh Mental wellbeing score (WEMWBS)	x	x	x	x			x			x			x
London Chest Activities of Daily Living Questionnaire (LCADL)	x	x	x	x			x			x			x
Short physical performance battery (SPPB)	x	x	x	x			x			x			x
Physical activity (accelerometry)	x	x	x	x			x			x			
Handgrip strength	x	x	x	x			x			x			x
Inflammatory markers (serum & sputum[#] samples)	x	x	x	x			x			x			x
Safety and tolerability AE/SAEs and bloods (FBC, U&E, LFTs, CRP)	x	x	x	x	x	x	x	x	x	x	x	x	x
Sputum inflammatory differential	x	x	x	x			x			x			x
Sputum[#] sample (sputum microbiome, systemic inflammation)	x	x	x	x			x			x			x
Exploratory blood samples (Trop I, BNP, FBC, serum & plasma)	x	x	x	x			x			x			x
Exploratory urine sample	x	x	x	x			x			x			x
Quadriceps ultrasound	x	x	x	x			x			x			x
Immunophenotyping & Microbiology samples (blood, sputum[#], urine)	x	x	x	x			x			x			x

[£] 12 lead ECG, done as part of the standard clinical care. If, in the opinion of investigator, the ECG is grossly abnormal (e.g. LBBB, prolonged QTc), it will be compared to old ECGs. If there are no old ECGs for comparison, the investigator will make a clinical judgement about the suitability of the patients to take part in trial.
[$] Chest X-ray: done as part of routine clinical care during acute admission. ^Results from historical or contemporaneous spirometry testing performed as part of usual care will be collected from hospital and primary care records where available. *Two eMRC dyspnoea scores will be recorded at visit 1 only (current and baseline/stable states). [#]Spontaneous sputum samples collected as part of standard of care.
Note: Trial assessments (e.g. Quality of Life/Symptoms Assessments) may be completed remotely by telephone consultation where possible and when necessary.
Additional note: Patients consented to truncated follow-up will follow schedule of procedures as defined in this table up until their final dosing visit whereby V13/Final Follow-up will then occur 4 weeks ±7 days later.

3 Outcomes and other variables

3.1 Primary Outcome

3.1.1 Definition and Derivation of Primary Outcome

Time from randomisation to next hospital readmission or death (all cause).

The time from randomisation to next hospital readmission or death (all cause) is defined as a time to event outcome measured in days. The date of randomisation as well as the date of readmission or death (whichever occurs first) will be used to calculate time to event. For participants not experiencing an event the time will be calculated from randomisation until last known follow-up assessment event-free. A variable to indicate event (with a value of 1) or no event (with a value of 0) will be derived. Details of the primary outcome analysis are included in section 5.5.

3.1.2 Hypothesis to be investigated

To evaluate the efficacy of mepolizumab initiated during hospitalisation on future hospital readmission or death (all cause) compared with placebo in severe exacerbations of eosinophilic COPD.

3.2 Secondary Outcomes

3.2.1 Definition and Derivation of Secondary Outcomes

Exacerbations and Healthcare Utilisation

- Time from randomisation to next hospital readmission or death due to a respiratory cause

The time from randomisation to next hospital readmission or death (due to a respiratory cause) is defined as a time to event outcome measured in days. The date of randomisation as well as the date of readmission or death due to respiratory causes (whichever occurs first) will be used to calculate time to event. For participants not experiencing an event the time will be calculated from randomisation until last known follow-up assessment event-free. A variable to indicate event (with a value of 1) or no event (with a value of 0) will be derived. Details of the primary outcome analysis are included in section 5.5.

- Total number of hospital readmissions all cause up to 48 weeks

The total number of hospital readmissions (all cause) is defined as a count outcome. The number of hospital readmissions (all cause) in total during the 48 (truncated follow-up

minimum 24) weeks corresponding to each participant will be calculated. Where no hospital admission have occurred a value of zero will be derived.

- Total number of moderate exacerbations up to 48 weeks

The total number of moderate exacerbations is defined as a count outcome. The severity of a COPD exacerbation will be deemed as "Moderate" if the participant required treatment with steroids or antibiotics and was not hospitalised (Oba, Y. et al, 2017). The number of moderate exacerbations each participant had over the course of 48 (truncated follow-up minimum 24) weeks will be calculated.

- Time from randomisation to treatment failure (defined as the composite of three endpoints: 1. treatment intensification with systemic corticosteroids and/or antibiotics for respiratory reasons; 2. step-up in hospital care for respiratory reasons including transfer to the intensive care unit or readmission; or 3. all-cause mortality)

The time from randomisation to treatment failure is defined as a time to event outcome measured in days. The date of randomisation and dates of treatment intensification and increase in hospital care (whichever is the latter) will be used to calculate time to event. Participants not experiencing both treatment intensification and increased hospital care will have time measured from randomisation until last known follow-up assessment event-free. A variable to indicate event (with a value of 1) or no event (with a value of 0) will be derived.

- Time from randomisation to death (all cause)

The time from randomisation to death (all cause) is defined as a time to event outcome measured in days. The date of randomisation and the date of death will be used to calculate time to event. For participants with no known death date the time will be calculated from randomisation until last known follow-up assessment. A variable to indicate event (with a value of 1) or no event (with a value of 0) will be derived.

- Time from randomisation to death (respiratory cause)

The time from randomisation to death (respiratory cause) is defined as a time to event outcome measured in days. The date of randomisation and the date of death where cause is defined as respiratory will be used to calculate time to event. For participants with no known death date the time will be calculated from randomisation until last known follow-up assessment. For participants with a date of death attributed to other (non-respiratory) causes the time will be calculated from randomisation until death. A variable to indicate event (with a value of 1) or no event (with a value of 0) will be derived.

- Time from randomisation to next hospital readmission (all cause)

The time from randomisation to next hospital readmission (all cause) is defined as a time to event outcome measured in days. The date of randomisation and the date of next hospital readmission following randomisation will be used to calculate time to event. Where hospital readmission doesn't occur during follow-up, time will be measured until the participant's last known follow-up assessment. A variable to indicate event (with a value of 1) or no event (with a value of 0) will be derived.

- Time from randomisation to next hospital readmission (respiratory cause)

The time from randomisation to next hospital readmission (respiratory cause) is defined as a time to event outcome measured in days. The date of randomisation and the date of next hospital readmission (respiratory cause) will be used to calculate time to event. Where hospital readmission for respiratory cause doesn't occur during follow-up, time will be measured until the participant's last known follow-up assessment. A variable to indicate event (with a value of 1) or no event (with a value of 0) will be derived.

- Time to discharge from index admission

Time to discharge from index admission is a continuous outcome defined as the time (measured in days) from index admission to discharge. The date of index admission and the date of hospital discharge will be used to calculate length in days and the resulting index admission duration, expressed in days, will be incorporated into the baseline characteristics for analysis and reporting. Participants with a date of death and no discharge date will not have a value for length of index admission and therefore not included in the analysis of this outcome measure.

Quality of Life/Symptoms (Weeks 0, 4, 8, 12, 24, 36, 48*)

*See section 1.2 – Truncated follow-up; Participants randomised from June 2023 will receive minimum 24 weeks follow-up.

- Breathlessness:
  - Extended MRC dyspnoea score (eMRC)

The extended MRC dyspnoea scale is defined as an ordinal outcome. It consists of five statements about a perceived grade of breathlessness related to activity, with the grades defined as shown below:

- Grade 1: Breathless only with strenuous exercise.
- Grade 2: Breathless when hurrying on the level or walking up a slight hill.
- Grade 3: Walks slower than peers or stops when walking on the flat at own pace.
- Grade 4: Stops after walking 100m, or for a few minutes, on the level.
- Grade 5: Too breathless to leave the house.

For participants who perceive themselves to be in a Grade 5 on the traditional MRCD scale, the eMRCD will categorise them as either 5a or 5b depending on their ability to manage personal care (i.e. washing and dressing) (Nerys, W.,2017; Steer J. et al, 2011).

The baseline value used in analysis should be the stable state value captured at baseline post randomisation, the actually value taken at baseline during the exacerbated state is for describing baseline characteristics only.

- Health Status
  - St George's Respiratory Questionnaire (SGRQ)
  - COPD Assessment Tool (CAT)

The St George's Respiratory Questionnaire (SGRQ-C COPD specific) score is defined as a continuous outcome. There are two parts to the questionnaire providing a total of 3 component scores (or subscales) as below;

- Part 1: Symptoms (8 items).
- Part 2: Activity (16 items)
- Part 2: Impacts (26 items).

Each questionnaire response has a unique empirically derived `weight'. The lowest possible weight is zero and the highest is 100. A Total and three component scores are calculated: Symptoms; Activity; Impacts.
The Symptoms component consists of all the questions in Part 1. The weights for Questions 1-7 are summed.
The Activity component is calculated from the summed weights for the positive responses to items Questions 9 and 12 in Part 2 of the questionnaire.
The Impacts component is calculated from Questions 8, 10, 11, 13, 14 in Part 2 of the questionnaire.
Then the Total score is calculated by summing the weights to all the positive responses in each component.
For each subscale and the total score, values range from 0 (no impairment) to 100 (maximum impairment) (Ferrer M. et al, 2002).

The COPD Assessment Tool (CAT) score is defined as a continuous outcome that ranges from 0 to 40 (inclusive) higher scores indicating a more severe health status impairment or a poorer control of COPD. It consists of eight items, with each item presented as a 6-point (0 to 5) differential scale, providing a score out of 40 indicating the clinical impact of the disease.

- Mental wellbeing
  - Warwick-Edinburgh Mental wellbeing score (WEMWBS)

The Warwick-Edinburgh Mental wellbeing score is defined as a continuous outcome that ranges from 14 to 70 (inclusive). The Questionnaire consists of 14 items with each item using a 5-point Likert scale: 1 ("None of the time"), 2 ("Rarely"), 3 ("Some of the time"), 4 ("Often") and 5 ("All of the time"). The total score sums all 14 items with higher scores indicating a higher level of mental wellbeing (Tennant R. et al, 2007).

- Functional
  - London Chest Activities of Daily Living Questionnaire (LCADL)

The London Chest Activities of Daily Living is defined as a continuous outcome that measures the limitation to perform activities of daily living by dyspnoea. It comprises 15 questions which are divided into four domains: self-care, household activities, physical activity and leisure activities. The questions in each of the four domains are scored as follows: 0 ("I wouldn't do it anyway"), 1 ("I do not get breathless"), 2 ("I get moderately breathless"), 3 ("I get very breathless"), 4 ("I have given this up") and 5 ("Someone else does this for me"). The LCADL total score sums all individual questions to give values in the range 0 to 75 (inclusive), with the highest score representing maximal disability (Muller, J. P. et al, 2013; Garrod, R. et al, 2000).

Physiological Measures (Weeks 0, 4, 8, 12, 24, 36, 48*)

*See section 1.2 – Truncated follow-up; Participants randomised from June 2023 will receive minimum 284 weeks follow-up.

- Frailty
  - Short physical performance battery (SPPB)
  - Handgrip Strength

The Short physical performance battery is defined as a continuous outcome that ranges from 0 (worst performance) to 12 (best performance) (Pavasini, R. et al, 2016). This outcome measures lower extremity function using tasks that are similar to daily activities and it examines 3 areas: static balance, gait speed and getting in and out of a chair. The limitations based on the SPPB cut-off scores are defined as follows: "Severe limitations" if score is between 0-3, "Moderate limitations" if score is between 4-6, "Mild limitations" if score is between 7-9 and "Minimal limitations" if score is between 10-12 (Puthoff M.L., 2008).
This secondary outcome will be derived as a categorical variable for descriptive statistics purposes.
Handgrip strength is defined as a continuous outcome that measures the amount of static force that the hand can squeeze around a dynamometer. This outcome is measured in Kilograms (Massy-Westropp N.M. et al, 2011).
*Values will be rounded to one decimal place.

Inflammatory Markers (Weeks 0, 4, 8, 12, 24, 36, 48*)

*See section 1.2 – Truncated follow-up; Participants randomised from June 2023 will receive minimum 24 weeks follow-up.

- Serum eosinophil count (total count)

The serum eosinophil count is defined as a continuous outcome that is measured in cells/mL. Values are rounded to two decimal places.

- Sputum eosinophil count (percentage)

The sputum eosinophil count (percentage) is defined as a continuous outcome that is expressed as a percentage (Belda, J. et al, 2000). Values are rounded to one decimal place.

Safety and Tolerability (all visits)

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

The number of adverse and serious adverse events is defined as a count variable. Furthermore, AE and SAE event rates will be reported as incidence rates per person years and calculated as (total number of events / sum of all follow-up times) *52 where;
-Total number of events is a count of all AE/SAEs observed.
-Follow-up time is calculated per participant from time of first dose until the last trial assessment is recorded.

- Clinical assessments and investigations (heart rate, blood pressure, temperature)

Heart rate, blood pressure and temperature are defined as continuous outcomes that are measured in bpm, mmHg and °C, respectively. Temperature values are rounded to one decimal place.

Exploratory Outcome Measures

- Physical Activity using accelerometry (Weeks 0, 4, 8, 12, 24, 36, 48*)

The analysis of physical activity accelerometer data from GeneActive will be treated as an exploratory analysis and will be conducted independently outside the scope of this Statistical Analysis Plan (SAP).

*See section 1.2 – Truncated follow-up; Participants randomised from June 2023 will receive minimum 24 weeks follow-up.

3.2.2 Hypotheses to be investigated

To assess the effects of mepolizumab on health status, well-being, exercise capacity, frailty, moderate exacerbations, healthcare usage and death compared with placebo in patients admitted to hospital with an eosinophilic exacerbation of COPD.

3.3 Exploratory Samples for future research (optional)

Details regarding the definition and analysis of Biomarkers, Muscle Wasting, Immunophenotyping and Microbiology outcomes measured at Weeks 0, 4, 8, 12, 24, 36 and 48 (Participants consented to the truncated follow-up will receive minimum 24 weeks follow-up), respectively, are not included in this SAP as the analysis will not be carried out by the LCTU.

3.4 Subgroups and/or interactions

Subgroup analyses of the primary outcome will be carried out on the stratification factors. These are baseline MRC dyspnoea score ((≤3, >3) and past hospitalisation in the previous 12 months ((0, ≥1) and WHO clinical progression score at baseline (4, 5, 6). A stratified Cox model will be fitted to allow the form of the underlying hazard function to vary across the levels of prognostic variables.

3.5 Other variables to be summarised

Other remaining variables of the trial will be summarized by treatment group and overall.

4 Analysis Sets/Populations

4.1 Protocol deviations

4.1.1 Major deviations

All doses of mepolizumab/placebo will be administered subcutaneously (SC) at the Respiratory BRC by an unblinded member of the study team. The prescribed dosage and mode of administration (see section 8.4 for dosage schedules) must not be altered. Injection time will be documented in the CRF. Any changes from the intended regimen must be recorded in the CRF. Participants will be allowed to miss <u>one</u> dose of the study drug only, or they will be discontinued from the trial treatment.

- Participant found to be Ineligible for the trial, randomized in error.
- Non-compliance with the randomised treatment:
    - Modification of the prescribed dosage during the Trial.
    - Change in the form of IMP before administration of mepolizumab or placebo according to the active protocol version.
- Receiving wrong treatment as per randomised allocation.
- Receiving non-permitted treatment during the Trial (i.e. participants with pre-existing helminth infections who should have been treated before taking part in the Trial, as stated in the Protocol).
- Missing more than one dose of the study drug whilst on treatment. The trial team identifies participants that have missed two doses of the study drug whilst on treatment and determines that treatment should be discontinued and give the reason for discontinuation of treatment in the end of treatment CRF as being due to non-compliance. Only participants with a discontinuation reason of non-compliance are deemed a major protocol deviation.

4.1.2 Minor deviations

Participants visit/assessment not performed as per protocol

4.2 Intention-to-treat Population

The primary analysis for each efficacy outcome will be by 'intention to treat' analysis; all the participants randomised into the trial (regardless of whether they received trial drug) will be analysed in their allocated group. Outcome data obtained from all participants will be included in the data analysis.

4.3 Modified intention-to-treat population

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

4.4 Per-protocol Population

The per protocol population will contain all participants randomised who do not reach any of the listed definitions for major protocol deviations. Individuals without a major deviation will be included in the per-protocol population whilst on trial treatment, this is considered to be 4 weeks after the last dose. If a participant dies before ending trial treatment, time is capped by death date.

4.5 Safety Population

The primary analysis of safety outcomes will be analysed using the safety population. The safety population will be comprised of the all individuals that received at least one injection of either the active dose or the placebo, with individuals that received any injections of the active dose being in the mepolizumab arm.

4.6 Other Analysis Populations

N/A.

5 General Issues for Statistical Analysis

Continuous Outcome data with symmetric distribution will be described with summary statistics such as the mean and standard deviation (SD). Skewed continuous Outcome data will be described using the median and interquartile range (IQR). Determination of symmetry will be made informally by visualisation, taking into account sample size for each variable, the nature of potential outliers, and similarity between mean and median values (recognising formal statistics to test for normality often lead to spurious results).

Categorical Outcome data will be summarised with numbers (absolute frequency) and percentages.

Summary tables for both continuous and categorical outcome data will be presented by treatment group and overall in the intention to treat population.

For continuous outcomes that follow a normal distribution, we will compute the adjusted mean change from baseline for each treatment arm, presenting it alongside the corresponding 95% confidence interval.

For non-normally distributed continuous outcomes, and if transformations prove ineffective in enhancing normality, we will resort to a non-parametric approach—specifically, the Wilcoxon rank-sum test (Mann-Whitney two-sample statistic) to compare outcome values between the two treatment arms at each time point without applying baseline adjustments. The calculated statistics will include the median, inter-quartile range, as well as the minimum and maximum values for each treatment arm.

All time to event analyses will be accompanied by Kaplan-Meier survival curves to compare the survival rate between the two groups.

To visually represent non-normally distributed outcomes, we will create a whisker plot, illustrating the median along with the 25th and 75th percentiles, minimum, and maximum values for each treatment arm.

For visual representation of all other normally distributed continuous outcomes, line plots will be produced for the adjusted mean change from baseline in each treatment arm alongside a 95% confidence interval using time since randomisation on x-axis and adjusted mean change from baseline at y-axis.

5.1 Derived/ Computed Variables

Treatment allocation received

The reason for Protocol deviation concerning participants who received incorrect trial drug/placebo and the treatment allocation variables will be used to derive a binary

variable that will indicate whether participants received/did not receive their randomised allocation.

Time window in between dosing visits

The actual date of dosing visits (1-12) corresponding to each participant will be used to derive a continuous variable that will represent the time window or intervals (measured in days) between doses.

Number of taken doses over 48 weeks (for truncated follow-up over minimum 24 weeks)

The binary variable of "dose administered (yes/no)" at each dosing visit (1-12) will be used in order to derive a count variable that will represent the number of taken doses during the Trial.

Modification in the prescribed dosage during Trial

The reason for Protocol deviation concerning participants who did not receive the correct dose of trial drug/placebo will be used to derive a binary variable that will indicate whether participants had a modification in their prescribed dosage.

Change in the mode of administration of Trial drug/placebo

The site of injection recorded at each dosing visit will be used to derive a binary variable that will indicate whether there has been a change in the mode of administration of the Trial drug/placebo over the course of 48 weeks (Participants consented to the truncated follow-up will receive minimum 24 weeks follow-up).

5.2 Multiple Testing

No corrections for multiple testing will be made as this trial has a single primary outcome.

5.3 Analysis Software

All clinical data will be extracted from a MACRO database.

It is anticipated that the statistical analysis will be performed using a current version of either STATA, SAS, or R (Versions will be recorded in the end of trial report).

6 Statistical Methodology

The statistical analysis will be based on external guidelines (e.g. ICH E3 and E9).

The date of data extraction will be included in the Statistical Report.

6.1 Disposition

Disposition of participants will be presented on the ITT population with respect to the number of randomised participants, completion status, reason for non-completion, treatment completion as per Protocol, number of doses received, protocol deviations and blinding status. Results will be tabulated and summarised over time by treatment group and overall.

A Consolidated Standards of Reporting Trials (CONSORT) diagram will display the flow of participants through the Trial (schulz et al, 2010).

A graph of cumulative recruitment will be presented in addition to summaries of recruitment (e.g. start and end date).

Data completeness (i.e. CRF return rate) will also be summarised by treatment group and overall for each CRF.

A swimmer plot of participants' treatment duration along with reasons for discontinuation of treatment will be produced per treatment arm.

6.2 Demographic and Baseline Characteristics

Demographics, baseline characteristics and medical history will be summarised by treatment group and overall. This will include the summary of the stratification factors: baseline eMRC dyspnoea stable state (≤3, >3) and number of past hospitalisations in the previous 12 months (0, ≥1).

Numbers (with percentages) for binary and categorical variables, and means (with standard deviations) where data meets the normality assumptions or medians (with lower and upper quartiles) if otherwise will be presented. Where data is log transformed improve normality and allow for parametric testing the geometric mean on the original scale (i.e. after anti-logging the calculation of the mean on the log scale) must be presented alongside standard deviations on the log scale.

There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

6.3 Treatment Adherence

The numbers (with percentages) of participants receiving treatment doses 1 through 12, duration of total treatment period (last dose – first dose / 7) in weeks, numbers and duration of treatment delays will be reported descriptively between the intervention and placebo arms. The proportion of participants receiving doses at each visit will be presented in Bar diagram, showing dose number on y-axis and percentage of participants on the x-axis. The number of doses received per participant will also be presented graphically.

6.4 Primary Outcome Analysis

6.4.1 Primary Analysis of Primary Outcomes

The primary analysis will take place on the intention to treat population. All participants will be included in the model using censored values for participants not experiencing an event during their follow-up period.

The primary analysis will fit the Cox proportional hazard model for the primary outcome of the time to re-hospitalisation or death (any cause) as the dependent variable, treatment group as an explanatory factor and baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months ((0, ≥1) (Stratification factors). This analysis will be accompanied by Kaplan-Meier survival curves alongside with log rank test to compare the survival rate between the two groups. A hazard ratio (HR) of the mepolizumab relative to placebo, with their associated two-sided 95% confidence interval and p-values will be reported. A p-value ≤0.05 will be considered as significant difference.

Time until event (re-hospitalisation or death from any cause) will be measured in days from randomisation until re-hospitalisation, death or 12-month follow-up assessment, whichever happens first. Participants with no event (no re-hospitalisation or alive) assessed during follow-up visits will be censored at the last assessment date free from event.

Participants who do not complete the 12-month follow-up will be included in the primary analysis; those without a recorded event will be censored. Participants who withdraw from the trial will be censored at the date of withdrawal and participants lost to follow up will be censored at the date last assessment.

Proportional hazard assumption for the Cox proportional hazard model will be checked using the statistical tests and graphical diagnostics based on the Schoenfeld residuals.

Where participants don't reach the 12 month assessment but do not experience an event the last date of assessment known to be event-free will be used as the censor

value (right censoring). This will apply to participants who are withdrawn and/or lost to follow-up for any reason or receive truncated follow-up as part of the revised protocol. In the event of encountering multiple events occurring at the same time *t*, Efron's method for dealing with tied survival times will be implemented when fitting the Cox model to the data.
The KM plot will illustrate survival times over time including numbers at risk and number of events at regular time intervals, median survival estimates and survival estimates at 48 weeks follow-up for both intervention and placebo groups. Contrary to the protocol, the logrank test statistic will not be presented alongside the KM plot. The only test statistic to be presented will be that associated with the treatment term in the Cox model which will be used to test the hypothesis that the hazard of an event is different in the mepolizumab arm compared to the placebo arm.
The hazard ratio (HR) and associated 95% confidence interval will be presented.
A value of 1.0 would indicate the same hazard ratio in the intervention arm as placebo; a value below 1.0 would indicate a reduction in the hazard ratio of the event in the intervention arm, whereas larger values would infer a greater hazard ratio.

Lastly, an assessment of the Cox model residuals will be made by producing the following plots:

- Martingale residuals plot: to test for non-linearity of continuous covariates.
- Deviance residuals plot: to evaluate deviation from the saturated model.
- Cox-Snell residuals plot: to assess Goodness-of-Fit.

If the proportional hazards (PH) assumption does not hold in Cox proportional hazards regression, we will consider using flexible parametric survival models, such as the Royston-Parmar model or other parametric survival models. These models allow for more flexibility in modeling the baseline hazard, which can capture non-proportional hazards.

6.4.2 Secondary Analyses of Primary Outcomes

The secondary analysis of the primary outcome will take place on a subset of participants defined by the per-protocol population with individuals being censored at the earliest of end of their trial treatment (4 weeks after last dose) or last follow-up. The analysis will otherwise match the approach described above for the primary analysis.

6.4.3 Sensitivity Analyses

No sensitivity analyses of the Primary Outcome have been planned according to the protocol.

6.5 Secondary Outcome Analyses

6.5.1 Primary Analysis of Secondary Outcomes

All secondary outcome (except for AEs and SAEs) will be analysed on the modified intention to treat population. The secondary outcomes of adverse and serious adverse event counts will be analysed on the safety population.

All time to event secondary outcomes will be analysed the same way as the primary outcome.

All count secondary outcomes, number of hospital readmissions and number of moderate exacerbations, will be analysed using a negative binomial regression model. If there is no evidence of over-dispersion, a Poisson regression model will be used in place.

All continuous longitudinal outcomes (repeated measurements) will be compared using mixed effects model with patient as a random effect to account for repeated measures over time. This method will enable handling of missing data within the follow-up visits.

This trial has a single primary outcome, therefore there will not be a formal adjustment for multiple significance testing.

6.5.1.1 Time to event analyses

Will utilise the same methodology and presentation as the primary time to event outcome

6.5.1.2 Continuous Longitudinal Outcomes

All continuous longitudinal outcomes (repeated measurements) will be compared using mixed effects model with explanatory variables of treatment arm, stratification variables, visit number in weeks (categorical) and baseline value as fixed effects with participant identification as a random effect to account for repeated measures over time. This method will be able to handle missing data during the follow-up measurements. Adjusted mean differences alongside two sided 95% CI and P-value will be reported for these outcomes. Mean and standard deviation at baseline and over 48 weeks of the observed data will be presented by treatment arm. The adjusted mean change from baseline in each arm (with 95% confidence intervals) and the adjusted mean difference between groups (with 95% confidence intervals) will be presented alongside the 2-sided p-value from the model.

The model residuals corresponding to the continuous longitudinal outcomes will be assessed for normality by performing the Shapiro-Wilk Test.

Data will be assessed for the normality assumption using visualisation, taking into account sample size for each variable, the nature of potential outliers, and similarity between mean and median values (recognising formal statistics to test for normality

often lead to spurious results). If the distribution of the variable is found to be far from normally distributed, a log transformation will be used to modify the non-normality. In these cases adjusted geometric mean on the original scale (i.e. after anti-logging the result on the log scale) alongside standard errors on the log scale will be presented of the observed data. Geometric mean ratios from the model (with associated 95% CI and 2-sided p-value) will be reported to compare treatment groups.
Should a log transformation not correct for non-normally distributed data a non-parametric test such as the Mann Whitney U test can be utilised to assess the distribution of ranks between the treatment arms. Adjustment for other variables in the model including baseline value will not be possible and the Median (inter-quartile range), minimum, maximum of the observed data in each treatment arm will be presented along side the 2-sided p-value.

Further analysis of the participant reported outcomes will be carried out assessing the treatment effect by visit. Mean and standard deviation (SD) in each treatment arm will be calculated at baseline and each follow-up time point for each outcome using the observed data.

A mixed effect model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, stratification variables, visit number in weeks (categorical), baseline value, and an interaction term between treatment and visit as fixed effects with participant identification as a random effect to account for repeated measures over time will be fitted for each outcome. Adjusted mean change from baseline in each treatment arm as well as adjusted mean difference between treatment arms at each time point with 95% confidence intervals and p-value will be reported.

6.5.1.3 Count Outcomes

A generalised linear model (assuming a negative binomial distribution, which accounts for variability among participants in the number of and frequency of the count variable) will be fitted for each count outcome measure with explanatory variables of treatment arm and stratification variables, and log-time on study as an offset. The offset (log-time), allows for different lengths of follow-up time for each participant (Keene et al, 2008). Time on study will be capped at 49 weeks. This assumes that missing data is missing at random (MAR), and will be applied where all of the available observed data are analysed without deletion nor imputation.

The count data is assumed to follow a negative binomial distribution with the over dispersion. If the dispersion is found to be non-significant (i.e no evidence of over-dispersion) we will consider the simpler Poisson model where the dispersion parameter equals to zero. The ratio of the rates (RR) on the intervention arm relative to placebo, associated two-sided 95% confidence interval (CI) and p-value will be reported. A value of 1.0 would indicate the same rate as placebo; the lower the ratio the greater reduction in exacerbations compared with placebo. A two-sided p-value ≤ 0.05 will be considered

as a significant difference in the number of COPD exacerbations in 48 weeks between the two treatment arms.

6.5.1.4 Categorical longitudinal Outcomes

Will utilise the same methodology as the continuous models but using an appropriate logit link in a generalised linear model. Odds ratios (and 95% confidence intervals) will be used to illustrate comparisons between treatment groups.

6.5.2 Secondary Analyses of Secondary Outcomes

The count outcomes (number of hospital readmissions and number of moderate exacerbations over 48 weeks) will be analysed in the per protocol (PP) population. Analysis methods will mirror those described in the primary analysis of secondary outcomes, except the offset will be log time on trial treatment (4 weeks after the last dose, capped by death).

6.5.3 Sensitivity Analyses

The primary analyses for all none time event outcomes (i.e continuous, binary and count outcomes) will consider any missing data to be missing at random (MAR) and complete case analysis carried out. However, if comparison of patterns of missingness and descriptive differences between treatment arms indicate this assumption is not valid, additional sensitivity analyses may be carried out and methods of imputation will be included in detail in the statistical analysis plan.

To ensure the reliability of the analysis of key secondary outcome measures, we will conduct a sensitivity analysis under various scenarios. This will involve evaluating the secondary outcomes; number of readmissions, number of exacerbations, and SGRQ (assessed for three sub-domains and the total score), to thoroughly assess the robustness of our results.

Individuals will be considered to have had some missing data for the two count variables if they have less than 47 weeks (48 weeks – 7day window) follow-up with the exception of those with planned truncated follow-up.

In the first approach, regardless of whether missingness is assumed to be random or non-random, we will perform the outlined statistical procedures. Additionally, we will provide descriptive characteristics of the missing group compared to the non-missing group, exploring potential similarities or dissimilarities between them. This comprehensive approach allows for a thorough examination of the impact of missing data on our study outcomes.

In the second approach, we are aware that throughout the trial, some participants may leave the study due to a high number of exacerbations or death before reaching their 48-week follow-up. This leads to missing data that is not at random, rendering

standard imputation methods inappropriate. Therefore, the data for key secondary outcomes for these participants will be analysed in the following way:

Pattern Mixture Model:
Robustness of the results will be assessed within the pattern mixture model. A pattern mixture model is a type of statistical model used to analyse data with missing values, especially when the missingness is not at random (MNAR).

This method is a 2-stage procedure where the 1st stage involves the use of multiple imputation to impute all missing values assuming data are "missing at random".

The 2nd stage involves changing the imputed values for those participants from the time that they leave the study due to a high number of exacerbations or death before reaching their 48-week follow-up.

For the 2nd stage, the following approach will be used:
1) Changing all imputed values for these participants to their last observation of the key secondary outcomes before they exit the study due to exacerbations or death. [a]
2) Adjusting all imputed values for participants who exit the study due to exacerbations or death to a constant value (i.e. the mean of the outcome variable in the control group). [b]

[a] For the count variables, observed data will be carried forward by imputing the number expected in 48 weeks to be at the same rate as for the observed period rounded to the nearest whole number.
[b] For the count variables, observed data will included for the time period observed with the number for the remaining time period being imputed at the rate observed in the control group (using all observed control data weighed for the time observed) rounded to the nearest whole number for that time period.

Note: For Stage 1, all missing data will be imputed using multiple imputation with chained equations in Stata 18 (or above). Stata's "MI" command will be used to carry out this analysis and No data will be imputed past point of death.
Overall, 50 imputations will be generated for any missing data for the key secondary outcome and all stratification variables, treatment arm, and baseline value will be used to aid the multiple imputation procedure. Imputed results will be combined using Rubin's rule which in Stata is the "mi estimate" command.

6.6 Subgroup Analyses

Subgroup analyses of the primary outcome will be carried out on the stratification factors. These are baseline eMRC dyspnoea stable state score ((≤3, >3) and past hospitalisation in the previous 12 months ((0, ≥1). A stratified Cox model will be fitted to allow the form of the underlying hazard function to vary across the levels of stratification variables.

Three subgroup analyses of the primary outcome will be carried out based on

1) baseline dyspnoea stable state score dichotomised by ≤3 and >3 and
2) past hospitalisation in the previous 12 months dichotomised by 0 and ≥1
3) WHO clinical progression score at baseline (4, 5, 6).

The primary outcome of time to hospital re-admission or death (all cause) will be summarised by each subgroup (low versus high) and analysed as described in section 5.5.1. In each subgroup model, an indicator variable to specify the stratification group (low or high) will be included and an interaction term between stratification variable and treatment group will assess the difference in treatment efficacy between low and high stratification variable groups.

6.7 Adjusted Analysis

Modelling of the primary and all secondary outcomes will be adjusted for the baseline eMRC dyspnoea stable state score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1), used as a stratification factor at randomisation.

Adjustment for stratification variables can only take place where the statistical model allows for specification of such variables.

6.8 Changes to the Planned Analysis

None.

7 Safety and Adverse events

All safety data will be presented according to the Safety population.

All adverse events will be listed including characteristics such as seriousness, duration, relatedness, severity, action taken and outcome.

Adverse events' frequencies by seriousness, relatedness and severity will be summarised by treatment group and overall.

Adverse events frequencies will also be presented by treatment arm for each MedDRA Coding system organ class observed.

Graphical illustrations of frequencies by arm in total and by system organ class will be presented.

Furthermore, AE and SAE event rates will be reported as incidence rates per person years and calculated as (total number of events / sum of all follow-up times) *52
where;
-Total number of events is a count of all AE/SAEs observed.
-Follow-up time is calculated per participant from time of first dose until the last trial assessment is recorded.

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9 Appendices

9.1 Appendix 1: Templates for Tables, Listings and Figures

Table1: Disposition of Patients by treatment arm

		Control, n (%)	Mepolizumab, n (%)	Total, n (%)
	Randomised patients			
	Completed trial follow-up (End of trial assessment)			
	Discontinued due to			
	Lost to follow-up			
	Withdrawn			
	Deaths			
	Remained on treatment for intended follow-up period			
	Discontinued treatment early			
	Reasons:			
	Participant decision			
	Adverse Event			
	Unable to Tolerate Drug			
	Participant non-compliance			
	Lost to Follow up			
	Investigator decision			
	Participant Ineligible			
	Withdrawn due to Medical Reasons			
	Death			
	Number of doses received			
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			

Figure 1: A Swimmer plot of participants' discontinuation from the trial with reasons

Table 1: Case Report Form (CRF) return

CRF		Placebo Returned/Expected (%)	Mepolizumab Returned/Expected (%)
Visit 1 (Week 0)	Follow-up due		
	Follow-up completed		
Visit 2 (Week 4)	Follow-up due [a]		
	Follow-up completed		
Visit 3 (Week 8)	Follow-up due [a]		
	Follow-up completed		
Visit 4 (Week 12)	Follow-up due [a]		
	Follow-up completed		
Visit 5 (Week 16)	Follow-up due [a]		
	Follow-up completed		
Visit 6 (Week 20)	Follow-up due [a]		
	Follow-up completed		
Visit 7 (Week 24)	Follow-up due [a]		
	Follow-up completed		
Visit 8 (Week 28)	Follow-up due [a]		
	Follow-up completed		
Visit 9 (Week 32)	Follow-up due [a]		
	Follow-up completed		
Visit 10 (Week 36)	Follow-up due [a]		
	Follow-up completed		
Visit 11 (Week 40)	Follow-up due [a]		
	Follow-up completed		
Visit 12 (Week 44)	Follow-up due [a]		
	Follow-up completed		
Visit 13 (Week 48)	Follow-up due [a]		
	Follow-up completed		

[a] Will be defined as participants who have passed the visit window stated in the Protocol.

Table 2: Demographic and Baseline Clinical Characteristics

Characteristics	Descriptive	Placebo (n=)	Mepolizumab (n=)	Total (n=)
Age	**N**			
	Mean [SD]			
	Median [IQR]			
	Min, Max			
Gender	**Male**			
	Female			

Ethnicity	**White**
	Asian or Asian British
Smoking status	**Current Smoker**
	Ex-Smoker
BMI	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Number of cigarettes per day	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Number of years smoked	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Number of emergency admissions (all cause) in previous 12 months	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Number of courses of steroids without antibiotics for your chest (COPD exacerbations) in previous 12 months	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Number of courses of antibiotics without steroids for your chest (COPD exacerbations) in previous 12 months	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Number of courses of both antibiotics and steroids for your chest (COPD exacerbations) in previous 12 months	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Systolic (mmHg) *Pre-Dose*	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Diastolic (mmHg) *Pre-Dose*	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Heart rate (bpm) *Pre-Dose*	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Temperature (°C)	**N**
	Mean [SD]

Pre-Dose	**Median [IQR]**
	Min, Max
SpO_2 (%) *Pre-Dose*	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Respiratory rate (per min) *Pre-Dose*	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Systolic (mmHg) *Post-Dose*	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Diastolic (mmHg) *Post-Dose*	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Heart rate (bpm) *Post-Dose*	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Temperature (°C) *Post-Dose*	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
SpO_2 (%) *Post-Dose*	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
Respiratory rate (per min) *Post-Dose*	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
eMRC dyspnoea score (stable state)	**2:** *Breathless when hurrying on the level or walking up a slight hill*
	3: *Walks slower than peers or stops when walking on the flat at own pace*
	4: *Stops after walking 100m, or for a few minutes, on the level*
	5A: *Too breathless to leave the house & independent in washing and/or dressing*

	5B: *Too breathless to leave the house & dependent in washing and dressing*
	Missing*
WHO: Highest level of intervention during baseline admission	No oxygen therapy
	Oxygen by mask or nasal prongs
	Oxygen by NIV or high flow
Time to discharge from index admission (days)	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
*FEV1, litre	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
*FEV1, %	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
*FVC, litre	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
*FVC, %	**N**
	Mean [SD]
	Median [IQR]
	Min, Max
*FEV1/FVC ratio, %	**N**
	Mean [SD]
	Median [IQR]
	Min, Max

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

Figure 2: Proportion of patients in each dose

Figure 3: Number of doses per patient

Figure 4: Kaplan-Meier survival curves of the primary outcome by randomised group

Table 4: Primary Analysis of Primary Outcome: the time from randomisation to next hospital readmission or death (all cause)

	KM survival estimates at 48 weeks		Cox PH Model[a]	
	Placebo (n=)	Mepolizumab (n=)	HR (95% CI)	p-value
Intention to treat analysis				

a The Cox proportional hazard model will be used for the primary outcome of the time to re-hospitalisation or death (any cause) as the dependent variable. The treatment group served as an explanatory factor, while baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) will be included as stratification factors.

Table 5: Protocol deviations by treatment arm and overall

	Placebo	Mepolizumab
Randomised participants		
Randomised participants **with Protocol Deviations**		
Participants with:		
No Protocol Deviations		
1 Protocol Deviation		
2 Protocol Deviations		
3 Protocol Deviations		
4 Protocol Deviations		
5 Protocol Deviations		
>=6 Protocol Deviations		

Table 5: Number of Major and Minor Protocol Deviations

	Placebo	Mepolizumab
Number of Major Protocol Deviations		
Description		
Participant ineligible for entry into Trial		
Number of Minor Protocol Deviations		
Description		
Participant ineligible for entry into Trial		
Non-compliance with treatment allocation		
Visit/assessment not performed as per Protocol		
Other		

Table 6: Number of participants with Adverse Events

	Placebo	Mepolizumab
Randomised participants		
Randomised participants **with Adverse Events**		
Participants with:		
No Adverse Events		
1 Adverse Event		
2 Adverse Events		
3 Adverse Events		
4 Adverse Events		
≥ 5 Adverse Events		

Figure 7: Frequency of AE term by treatment arm

Table 7: Prevalence of AEs and SAEs by relatedness and severity

	Placebo	Mepolizumab
Number of Adverse Events		
Severity		
Mild		
Moderate		
Severe		
Fatal		
Missing		
Outcome		
Resolved		
Resolved with Sequelae		
Continuing		
Fatal*		
Unknown		
Missing		
Treatment		
None		
Concomitant Medication		
Non-drug therapy		
Concomitant Medication and Non-drug therapy		
Missing		
Action taken for Adverse Event		
None		
Study interrupted		
Study discontinued		
Missing		

	Placebo	Mepolizumab
Relatedness		
Not related		
Unlikely		
Possible		
Probable		
Definite		
Missing		
Serious Adverse Event?		
Yes		
No		
Missing		
Expectedness		
Yes		
No		
Missing		

9.2 Appendix 2: Line listing of the adverse events

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