UNIVERSITY OF LEICESTER

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

Mepolizumab for COPD Hospital Eosinophilic admissions Pragmatic trial (COPD-HELP)

Trial Protocol Version 9.1; 10/05/2024

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SPONSOR:	University of Leicester
SPONSOR Reference:	0690
FUNDER:	GlaxoSmithKline (GSK)

Confidentiality Statement

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

This protocol has regard for the HRA guidance and order of content

SIGNATURE PAGE

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

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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

VERSION: Version 9.1; 10/05/2024

For and on behalf of the Trial Sponsor:

Signature: Date: ...../...../.....

.....

Name (please print):

.....

Position: .....

Chief Investigator:

Signature: ..... Date: ...../...../.....

Name: (please print):

.....

Principal Investigator:

Signature: ..... Date: ...../...../.....

Name: (please print):

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Principal Statistician

Signature: ..... Date: ...../...../.....

Name: (please print):

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ii. 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

iii. TRIAL SUMMARY

Trial Title	A Randomised Controlled Trial of Mepolizumab Initiated Following Admission to Hospital for a Severe Exacerbation of Eosinophilic COPD
Short title	Mepolizumab for COPD Hospital Eosinophilic admissions Pragmatic trial
Trial acronym	COPD-HELP
Chief Investigator	Prof Christopher Brightling
Principal Investigator	Dr Neil Greening
Clinical Phase	Phase IIb
Trial Design	Interventional double-blinded, placebo, parallel, randomised controlled trial
Trial Participants	Patients admitted to hospital with an exacerbation of eosinophilic COPD
Planned Sample Size	238
Treatment duration	Mepolizumab 100mg will be administered subcutaneously once every 4 weeks up to 44 Weeks, minimum 20 weeks
Follow up duration	Up to 48 weeks, minimum 24 weeks
Planned Trial Period	4 years
Investigational Medicinal Product(s)	Mepolizumab
Formulation, Dose, Route of Administration	100mg powder for solution or solution in pre-filled syringe for injection. One subcutaneous injection every 4 weeks. Humanised monoclonal antibody which inhibits the bioactivity of the cytokine interleukin-5 (IL-5)
Eligibility criteria	**Inclusion criteria** 1. Symptoms typical of COPD when stable (baseline eMRC dyspnoea grade 2 or more). 2. A clinician defined exacerbation of COPD requiring admission to hospital. 3. Serum eosinophil count of ≥ 300 cells/μL either at time of admission or at any one time in the preceding 12 months. 4. Smoking pack years ≥ 10 years. 5. Age ≥ 40 years. 6. Established on inhaled corticosteroids (ICS) prior to this admission. 7. Willing and able to consent to participate in trial. 8. Able to understand written and spoken English. **Exclusion criteria** 1. COPD patients without eosinophilia (defined as persistently < 300 cells/μL within the last 12 months). 2. Other conditions that may be the cause of eosinophilia (such as hypereosinophilic syndrome, eosinophilic granulomatosis, eosinophilic oesophagitis or parasitic infection). 3. Patients whose treatment is considered palliative (life expectancy < 6 months).

	4. Other respiratory conditions including active lung cancer, interstitial lung disease, primary pulmonary hypertension or any other conditions that in the view of the investigator will affect the trial. 5. Known history of anaphylaxis or hypersensitivity to mepolizumab or any of the excipients (sucrose, sodium phosphate dibasic heptahydrate, polysorbate 80). 6. Unstable or life-threatening cardiac disease including myocardial infarction or unstable angina in the last 6 months, unstable or life-threatening cardiac arrhythmia requiring intervention in the last 3 months and New York Heart Association (NYHA) Class IV heart failure. 7. Decompensated liver disease or cirrhosis. 8. Pregnant, breastfeeding, or lactating women. Women of child-bearing potential must agree to use appropriate methods of birth control and have a negative blood serum pregnancy test performed after randomisation but prior to first dosing with randomised treatment.* 9. Participation in an interventional clinical trial within 3 months of visit 1 or receipt of any investigational medicinal product within 3 months or 5 half-lives. 10. Known blood born infection (e.g. HIV, hepatitis B or C). * Women of child bearing potential (WOCBP) – A woman is defined as being of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.	
	Objectives	**Outcome Measures**
Primary	To evaluate the efficacy of mepolizumab initiated following hospitalisation on future hospital readmission or death (all cause) compared with placebo in severe exacerbations of eosinophilic COPD.	Time from randomisation to next hospital readmission or death (all cause).
Secondary	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.	**Exacerbations and Healthcare Utilisation** • Time from randomisation to next hospital readmission or death due to a respiratory cause • Total number of hospital readmissions all cause up to 48 weeks • Total number of moderate exacerbations up to 48 weeks • 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) • Time from randomisation to death (all cause)

		• Time from randomisation to death (respiratory cause)
		• Time from randomisation to next hospital readmission (all cause)
		• Time from randomisation to next hospital readmission (respiratory cause)
		• Time to discharge from randomisation
		
		Quality of Life/Symptoms (Weeks 0, 4, 8, 12, 24, 36, 48*)
		• Breathlessness:
		  ○ Extended MRC dyspnoea score (eMRC)
		• Health Status
		  ○ St George's Respiratory Questionnaire (SGRQ)
		  ○ COPD Assessment Tool (CAT)
		• Mental wellbeing
		  ○ Warwick-Edinburgh Mental wellbeing score (WEMWBS)
		• Functional
		  ○ London Chest Activities of Daily Living Questionnaire (LCADL)
		
		Physiological Measures (Weeks 0, 4, 8, 12, 24, 36, 48*)
		• Frailty
		  ○ Short physical performance battery (SPPB)
		  ○
		  ○ Handgrip Strength
		
		Inflammatory Markers (Weeks 0, 4, 8, 12, 24, 36, 48*)
		• Serum eosinophil count (total count)
		• Sputum eosinophil count (percentage)
		
		Safety and Tolerability (all visits)
		• Adverse Events (AEs)
		• Serious Adverse Events (SAEs)
		Clinical assessments and investigations (heart rate, blood pressure, temperature)
		
		Exploratory Outcome Measures
		• Physical Activity using accelerometery (Weeks 0, 4, 8, 12, 24, 36, 48*)
		
		**See section 4.1 – Truncated follow-up; Patients randomised from July 2023 will receive minimum 24 weeks follow-up.*

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
GlaxoSmithKline	Financial support Drug supply
NIHR Leicester Biomedical Research Centre-Respiratory Theme	Infrastructure support
NIHR Leicester Clinical Research Facility	Infrastructure support

v. ROLE OF TRIAL SPONSOR AND FUNDER

The trial sponsor (University of Leicester) will be responsible for all aspects of the trial as per ICH-GCP and in conformance with the applicable regulatory requirements. The CI, delegated by the sponsor, is responsible for the proper conduct and management of the trial. The Leicester Clinical Trials Unit (LCTU), University of Leicester, will provide full research management services. A service level agreement is in place outlining the responsibilities of LCTU.

The funder (GSK), will be responsible for funding the study and supplying the Investigational Medicinal Product (IMP) and matched placebo for doses after 29 Feb 2024.

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

Trial Management Group (TMG)

The TMG will comprise of the study Chief Investigator, Principal Investigator/Research Fellow(s), Trial Manager, Senior Trial Manager, and Trial Statistician. As this is a single centre study, members of the site recruiting team will attend meetings as observers and contribute to recruitment discussions. The TMG will oversee the operational aspects of the trial, which include the processes and procedures employed, and the day-to-day activities involved in study conduct. The day-to-day management of the study will be undertaken by the Trial Manager based in the Leicester Clinical Trials Unit. The TMG is responsible for all aspects of the study (including protocol compliance, safety reporting, recruitment rate, budget management, etc.) and for ensuring appropriate action is taken to safeguard study participants and the quality of the study. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

Trial Steering Committee (TSC)

The TSC will comprise of an Independent Chairperson and two other independent members who may include clinicians and statisticians. The Chief Investigator, Principal Investigator, and other members including Patient Representative will also attend but do not having voting privileges. The TSC will provide oversight of the study and monitor the progress of the study taking into account reports and recommendations from the DSMC, to ensure the study is being conducted in accordance with the protocol, relevant regulations and the principles of GCP.

Data Safety Monitoring Committee (DSMC)

The DSMC will consist of independent experts who will assess participant safety and conduct of the clinical trial. The DSMC will adopt a DAMOCLES charter to define its terms of reference and operation and will make their recommendations to the TSC. The DSMC will meet on a regular basis as specified in the DSMC charter, prior to each TSC meeting to review the study information and accruing data during the conduct of the study.

vii. PROTOCOL CONTRIBUTORS

Prof Christopher Brightling, Chief Investigator, University of Leicester
Dr Neil Greening, Principal Investigator, University of Leicester
Dr Shaun Barber, Senior Statistician, Leicester Clinical Trials Unit
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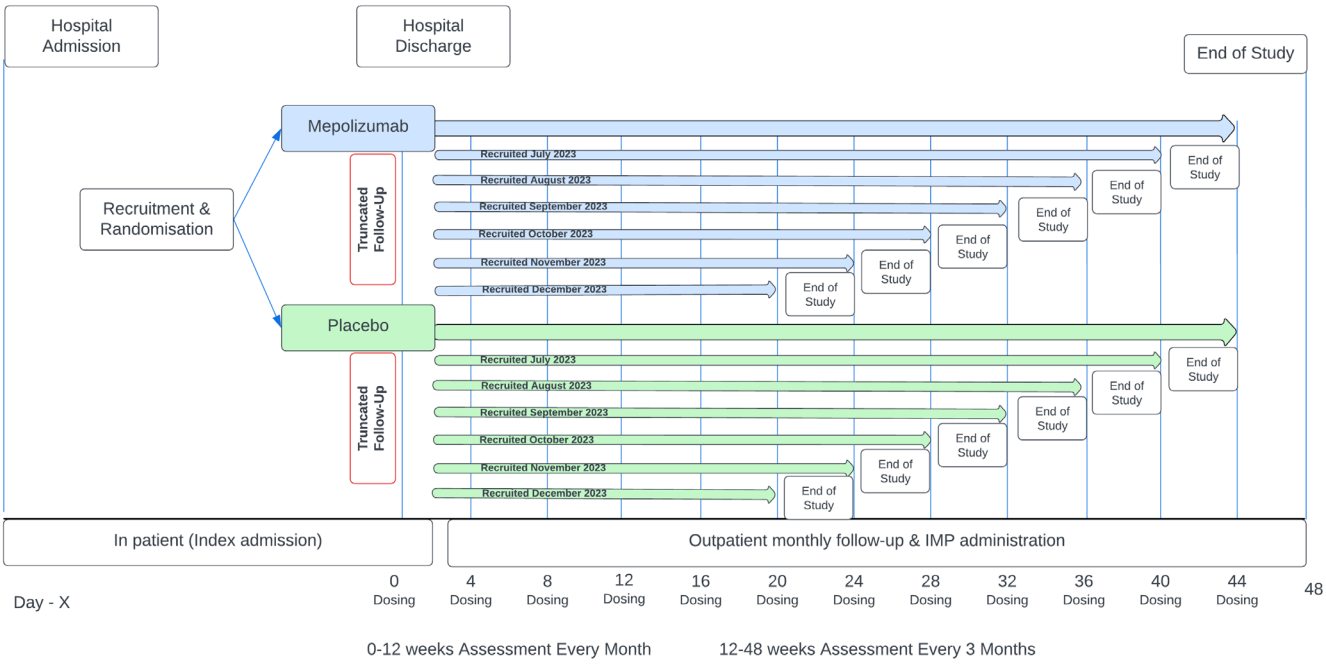
viii. KEY WORDS:

Pulmonary Disease, Chronic Obstructive
Clinical Trials, Phase IIb
Hospitalization
Eosinophils
Biological Products

ix. TRIAL FLOW CHART

Please note for the diagram below, the End of Study for the truncated follow-up participants (see section 4.1) will be a Final Follow-Up (no dosing) visit that occurs 4 weeks ± 7 days after their final dosing visit.



1 BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD) is a major healthcare priority internationally. It is the cause for 5.8% of worldwide deaths (3.28 million annually; www.goldcopd.com, accessed 2019), making it the fourth most common cause of death. Importantly, COPD is a long-term condition, with patients living with it for many years.

The natural history of COPD is punctuated with exacerbations, which are temporary worsening of symptoms that require additional therapy. Severe exacerbations, defined as requiring unscheduled hospitalisation, in particular are associated with poor outcome with a three month hospital readmission rate of 43% and a mortality rate of 12% (www.RCPLondon.ac.uk; accessed 2019).

The aetiology of exacerbations are heterogeneous, with a number of factors driving these events. This includes viral and bacterial infections, as well as environmental triggers. More recently, significant eosinophilic inflammation has been shown to be present at the time of an exacerbation in a sub-set of patients with COPD, and evidence suggests that these patients are more likely to respond to corticosteroids. Two trials of mepolizumab, an anti-IL-5 monoclonal antibody, have shown reductions in moderate exacerbation frequency in COPD (Yousef *in press*). However, the effects of mepolizumab in a higher risk population are unknown.

2 RATIONALE

Patients admitted to hospital with an exacerbation of COPD are at high risk of readmission, of which a proportion are driven by eosinophilic inflammation. Whilst oral corticosteroids are beneficial in exacerbations, a considerable proportion of patients experience treatment failure, with 50% of patients readmitted within 3 months (www.RCPLondon.ac.uk; accessed 2019).

Therapy, such as mepolizumab, reduces eosinophil count and has been shown to reduce exacerbation frequency when given in the stable state in both eosinophilic asthma (Papi et al. 2018) and COPD (Yousef *in press*).

We hypothesise that starting mepolizumab at the time of a hospitalisation for an exacerbation of COPD in patients with significant eosinophilia will result in a reduction in readmission to hospital in a high-risk population.

2.1 Assessment and management of risk

Mepolizumab is licensed and used clinically for severe asthma. It has been utilised in two randomised controlled trials in COPD comprising 865 patients in the treatment arms. The overall safety profile is good with no difference in reported side effects between treatment and placebo. The most common reported side effect is headaches (>1 in 10), followed by local injection site reactions expected in 3-8% of the population, similar in placebo and active drug (Pavord et al. 2017; Papi et al. 2018).

Beyond standard of care, the participants will undergo additional blood tests, breathing tests, airway sampling, urine tests, faeces sampling, and a subcutaneous IMP. These are all common routine tests. The blood, breath and airway sampling has minimal risk and mild discomfort. We will also monitor and analyse all potential cases of anaphylaxis and major adverse cardiac events (MACE).

This trial is categorised as:

- Type B = somewhat higher than the risk of standard medical care

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

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

3.2 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.

3.3 Outcome measures/endpoints

3.3.1. Primary Outcome Measure

The primary outcome is the time from randomisation to next hospital readmission or death (all cause).

3.3.2. Secondary Outcome Measures

3.3.2.1. Exacerbations and Healthcare Utilisation

- Time from randomisation to next hospital readmission or death due to a respiratory cause
- Total number of hospital readmissions all cause up to 48 weeks
- Total number of moderate exacerbations up to 48 weeks
- 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)
- Time from randomisation to death (all cause)
- Time from randomisation to death (respiratory cause)
- Time from randomisation to next hospital readmission (all cause)
- Time from randomisation to next hospital readmission (respiratory cause)
- Time to discharge from randomisation

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

- Breathlessness
  - Extended MRC dyspnoea score (eMRC)
- Health Status
  - St George's Respiratory Questionnaire (SGRQ)
  - COPD Assessment Tool (CAT)
- Mental wellbeing
  - Warwick-Edinburgh Mental wellbeing score (WEMWBS)
- Functional
  - London Chest Activities of Daily Living Questionnaire (LCADL)

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

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

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

- Serum eosinophil count (total count)
- Sputum eosinophil count (percentage)

3.3.2.5 Safety and Tolerability (all visits)

- Adverse Events (AEs)
- Serious Adverse Events (SAEs)
- Clinical assessments and investigations (heart rate, blood pressure, temperature)

3.3.2.6 Exploratory Outcome Measures

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

3.4 Exploratory Samples for Future Research (optional)

Additional samples (listed below) will be collected for exploratory analysis in future ethically approved research.

3.4.1 Biomarkers (Weeks 0, 4, 8, 12, 24, 36, 48*)

- Sputum inflammatory differential
- Sputum sample
  - Sputum microbiome
  - Systemic inflammation
- Blood sample
  - Cardiac biomarkers (Trop I and BNP)
  - FBC
  - Serum and plasma
- Urine sample

3.4.2 Muscle Wasting (Weeks 0, 4, 8, 12, 24, 36, 48*)

- Quadriceps size (measured by ultrasound)

3.4.3 Immunophenotyping and Microbiology – multiscale 'omics: immunotyping and microbiology (Weeks 0, 4, 8, 12, 24, 36, 48*)

- Blood – DNA (visit 1 only), RNA
- Sputum – RNA, Protein multiplex, immunology, microbiology (micro/metagenomics)
- Urine – lipidoproteinomics, protein multiplex

**See section 4.1 – Truncated follow-up; Patients randomised from July 2023 will receive minimum 24 weeks follow-up.*

3.5 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective	Time from randomisation to next hospital readmission or death (all cause)	Time to event between randomisation and first event, up to 48 weeks.
Secondary Objectives Exacerbation and healthcare usage	Time from randomisation to first hospital readmission or death (respiratory cause)	Time to event, up to 48 weeks.
	Total number of hospital readmissions (all cause)	48 weeks (minimum duration of trial treatment of 24 weeks)
	Total number of moderate exacerbations	48 weeks (minimum duration of trial treatment of 24 weeks)
	Time from randomisation to treatment failure	Time to event, up to 48 weeks.
	Time from randomisation to death (all cause)	Time to event, up to 48 weeks.
	Time from randomisation to death (respiratory cause)	Time to event, up to 48 weeks.
	Time from randomisation to first hospital readmission (all cause)	Time to event, up to 48 weeks.
	Time from randomisation to first hospital readmission (respiratory)	Time to event, up to 48 weeks.
	Time to discharge from randomisation	Time from randomisation to discharge, up to 48 weeks.
Quality of Life/Symptoms	Extended MRC dyspnoea score (eMRC)	Weeks 0, 4, 8, 12, 24, 36, 48* **See section 4.1 – Truncated follow-up; Patients randomised from July 2023 will receive minimum 24 weeks follow-up.*
	St George's Respiratory Questionnaire (SGRQ)	
	COPD Assessment Tool (CAT)	
	Warwick-Edinburgh Mental wellbeing score (WEMWBS)	
	London Chest Activities of Daily Living Questionnaire (LCADL)	
Physiological Measures	Short physical performance battery (SPPB)	Weeks 0, 4, 8, 12, 24, 36, 48* **See section 4.1 – Truncated follow-up; Patients randomised from July 2023 will receive minimum 24 weeks follow-up.*
	Handgrip Strength	

Inflammatory Markers	Serum eosinophil count	Weeks 0, 4, 8, 12, 24, 36, 48* **See section 4.1 – Truncated follow-up; Patients randomised from July 2023 will receive minimum 24 weeks follow-up.*
	Sputum eosinophil count	
Safety and Tolerability	AE event rate per year in the 48 weeks of the trial from first dose	48 weeks* **See section 4.1 – Truncated follow-up; Patients randomised from July 2023 will receive minimum 24 weeks follow-up.*
	SAE event rate per year in the 48 weeks of the trial from first dose	
	Clinical assessments and investigations	
Exploratory Objective Physiological Measures	Physical activity using accelerometry	Weeks 0, 4, 8, 12, 24, 36, 48* **See section 4.1 – Truncated follow-up; Patients randomised from July*

4 TRIAL DESIGN

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

Once eligibility criteria are met and written informed consent is obtained at the initial visit, patients will be randomised into a 48-week treatment period in which they will receive monthly subcutaneous injections of either 100 mg mepolizumab or a matching placebo. Secondary outcomes will be measured at baseline (week 0), 4 weeks, 8 weeks, 12 weeks, 24 weeks, 36 weeks and 48 weeks. Treatment groups will remain blinded until the analysis is complete.

4.1 Truncated follow-up

Participants randomised from July 2023 to December 2023 will be consented to a truncated follow-up model, whereby the timing of the last participant 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. Participants will be dosed for a minimum of 20 weeks (participants will be dosed at baseline, therefore all participants will receive at least 6 doses), 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.

5 TRIAL SETTING

This is a single centre trial. Recruitment will be from inpatients admitted via the Clinical Decisions Unit (CDU) at Glenfield Hospital, University Hospitals of Leicester. This admissions unit admits over 95% of all exacerbations of COPD in Leicestershire (catchment population circa. 1 million) and is the second largest acute hospital trust for hospital admissions in the UK.

6 PARTICIPANT ELIGIBILITY CRITERIA

Eligibility criteria for this trial have been carefully considered to ensure the safety of the patients included in the trial, the recruited cohort is suitable for analysis, and the results of the trial are relevant to the patient population. Participants must meet all the inclusion criteria and none of the exclusion criteria. Eligibility will be confirmed by a physician.

6.1 Inclusion criteria

1. Symptoms typical of COPD when stable (baseline eMRC dyspnoea grade 2 or more).
2. A clinician defined exacerbation of COPD requiring admission to hospital.
3. Serum eosinophil count of ≥ 300 cells/μL either at time of admission or at any one time in the preceding 12 months.
4. Smoking pack years ≥ 10 years.
5. Age ≥ 40 years.
6. Established on inhaled corticosteroids (ICS) prior to this admission.
7. Willing and able to consent to participate in trial.
8. Able to understand written and spoken English.

6.2 Exclusion criteria

1. COPD patients without eosinophilia (defined as persistently < 300 cells/μL within the last 12 months).
2. Other conditions that may be the cause of eosinophilia (such as hypereosinophilic syndrome, eosinophilic granulomatosis, eosinophilic oesophagitis or parasitic infection).
3. Patients whose treatment is considered palliative (life expectancy < 6 months).
4. Other respiratory conditions including active lung cancer, interstitial lung disease, primary pulmonary hypertension or any other conditions that in the view of the investigator will affect the trial.
5. Known history of anaphylaxis or hypersensitivity to mepolizumab or any of the excipients (sucrose, sodium phosphate dibasic heptahydrate, polysorbate 80).
6. Unstable or life-threatening cardiac disease including myocardial infarction or unstable angina in the last 6 months, unstable or life-threatening cardiac arrhythmia requiring intervention in the last 3 months and New York Heart Association (NYHA) Class IV heart failure.
7. Decompensated liver disease or cirrhosis.
8. Pregnant, breastfeeding, or lactating women. Women of child-bearing potential must agree to use appropriate methods of birth control and have a negative blood serum pregnancy test performed after randomisation but prior to first dosing with randomised treatment.*
9. Participation in an interventional clinical trial within 3 months of visit 1 or receipt of any investigational medicinal product within 3 months or 5 half-lives.
10. Known blood born infection (e.g. HIV, hepatitis B or C).

* Women of child bearing potential (WOCBP) – A woman is defined as being of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

7 TRIAL PROCEDURES

See appendix 1 for detailed visit structure and trial procedures.

7.1 Participant Identification and Recruitment

Trial participants will be from inpatient admissions in the Clinical Decisions Unit (CDU) at Glenfield Hospital, University Hospitals of Leicester. This admissions unit admits over 95% of all exacerbations of COPD in Leicestershire (catchment population circa. 1 million) and is the second largest acute hospital trust for hospital admissions in the UK. The unit admits approximately 150 patients per month with an exacerbation of COPD.

Potential participants to the trial will be identified as soon as practically possible when they are admitted to the clinical decisions unit (CDU) at Glenfield Hospital by members of their healthcare team. Following admission onto a medical ward, potential participants will be approached by a member of their healthcare team and asked if they would like to consider taking part in the study. If the patient is willing to consider participating in the trial, they will be approached by a member of the research team for further information and consent. On many occasions the healthcare team will also be members of the research team.

7.1.1 Screening

Potential participants will be required to meet a number of eligibility criteria before consent. All potential patients who are screened will have their pseudonymised data (initials and year of birth) added to the screening log and participants will then be assessed for eligibility as per inclusion/exclusion criteria from their patient notes. Eligibility will be confirmed by a physician. If eligible, participants will be approached and asked if they wish to take part in the trial. Once Informed Consent has been given participants will then be randomised into the trial via the web-based randomisation system. The screening log will be maintained by trial staff within the Investigator Site File (ISF). Participants who are deemed not to be eligible or who decline to take part in the trial will be screen failed and their screening log entry identified as screening failure along with the details of their ineligibility/declined invitation. Otherwise, details pertaining to the randomisation (date of consent, randomisation and trial ID) will be completed for all participants who are randomised.

7.1.2 Payment

Participants will be reimbursed for travel expenses at the usual NHS Trust rate (up to a maximum of £50 per visit) payable on production of original receipts at all trial visits. Participants will not receive any additional payment for taking part in the trial.

7.2 Informed Consent

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

Due to the nature of the study (acute illness resulting in hospitalisation), the participant can be consented at any point within their inpatient stay, or within one week of discharge. Participants will be given time to consider the information and have the opportunity to question the researcher, or other independent parties, to decide whether they will participate in the trial. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent, which will contain information that conforms to current data sharing and handling requirements.

The process for obtaining informed consent will be in accordance with the REC guidance, and GCP and any other applicable regulatory requirements, which may be introduced. Trial procedures including baseline assessments will not be undertaken until the informed consent form has been signed and dated by the participant. Should there be any subsequent amendment to the final protocol, which might affect their participation in the trial, then these will be discussed with the participant and, if applicable, continuing consent will be obtained using an amended consent form.

The original signed consent form will be retained at the study site within the Investigator Site File (ISF). One copy will be given to the participant, and a second copy retained in their medical notes.

7.2.1 Additional consent for biological specimens and future research

Additionally, participants will be given the opportunity to consent to access their primary care records (historical and during the trial), as well as to the storage of their biological specimens in a HTA approved bio-bank at the University of Leicester for future ethically approved research. This is optional and participants will be able to opt out of this without affecting their involvement in the trial. Both data and samples will be pseudonymised and may be transferred externally to collaborators with a further materials transfer agreement.

The research team will also seek permission to use participants' postcodes for future research investigating the link between their disease progression and the environmental pollution in the area in which they live. This will involve linking participants' health data outcomes (e.g. exacerbations) with their postcode by members of the University of Leicester. With consent, data will be transferred encrypted from the University Hospitals of Leicester NHS Trust to named individuals at the University of Leicester for analysis.

7.3 Randomisation

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.

7.3.1 Method of implementing the randomisation/allocation sequence

Once the participant has provided written consent to the trial and a physician has confirmed eligibility, randomisation will be performed. Unblinded personnel (authorised and trained) will enter data pertaining to consent, eligibility, pseudonymised identification and stratification onto the randomisation CRF. This data is required to be input into the online randomisation system in order to allocate the participant to a treatment arm. The randomisation system will generate a unique trial ID and determine allocation to either mepolizumab or placebo. The data recorded as part of randomisation will be held by the Sealed Envelope system with restricted access to the trial statistician for safety and DSMC reporting, pharmacy staff, the unblinded trial personnel, and Sponsor only.

7.4 Blinding

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 DSMC 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, where applicable, and dosing the participants.

The IMP, and matched placebo for those dosed from 01 March 2024, will be formulated and packaged by GSK. The placebo treatment will be saline solution for participants dosed before 01 March 2024, with those dosed on or after using a matched placebo from GSK in a pre-filled syringe.

The entire Pharmacy team are unblinded and will take receipt of the IMP and placebo in accordance with their local SOPs and complete the necessary documentation including the accountability logs which will be maintained securely in the trial Pharmacy Site File. They will provide the IMP/placebo to the unblinded trial personnel only. The Unblinded trial personnel will collect and transfer the unprepared IMP/placebo or pre-filled syringes making sure that they are not visible to anyone during transport i.e. transferred in a closed non-transparent bag.

The unblinded trial personnel are designated on the Delegation Log and will be responsible for randomisation and trial drug preparation, reconstitution and administration, which will take place in Glenfield Hospital out of sight of

blinded trial personnel or the participant, with clear warning notices that unblinded IMP is being prepared. All documentation of IMP/placebo preparation, randomisation CRF and prescription containing information about randomisation for each participant, will be kept in a folder in a sealed box or in a secure location not known to the blinded team. A label will be added directly to the syringe containing only the trial ID, initials, a statement that it is 'either drug mepolizumab or placebo within', date, time of preparation, and the initials of the unblinded person preparing it.

This 'blinded label syringe' will be handled by unblinded trial personnel to be administered to the participant on site. There may be slight colour and viscosity differences between the IMP and placebo, which will be mitigated by using an unblinded member of the study team to administer the treatment to the participant.

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

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

7.5 Emergency Unblinding

The need for code breaking will, if possible, be discussed with the Chief Investigator or designee. The Principal Investigator or delegated Co-Investigator at site will authorise the code break and decide on further management including the need to inform regulatory authorities. Emergency unblinding will be available to the investigator / pharmacist / Sponsor via the web based Sealed Envelope system. The username and password will be tested in advance of the first participant enrolled onto the trial. The Sealed Envelope system will be fully audit traceable until the end of the trial to ensure that blinding has not been compromised. Unblinding will only occur in the case of a medical emergency 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. In the case of a serious adverse event that is deemed at least possibly related to the allocated treatment, the trial treatment will be discontinued. If unblinding occurs, the investigator must record the reason for unblinding, as well as the date and time of the event in the site file and medical notes. Corresponding information will be recorded in the CRF by the investigator. It will also be documented at the end of the trial in any final trial report and/or statistical report. The CI/Investigating team will notify the Sponsor and the Leicester Clinical Trials Unit in writing as soon as possible following the code break, detailing the necessity of the code break. In the case of unblinding an individual participant for safety reasons, appropriate follow-up of safety related events is required until the event(s) has satisfactorily resolved.

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.

7.6 Baseline data

Baseline measures will be completed following obtaining of informed consent and randomisation, and prior to first dosing (see section 8.4) as soon as participants are stable and within seven days of discharge. Please see Trial Assessments (section 7.7) below for assessment details.

7.7 Trial assessments

The trial visit schedule and assessments are summarised in Appendix 1. Trial assessments (e.g. Quality of Life/Symptoms Assessments) may be completed remotely by telephone consultation, where possible, and when necessary. Details of all trial visits are presented below.

7.7.1 Visit 1 (Week 0) – Consent & First Dosing

The following procedures will be performed:

- Eligibility checklist from routinely collected data
- Informed consent
- Randomisation
- Baseline measures
    - ECG, Chest x-ray & ABG (completed as part of standard care)
    - Quality of Life /Symptoms Assessments (eMRC X2 for stable and exacerbated states; SGRQ; CAT; WEMWBS; LCADL)
    - Physiological Measures (SPPB; accelerometry; handgrip strength)
    - Inflammatory markers (serum eosinophil count; sputum* eosinophil count)
    - Lung Function[$] (Spirometry data Forced Expiratory Volume in 1 second (FEV1); Forced Vital Capacity (FVC); FEV1 % predicted; FEV1/FVC
- Baseline exploratory measures
    - Biomarkers (Sputum* inflammatory differential; sputum* sample: microbiome, systemic inflammation; blood sample: Trop I, BNP, FBC, serum, plasma; urine sample)
    - Muscle wasting (quadriceps ultrasound)
    - Immunophenotyping & Microbiology (Blood: RNA, DNA; Sputum*: RNA, Protein multiplex, immunology, microbiology; Urine: lipoproteinomics, protein multiplex)
    - Respiratory disease progression assessment: WHO Clinical Progression Scale
- First dosing (see section 8.4).

[$]*Results from historical or contemporaneous spirometry testing performed as part of usual care will be collected from hospital and primary care records where available*

***Please note that for patients consented to the study during the truncated follow-up phase (July 2023 to December 2023), not all visits listed below will be completed (see section 7.7.5).**

7.7.2 Visits 2-4, 7 & 10 (Weeks 4, 8, 12, 24, 36; each visit ± 7 days) – Data collection

The following procedures will be performed:

- Review concomitant medication
- Safety & tolerability (AEs; SAEs, Vital signs, Clinical assessments and investigations)
- Urine pregnancy test (if applicable)
- Dosing (see section 8.4)
- Outcome measures
    - Quality of Life /Symptoms Assessments (eMRC; SGRQ; CAT; WEMWBS; LCADL).
    - Physiological Measures (SPPB; accelerometry; handgrip strength)
    - Inflammatory markers (serum eosinophil count; sputum* eosinophil count)
- Exploratory measures
    - Biomarkers (Sputum* inflammatory differential; sputum* sample: microbiome, systemic inflammation; blood sample: Trop I, BNP, FBC, serum, plasma; urine sample)
    - Muscle wasting (quadriceps ultrasound)
    - Immunophenotyping & Microbiology (Blood: RNA; Sputum*: RNA, Protein multiplex, immunology, microbiology; Urine: lipoproteinomics, protein multiplex)

7.7.3 Visits 5, 6, 8, 9, 11, 12 (Weeks 16, 20, 28, 32, 40, 44; each visit ± 7 days) – Dosing only

The following procedures will be performed:

- Review concomitant medication
- Safety & tolerability (AEs; SAEs, Vital signs, Clinical assessments and investigations)
- Urine pregnancy test (if applicable)
- Dosing (see section 8.4).

7.7.4 Visit 13/Final Follow-up (Week 48 ± 7 days) – Final Follow-up (no dosing)

The following procedures will be performed on all participants who completed the trial treatment schedule. Those participants who discontinued treatment prior to visit 12 but remain in the trial will be invited to hospital to attend this final visit.

- Review concomitant medication
- Safety & tolerability (AEs; SAEs, Vital signs, Clinical assessments and investigations)
- Urine pregnancy test (if applicable)
- Outcome measures
    - Quality of Life /Symptoms Assessments (eMRC; SGRQ; CAT; WEMWBS; LCADL)
    - Physiological Measures (SPPB; handgrip strength)
    - Inflammatory markers (serum eosinophil count; sputum* eosinophil count)
- Exploratory measures
    - Biomarkers (Sputum* inflammatory differential; sputum* sample: microbiome, systemic inflammation; blood sample: Trop I, BNP, FBC, serum, plasma; urine sample)
    - Muscle wasting (quadriceps ultrasound)
    - Immunophenotyping & Microbiology (Blood: RNA; Sputum*: RNA, Protein multiplex, immunology, microbiology; Urine: lipoproteinomics, protein multiplex)

7.7.5 Truncated follow-up

Patients consented from July 2023 will be followed-up on a truncated visit model, with at least 20 weeks of dosing. Where applicable, the Visit 13 Final Follow-up (no dosing) visit will occur 4 weeks ± 7 days from final dosing visit. It will follow the same schedule of assessments as listed in section 7.7.4. Patients will only complete the visits as per the schedule outlined above up until their final dosing visit.

**please note that due to COVID-19 infection risk protocols within the hospital, only spontaneous sputum samples are collected as part of the standard of care*

7.8 Withdrawal criteria

Specified criteria for discontinuation of trial treatment will be for participants that miss more than one dose of the trial treatment or who delay a dose for >4 weeks. The only exception will be when this delay is due to a COPD exacerbation resulting in hospitalisation, in which instance the next dose will be administered at the next due date or as soon as possible afterwards to allow the participant to recover.

Every effort should be made by the research team to keep the participants in the trial. However, participants have the right to withdraw their consent to take part in the trial at any time without having to give a reason and this will not affect their future care. Withdrawal of consent details and reasons (if known) should be recorded on the CRF and in the medical notes.

The investigator may discontinue treatment of a participant at any time if they are not compliant with the trial protocol or to protect the participant's safety and well-being after consultation with the CI. The IMP may also be discontinued in the case of an adverse event which the investigator considers sufficient to jeopardise the safety of the participant. Participants who want to discontinue trial treatment should be encouraged to remain in the trial and

to continue to be followed-up as per the protocol or as per routine care. Participants who discontinue treatment, for whatever reason, will be asked for their consent to continue collecting data, as a minimum this must include data on hospital admissions and deaths for the remainder of the trial (48 weeks) in order to answer the primary outcome. Those declining this will be withdrawn from the trial (thus withdrawing their consent).

Every effort should be made to keep the participant in the trial to collect important efficacy and safety data. Additionally, there are a number of trial assessments (e.g. Quality of Life measures/Symptom Assessments) that may be collected over the telephone if the participant agrees to be contacted. Withdrawals from the trial should be discussed with the CI or their deputy and the Trial Manager. If a participant has withdrawn/discontinued from the trial for any reason, then his/her screening and trial ID number(s) cannot be issued to another participant.

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

A participant will be considered to have completed the trial if they continue to take trial treatment until Visit 12 (Week 44) and attend Visit 13 and/or the Final Follow-up (referred to as Week 48, unless in the truncated follow-up group; for those, this visit is referred to as the Final Follow-up and will not necessarily occur 48 weeks post randomisation). For those on a truncated follow-up, participants will be considered to have completed the trial if they continue to take trial treatment until their final dosing visit (determined by when they are consented and join the study) and attend the Visit 13/Final Follow-up. For the truncated follow-up, this final follow-up will occur 4 weeks ± 7 days from their final dosing visit.

7.9 Storage and analysis of research samples

Research samples will be collected as detailed in section 7.7 and Appendix 1. Full requirements for research sample collection and storage are detailed in the trial laboratory manual provided with the Investigator Site File.

The following blood samples will be processed by the University Hospitals of Leicester NHS Trust central pathology labs and will be collected at room temperature from the trial site. These samples will likely be taken as part of routine care at the index admission but will be considered research samples at subsequent visits. These samples are not stored for the purposes of the study and are either used or destroyed during the testing process. The results of these blood tests will be printed and stored within the Case Report Form (CRF), as well as uploaded into the database.

- Biochemistry Profile – Full (including U&E, LFTs)
- Full Blood Count (FBC)
- C-Reactive Protein (CRP)
- Trop I and BNP

The following samples will be analysed for research purposes to answer secondary outcomes and for future ethically approved research by the research team and processed at the Respiratory BRC laboratories, University of Leicester. Samples will be kept on ice or stored in monitored -20°C or -80°C freezers prior to analysis, unless contraindicated.

- Urine sample
- Sputum sample (collected on ice and processed at 4°C as soon as possible and within 2 hours of expectoration) including RNA
- Blood samples including:
    - FBC
    - Serum and plasma
    - DNA (visit 1 only) and RNA

All samples collected for exploratory future analysis will be stored within the Respiratory BRC. The Respiratory BRC is a registered Tissue Bank and all samples are stored in accordance with the Human Tissue Act 2014. Disposal will be according to local laboratory procedures.

7.10 Pandemic guidance

In the event of a pandemic (e.g. COVID-19) or local/national lockdowns which may affect COPD-HELP participants, the trial team will check ahead of scheduled trial visits that participants are able to attend in line with local NHS Trust policy. Government guidelines with regards to testing and self-isolation should be followed if a participant experiences symptoms, tests positive and/or must self-isolate. Dosing may be delayed up to 4 weeks and trial visits will be rescheduled following completion of the government required self-isolation period/a negative test.

It is unavoidable that participants will need to attend hospital in order to take part in the trial. However, the trial team will ensure participants spend the least amount of time in hospital as possible in order to reduce the risk of transmission in participants and staff. Few assessments may be performed remotely including; Quality of Life / Symptoms Assessments (eMRC; SGRQ; CAT; WEMWBS; LCADL), review of concomitant medication and adverse events/SAEs.

Collection of follow up data will be consistent with clinical care without compromising the scientific validity of the trial, ensuring safety assessments and key endpoints of the trial are met.

To facilitate descriptive characterisation of participants who have not been able to undergo spirometry testing as part of the study, results from historical or contemporaneous spirometry testing performed as part of usual care will be collected from hospital and primary care records where available.

7.11 End of trial

This trial will end when the specified number of participants have been recruited, all participants have completed their last follow up visit, data validation has taken place and the database is locked and statistical analysis complete.

Data reported in the final report to REC and MHRA within 12 months of the End of Trial will include the primary and secondary outcomes (see sections 3.3.1 and 3.3.2).

Participants who become lost to Follow Up will be followed-up via their hospital records until 48 weeks to collect information on the number of exacerbations, number of hospitalisations and death. Those consented to truncated follow-up (consented to study from July 2023 onward) will be followed-up via their hospital records until their Final Follow-up visit which will occur 4 weeks ± 7 days from what would have been their final dosing visit (based on when they are consented to the trial).

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee or the Sponsor
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA)
- Following recommendations from the Data Safety Monitoring Committee (DSMC) or otherwise the Trial Steering Committee (TSC) determine the trial should stop
- Funding for the trial ceases

8 TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product(s)

The Investigational Medicinal Product (IMP) for this trial is mepolizumab 100mg powder for solution for injection, or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe. Mepolizumab is a humanized monoclonal antibody used for the treatment of severe eosinophilic asthma. It recognizes and blocks interleukin-5, a signalling protein of the immune system.

Drug Name	Dosage	Description
Mepolizumab (powder)	100mg/ml	Supplied as lyophilisate in vials with a nominal filling volume of 10 ml containing 100mg landiolol mepolizumab and inactive ingredients sucrose, sodium phosphate dibasic heptahydrate and polysorbate 80.
Mepolizumab (pre-filled syringe)	100mg/ml	Supplied as 1 ml solution in a glass syringe containing 100 mg mepolizumab, citric acid monohydrate, polysorbate 80, sodium phosphate dibasic heptahydrate and sucrose.
Placebo (pre-filled syringe)	N/A	Supplied as 1 ml solution in a glass syringe containing edetate disodium dihydrate, citric acid monohydrate, polysorbate 80, sodium phosphate dibasic heptahydrate and sucrose.

8.2 Regulatory status of the drug

Mepolizumab is currently licensed in the UK for the treatment of severe refractory eosinophilic asthma and has been NICE approved for patients who have adhered to an optimised standard treatment plan.

8.3 Product Characteristics

The Summary of Product Characteristics (SmPC) will be used to obtain information on how to use the medicine and to assess expectedness of events (known as the reference safety information). The SmPC will be provided in the Investigator and Pharmacy Site Files. A new SmPC will be used from 01 March 2024 to reflect the new constitution of the IMP from this date (Nucala 100 mg solution for injection in pre-filled syringe, date of revision of text 23 May 2023).

8.4 Dosage and excipients

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.

8.4.1 Truncated follow-up

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 with first dose administered at baseline); 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.

Due to IMP expiry dates and availability of replacement stock, any doses administered from 01 March 2024 will be with IMP or matched placebo solution for injection in a pre-filled syringe.

8.5 Dosage modifications

The dosing regimen in this eosinophilic COPD patient population is as per the licensed indication (severe refractory eosinophilic asthma). In the two clinical studies undertaken using mepolizumab in COPD patients, the safety profile of the drug was in line with the severe refractory eosinophilic asthmatic population. There will be no dose modification during the trial (see Section 8.10 for non-IMP medication changes). No dose adjustments are required for elderly patients.

If a participant has an anaphylactic reaction to the drug or placebo, they will discontinue from trial treatment and be withdrawn from the trial. If the participant is willing, and where appropriate, they will be contacted at their 48 week/Final Follow-up time point to collect information on any additional exacerbations since discontinuation. If the study treatment is stopped due to a clinical reason, such as an allergic reaction, IMP will not be restarted in the same participant.

8.6 Packaging and labelling

GlaxoSmithKline (GSK) are providing commercially produced mepolizumab, and matched placebo for doses from 01 March 2024, for use in the COPD-HELP trial from GSK, Parma Italy. GSK will arrange for delivery of mepolizumab and matched placebo, where applicable, to a third-party company, who will be responsible for labelling in line with Annex 13 of the EU Guidelines for Good Manufacturing Practice and QP release of the IMP. The third-party company will then arrange for delivery of the labelled mepolizumab and matched placebo, where applicable, to the recruiting site at regular intervals according to trial requirements communicated by Pharmacy. Allocation of trial medication (mepolizumab or placebo) will be managed by Sealed Envelope (web-based randomisation system). The mepolizumab or placebo will be prepared and a blinded label applied to the syringe by unblinded trial personnel (see section 7.3-7.5 on Blinding and Randomisation). All information will be documented on an unblinded participant IMP/placebo preparation worksheet by the unblinded trial personnel, the pharmacist will maintain unblinded accountability logs.

8.7 Drug supply, storage, dispensing and returns

The trial funder, GlaxoSmithKline (GSK), will supply the mepolizumab free of charge for the duration of the trial; they will also supply the matched placebo to the pre-filled syringes used for dosing from the 01 March 2024. Mepolizumab and matched placebo, where applicable, will be provided as open-label product to unblinded

pharmacy and trial staff. Unblinded staff will be responsible for the receipt and storage. GSK will supply sufficient mepolizumab and matched placebo, where applicable, to treat all participants. The participating centre (University Hospitals of Leicester, UHL) will be allocated an initial supply of trial mepolizumab at site activation. Stock levels at UHL pharmacy will be monitored by the clinical trials pharmacy team. When mepolizumab supplies reach a pre-determined level then Pharmacy will request further supply of mepolizumab. Placebo will be prepared from clinical stock of saline at Glenfield Hospital up until 29 February 2024, whereby from 01 March 2024, the study will use the solution for injection in pre-filled syringe with pre-filled matched placebo syringes.

At site the mepolizumab and matched placebo, where applicable, will be stored between 2-8°C. Storage of mepolizumab and matched placebo, where applicable, at site will be in a secure location, in a temperature-controlled environment, with a temperature log maintained for each working day. Any temperature excursions must be reported to the coordinating centre as soon as they are identified.

The local site Clinical Trials Pharmacist is responsible for ensuring mepolizumab/placebo accountability, including reconciliation of mepolizumab/placebo and maintenance of mepolizumab/placebo records, throughout the course of the study in accordance with UK regulatory requirements. Mepolizumab/placebo may be dispensed only by specifically authorised personnel. Responsibility for certain tasks related to the management of the mepolizumab/placebo will be delegated to the site pharmacy clinical trials staff and other members of the site trial team.

Mepolizumab/placebo is supplied for use in the COPD-HELP Trial and must only be prescribed for participants randomised into this trial. Prescriptions should be made available for review as source data, if required.

Where a vial or pre-filled syringe of mepolizumab has been allocated or has been reconstituted but not administered to the participant, if a full cold chain (documentation by the unblinded members of the research team) of time into fridge after leaving pharmacy and time returned to pharmacy is present, the pharmacist who receives the returned stock with seek permission from the sponsor to return the IMP back to stock, otherwise stock will be returned to Pharmacy and placed in quarantine until permission to destroy is received from the Sponsor.

8.8 Preparation of Investigational Medicinal Product (IMP)

Mepolizumab, as a powder, is supplied in lyophilised white powder requiring reconstitution prior to administration, used for dosing visits up to and including 29 February 2024. It is preferable to confirm the participant will be attending for their visit before writing up the prescription to avoid wastage. A mechanical reconstitution device (swirler) is required. Reconstituted mepolizumab must be discarded within eight hours if not administered. Detailed instructions for preparation and reconstitution of mepolizumab or the placebo are provided in the Pharmacy Management Manual. For dosing visits from 01 March 2024, mepolizumab will be in the form of a solution for injection in a pre-filled syringe. The pre-filled syringe will be removed from the refrigerator and administered within eight hours once the pack has been opened. The pack should be discarded if not administered within eight hours.

Dispensing will be recorded on the appropriate trial specific accountability forms. Mepolizumab must not be used for any other purpose than the present study. Mepolizumab/placebo that has been dispensed from pharmacy and prepared for administration to a participant must not be re-dispensed or re-issued to a different participant. Unused mepolizumab and matched placebo, where applicable, at the end of the trial or which has expired will be returned to the local pharmacy to be recorded and final accountability performed.

Further details regarding the mepolizumab will be provided in the Pharmacy Management Manual.

8.9 Known drug reactions and interaction with other therapies

The most commonly reported adverse reactions in clinical trials for participants with severe refractory eosinophilic asthma included headache (≥1/10), injection site reactions (≥1/1000) and back pain (≥1/1000) (Pavord et al. 2017). The most common manifestation reported with local injection site reactions included pain, erythema, swelling, itching and burning sensation. For the full list of undesirable effects please refer to section 4.8 of the approved version of the Summary of Product Characteristics (SmPC) for Mepolizumab provided in the Investigator Site Files (ISF).

8.10 Concomitant medication

No interaction studies have been performed and there are no noted contraindications. Due to the mechanism of action of Mepolizumab, the potential of drug-drug interactions is considered to be low. Therefore, there are no restrictions on concomitant use of other medications. Patients will continue to receive all their normal medication for other conditions as clinically indicated and prescribed by their physician unless otherwise clinically indicated. Changes to baseline concomitant medication will be assessed at every trial visit and recorded in the Case Report Form (CRF).

8.11 Trial restrictions

Immediate (within hours of administration) and delayed (typically within several days) acute and delayed systemic reactions have been observed following administration of Mepolizumab. This includes hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm, and hypotension).

Patients with pre-existing helminth infections should have been treated before entering the trial. If a participant becomes infected with a helminth infection and do not respond to anti-helminth treatment, temporary discontinuation of trial treatment should be considered. As helminth infections are very rarely seen in the UK, this is not expected to occur in this trial.

There is limited data on from the use of Mepolizumab in pregnant women. Animal studies have shown the drug to cross the placental barrier, though the potential to a human foetus is unknown. As a precautionary measure women of child-bearing potential (WOCBP) will receive a pregnancy test prior to trial treatment and must agree to use an acceptable method of birth control (see section 9.6 Pregnancy and pregnancy reporting) throughout the study duration. A urine pregnancy test will be undertaken prior to each subsequent administration of IMP following the baseline visit and at the final Visit 13/Final Follow-up.

In order to improve the traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly noted in the accountability log seen only by members of the unblinded trial team.

8.12 Assessment of compliance with treatment

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.

See section 10 for a description of how non-compliance will be handled in the analysis.

8.13 Name and description of each Non-Investigational Medicinal Product (NIMP)

Sterile saline solution will be used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe will be used. Mepolizumab/placebo will be administered by an unblinded member of the study team so that the Investigator(s) and participants cannot distinguish Mepolizumab from placebo.

9 PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. Clinical outcomes (e.g. moderate exacerbations not requiring hospitalisaton) are exempt from adverse event recording and will be captured on the relevant case report form.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which 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. Clinical outcomes that require inpatient hospitalisation or prolongation of existing hospitalisation are exempt from serious adverse event reporting, unless the investigator deems the event to be related to the administration of the study drug. Clinical details about these outcomes will be routinely collected in the case report form.
Serious Adverse Reaction (SAR)	An adverse reaction deemed to be serious (i.e. results in death, is life-threatening, results in persistent or significant disability/capacity, consists of a congenital anomaly or birth defect.) and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information:

Reaction (SUSAR)	• in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

9.2 Recording and reporting of SAEs, SARs AND SUSARs

All SAEs / SUSARs occurring following first administration of IMP/placebo until the final trial visit (week 48/Final Follow-up) or 28 days post cessation of trial treatment where this occurs earlier than protocolised (the length of the withdrawal period of mepolizumab; please see pharmacokinetic details within section 5.2 of the Summary of Product Characteristics), must be recorded on the SAE Form and sent to the Sponsor and the Leicester Clinical Trials Unit (LCTU) within 24 hours of the research staff becoming aware of the event. The LCTU will work with Sponsor to review and track all SAEs. Once all resulting queries have been resolved, the Sponsor will send an acknowledgement of the closure of the SAE, all correspondence and signed SAE forms will be retained in the Investigator Site File, within the Trial Master File and electronically on the Sponsor SAE database.

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

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

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

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

9.3 Responsibilities

Principal Investigator (PI) or suitably trained delegate:

1. Checking for AEs when participants attend for treatment / follow-up.
2. Using medical judgement in assigning seriousness, causality and whether the event was anticipated using the Reference Safety Information approved for the trial.
3. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.

4. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

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

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

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

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

Trial Steering Committee (TSC):

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

Data Safety Monitoring Committee (DSMC):

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

9.4 Notification of deaths

Deaths will be reported to the Sponsor in accordance with the SAE reporting timeline described previously and within 24 hours of the investigator becoming aware of it. In instances where participants that have discontinued treatment early and are >28 days post last dose (not meeting SAE reporting criteria) a death notification CRF will be completed. Severe exacerbations are associated with a mortality rate of 12%.

9.5 Pregnancy and pregnancy reporting

Limited data is available on the use of mepolizumab during pregnancy. Mepolizumab crosses the placental barrier in monkeys. Animal studies do not indicate reproductive toxicity. The potential for harm to a human foetus is unknown. The manufacturer advises to avoid use during pregnancy unless the benefit outweighs risk.

MHRA guidelines (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf accessed from https://www.gov.uk/government/publications/common-issues-identified-during-clinical-trial-applications/common-issues-clinical) for use of IMPs with an unlikely risk of human teratogenicity / fetotoxicity advise that women of child-bearing potential (WOCBP) must have a negative blood serum pregnancy test performed prior to first administration of trial treatment, a negative urine pregnancy test at each subsequent visit prior to dosing, and must agree to use an acceptable method of birth control for the duration of the trial. However, given the average age range of the disease population, this will not be a significant proportion of participants. Additional testing will also occur at any time during the trial if a menstrual period is missed or as required by local law.

A woman is defined as being of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide 5
- cap, diaphragm or sponge with spermicide

Additional, highly effective contraceptive measures (i.e. a failure rate of less than 1% per year when used consistently and correctly) may also be used. These are defined as:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion

- vasectomised partner (provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments).

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

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

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

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

9.6 Overdose

The dose of mepolizumab considered to be an overdose has not been defined. Single doses of up to 1500 mg were administered intravenously in a clinical trial to patients with eosinophilic disease without evidence of dose-related toxicities. There are no known antidotes. The investigator should use clinical judgement in treating the symptoms of a suspected overdose.

9.7 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

Please refer to the following website for details on clinical trials safety reporting: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

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

Following an adverse reaction (AR) the participants will be followed-up for an appropriate length of time as dictated by the nature of AR and their clinical needs. ARs will continue to be recorded and reported for up to 4 weeks after the last dose of IMP has been administered. Any SUSAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred until resolved.

9.9 Development safety update reports

Within 60 days following the anniversary of the authorisation date for the trial, a Development Safety Update Reports (DSURs) will be sent by the Chief Investigator to the MHRA and the Main Research Ethics Committee. A copy of the report will also be sent to GSK (as the trial funder/drug supplier), the University of Leicester (as the trial Sponsor), and all host organisations. The LCTU will prepare the DSUR report on behalf of the CI and submit to the Sponsor who is responsible for reporting to the Competent Authority (MHRA) within the specified time frame.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

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.

10.2 Planned recruitment rate

Recruitment will be over a 3-year period. Admission rates are increasing year-on-year therefore we would expect a minimum 1,953 patients admitted with COPD over this time. Eosinophil count was collected as part of the National COPD audit, where 24% of patients had an eosinophil count of ≥ 0.3x109. Therefore, it is anticipated that at least 469 patients will be hospitalised with an eosinophilic exacerbation of COPD. Based on recruitment of 50% of these patients, then a recruitment target of 13 per month would be expected.

10.3 Statistical analysis plan

A separate, version controlled Statistical Analysis Plan (SAP) will contain full details of all statistical analyses and an initial version prepared prior to the first DSMC. Modifications made to the SAP during the conduct of the trial will be detailed in a summary of changes table with the reason(s) for their change in subsequent statistical analysis plans versions.

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

A total of 238 participants will be randomised in a 1:1 ratio to receive mepolizumab or a matching placebo. For safety and tolerability, AEs, SAEs, vital signs, physical examinations, ECGs and clinical laboratory assessment at specific time points will be evaluated. All safety data will be summarised descriptively. Number and percentage of AEs will be presented for each treatment by preferred AE term and system organ class of the current Medical Dictionary for Regulatory Authorities (MedDRA) dictionary.

10.3.1 Summary of baseline data and flow of patients

A diagram of participant flow through the trial is presented in Appendix 2.

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

The baseline variables that will be summarised include the following:

- Age
- Gender
- Ethnicity
- Medical history
- Physical exam
- Vital signs
- Extended MRC dyspnoea score (eMRC)
- Electrocardiogram (ECG)
- Exploratory blood samples (Trop I, BNP, FBC, serum & plasma)
- Spirometry
- WHO Clinical Progression Score

10.3.2 Primary outcome analysis

The main approach to primary analyses will be intention-to-treat (ITT), where the ITT population consist of all randomised participants. 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 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 Schoenfield residuals.

10.3.3 Secondary outcome analysis

All secondary end-points will be analysed using the ITT population, with the exception of adverse events, for which we will analyse the safety population, consisting of all participants who received at least one dose of trial medication. The count outcomes, number of hospital readmissions and number of moderate exacerbations over 48 weeks, will be analysed using the per protocol (PP) population where patients will be included in the analysis if they have a received a minimum duration of trial treatment of 24 weeks.

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 binary secondary outcomes will be compared between treatment groups using logistic regression.

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.

10.3.4 Exploratory outcome analysis

All exploratory outcomes will be analysed using appropriate statistical tests according to the nature of the variables. No formal hypotheses testing will be performed.

10.4 Subgroup analyses

Subgroup analyses of the primary outcome will be carried out on the stratification factors: 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.

10.5 Adjusted analysis

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

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

There will be no interim analysis with formal criteria for the premature termination of the trial. The DSMC will receive reports on the safety outcomes and trial conduct summaries every 3-6 months (as defined in the charter), with their main focus being to ensure the safety of the trial. DSMC reports will include AEs, SAEs, demographics and follow-up assessment completeness. The open session of the DSMC will only report summary data overall, and will not be split by treatment arm. Adverse event summaries and line listings split by treatment arm will be restricted to the closed part of the DSMC report.

There will not be any formal test or criteria for early stopping of the trial. The DSMC will advise on stopping the trial only if the acquired data provides proof that continuation would be considered futile due to lack of adequate or for emerging safety concerns.

10.7 Participant population

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

Some of the secondary outcomes i.e. number of hospital readmissions and number of moderate exacerbations over 48 weeks, will be analysed on the per-protocol population where patients will be included in the analysis if they have a received a minimum duration of trial treatment of 24 weeks.

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

For participants without a primary outcome event during the final analysis will be censored at the date of last assessment or last seen. Therefore, there will not be any imputation for the analyses of time to event outcomes.

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.

10.9 Other statistical considerations.

Statistical data validation will take place prior throughout the trial and prior to database lock. The End of Trial Report (ETR) will document the results of all analyses as described in the SAP alongside the date of database lock. Any analyses that are carried out in addition to those specified in the SAP will be described as unplanned in the ETR. Analysis may be performed using any combination of SAS, Stata and R and details of software packages used reported in the ETR

11 DATA MANAGEMENT

LCTU will be responsible for Data Management for the trial and will undertake data validation, database queries/reviews in line with their SOPs.

11.1 Data collection tools and source document identification

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

- Medical Records
- Paper CRFs
- Laboratory Reports
- Printouts from equipment (i.e. spirometry)
- Participant reported outcome questionnaires

Data collection tools will comprise of:

- Macro Database (transcribed from CRFs) and direct source data entry
- Participant reported outcome questionnaires
- Excel spreadsheet (spirometry data collection only)

The research team will seek consent from participants to re-contact them about taking part in future ethically approved research, some of which may be based on their results, phenotype, genotype, and response to treatment following the completion of the current trial. The team will seek permission to use participants' postcodes for future studies that will link the outcomes with environmental pollution. This is outlined in the PIS and consent form and participants will be able to opt out without affecting their involvement in the trial.

The team will also request the ability to extract primary and secondary care patient data in order to understand the outcomes and mechanisms of the intervention. These data will only be viewed by the trial team. This data linkage is to corroborate previous exacerbation history in order to explore the severity of the event (e.g. respiratory failure) prior to, during, and for up to five years after the end of the trial. Primary care records also contain serial spirometry, which in the very rare event of pregnancy allows investigation of obstetric care.

11.2 Data handling and record keeping

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

During the trial all CRFs will be stored in a secure area accessible to trial site and sponsor staff. Each enrolled participant will be allocated a unique trial ID so that the CRFs and electronic database remains pseudonymised.

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

11.3 Documentation storage, access and security

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

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

The trial team will keep participant contact information for 10 years after the study has finished where participants have consented to being contacted about future research. Consent forms and details of record linkage (i.e., trial ID numbers/pseudonyms) will be archived for 25 years as part of the research data so that in the event of the data being challenged, this will allow for verification of the quality of the data.

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

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

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

Pre-specified anonymised data and samples may be shared between the Sponsor and Funder after the trial is completed and the statistical analysis plan has been executed.

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

11.4 Data base management and archiving

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

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

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

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

12 MONITORING, AUDIT & INSPECTION

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

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

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

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

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

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

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

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

13.2 Peer review

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

13.3 Public and Patient Involvement (PPI)

The trial will be included amongst the studies discussed with the PPI group within the Respiratory BRC. Patient representatives will also be invited to sit on the Trial Steering Committee (TSC).

13.4 Regulatory Compliance

The trial will not commence until Clinical Trial Authorisation (CTA) is obtained from MHRA and REC, and Sponsor Green Light has been issued. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research (2017) and the Medicines for Human Use (Clinical Trials) Regulations, 2004. The Sponsor responsible for checking research governance arrangements will be the University of Leicester.

13.5 Protocol compliance

The trial team will monitor and review protocol compliance, deviations from the protocol will be captured both within the source data and the LCTU CDMS. Mepolizumab/placebo accountability will be monitored throughout the trial period. Where deviations frequently reoccur, this may meet the criteria for a Serious Breach of GCP and will be reported in line with Section 13.7. The trial team will not be required to report protocol deviations in instances where a participant is unable to produce a sample. Protocol deviations are not required for trial assessments omitted during a pandemic.

13.6. Possible side effects of the trial medication and placebo

Known drug reactions are detailed in section 8.9.

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

Any serious breach (a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the participants of the trial; or the scientific value of the trial) will be reported to Sponsor immediately and within 24 hours of discovery.

13.8 Data protection and patient confidentiality

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

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

- The creation of a unique trial ID number, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters;
- Secure maintenance of the data, in both electronic and paper forms and the linking code in separate locations;

- Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis;
- Paper based pseudonymised trial records will be stored in locked filing cabinets within a locked office. Electronic records will be stored on secure University of Leicester Information Management & Technology (IM&T) server systems;
- The database will be password protected and only researchers collecting data will have access. All data collected during the trial will be stored pseudonymously;
- Participants' contact details will be held separate to the trial visit data and used to arrange data collection visits by the research team or direct care team.

Any data transmitted will be done securely in approved University of Leicester methods (i.e. encrypted file transfer, internal email system) in accordance with LCTU SOPs.

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

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

13.10 Indemnity

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

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

13.11 Amendments

Amendments will be submitted by or on behalf of the CI after approval by the Sponsor and will be implemented following all required ethical, competent authority and Sponsor approvals.

13.12 Post-trial care

After trial completion participants will be discharged back to the care of their GP. They will not be followed up by the trial team, apart from in the case of an adverse reaction to IMP or an unresolved SAE.

Incidental findings from routine assessments (e.g. abnormally elevated LFTs) will be referred to the participant's GP or suitable clinician for follow up. Incidental findings from non-routine/exploratory assessments, particularly those analysed after the completion of the trial, will not be referred for investigation.

13.13 Access to the final trial dataset

CI and his appointed deputies will have access to the analysed trial dataset following execution of the SAP and completion of the ETR.

14 DISSEMINATION POLICY

14.1 Dissemination policy

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

At the end of the trial participants will be invited, where possible, to attend a dissemination event to inform them of the results of the trial and to thank them for their participation.

14.2 Authorship eligibility guidelines and any intended use of professional writers

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

15 REFERENCES

Global Initiative For Chronic Obstructive Lung Disease. 2018. 'GOLD COPD'. https://goldcopd.org/.

Papi, Alberto, Christopher Brightling, Søren E. Pedersen, and Helen K. Reddel. 2018. 'Asthma', *The Lancet*, 391: 783-800.

Pavord, Ian D., Pascal Chanez, Gerard J. Criner, Huib A.M. Kerstjens, Stephanie Korn, Njira Lugogo, Jean-Benoit Martinot, Hironori Sagara, Frank C. Albers, Eric S. Bradford, Stephanie S. Harris, Bhabita Mayer, David B. Rubin, Steven W. Yancey, and Frank C. Sciurba. 2017. 'Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease', *New England Journal of Medicine*, 377: 1613-29.

Physicians, Royal College of. 2018. 'National Asthma and COPD Audit Programme '. www.RCPLondon.ac.uk.

Yousef, Ibrahim, Greening, Brightling in press. 'T2-directed Biologics in COPD ', *Journal of Allergy and Clinical Immunology: In Practice*.

16 APPENDICES

Appendix 1: Schedule of Procedures

Appendix 2: Participant Trial Flow Chart

Appendix 3: Amendment History

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16.1 Appendix 1 – Schedule of procedures

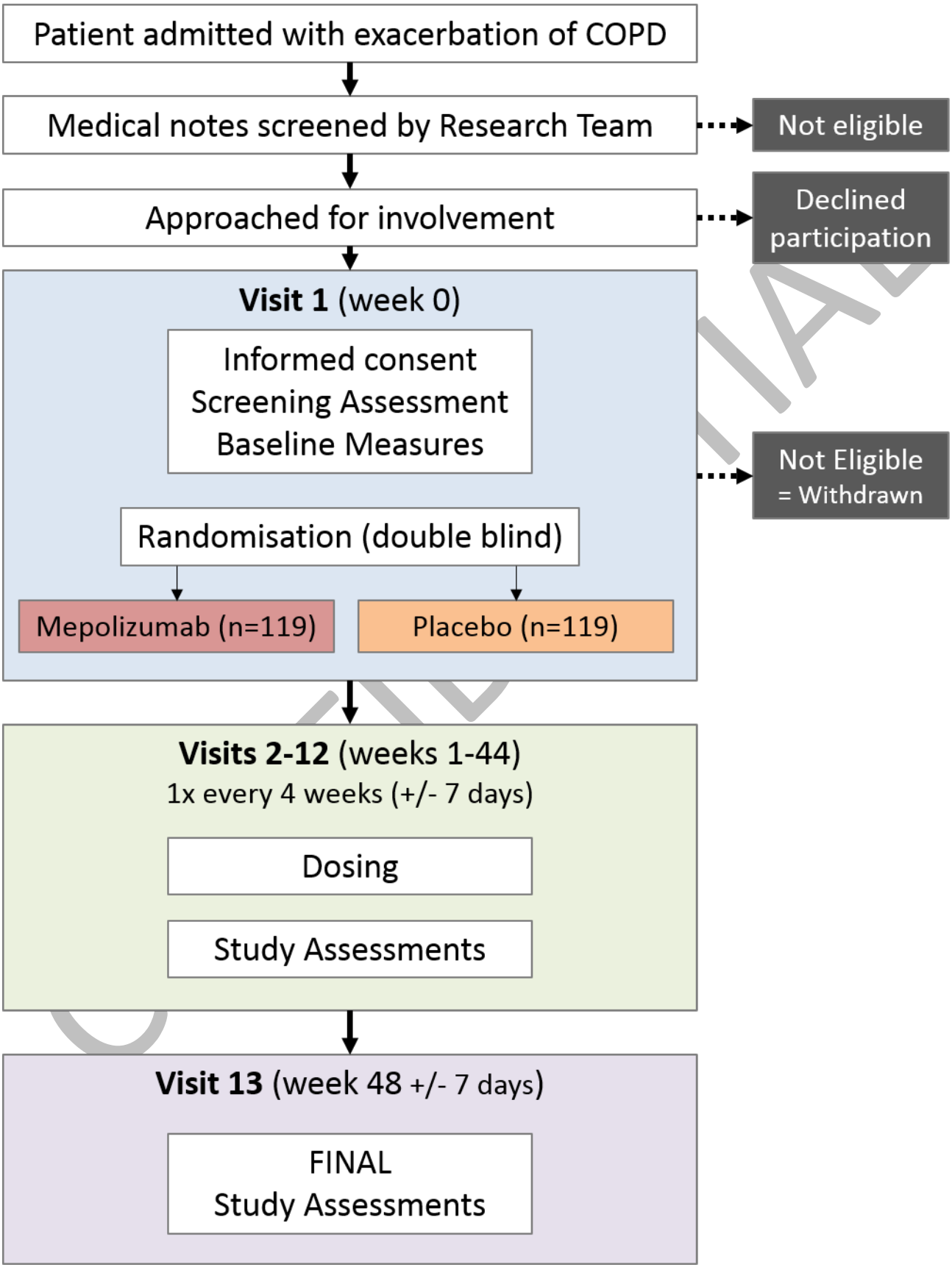
Trial assessment	Randomised treatment (visit window +/- 7 days)												
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13/Final follow up
	Wk0	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48
Consent	x												
Review Inclusion & Exclusion	x												
Randomisation	x												
Dosing	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
Trial assessment	**Randomised treatment (visit window +/- 7 days)**												
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V 10**	**V 11**	**V 12**	**V13/Final follow up**
	Wk0	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	**Wk28**	**Wk32**	**Wk36**	**Wk40**	**Wk44**	**Wk48**
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.

16.2 Appendix 2 – Participant Trial Flow Chart



16.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date	Author(s) of changes	Details of changes made
1	2.0	15th October 2019	Eleanor Taylor	Changes made in response to MHRA Non-Acceptance. • Amendment to wording of Emergency Unblinding Section 7.5 to clarify that the site Investigator has the ability to unblind a participant in an emergency
2	3.0	17th October 2019	Eleanor Taylor	• Inclusion of REC number & ClinicalTrials.gov ID • Removal of safety blood samples from visits 5&6, 8&9, 11&12 from table in Appendix 1 (included in error) • Removed section 3.4.4 'Follow up Hospital Episodes' in exploratory outcomes as this was included in error • Section 7.10 End of Trial – Changed 'Hospital Episodes Statistics' to 'hospital records' in • Section 7.7.4 Visit 13 – Removed urine pregnancy test as not necessary as no dosing on this visit (included in error) • Correction to typographical errors throughout document • Section 11.3 – Clarification of the sponsor keeping identifiable data for 25 years after the study has finished and the site keeping contact details for future research for up to 10 years
3	4.0	6th January 2020	Eleanor Taylor	• Section viii Key Words – correction of Phase III to Phase IIb. • Section 7.7.4 Visit 13 – Reinstated urine pregnancy test that was removed in version 3.0. This is required at end of IMP exposure. • Section 8.11 – Addition to final sentence of 3rd paragraph to clarify requirement for urine pregnancy test at Visit 13. • Appendix 1 – add urine pregnancy test to Visit 13 in schedule procedures. • Appendix 1 – correction to safety & tolerability measures. AE/SAEs were removed in error in previous version with the removal of safety blood samples from

				visits 5&6, 8&9, 11&12. These have now been reinstated.
4	5.0	6th March 2020	Eleanor Taylor	• Section 7.2 Informed Consent – Amendment made to first sentence of second paragraph to include participants that may be admitted and discharged within one week. Wording changed from 'Due to the nature of the study (acute illness resulting in hospitalisation), the participant can be consented at any point within their inpatient stay, or within one week of their index hospital admission' to 'Due to the nature of the study (acute illness resulting in hospitalisation), the participant can be consented at any point within their inpatient stay, or within one week of discharge'. • Section 7.2.1 – Title amended from 'Additional consent for biological specimens' to 'Additional consent for biological specimens and future research'. 'Anonymised' changed to 'pseudonymised'. Additional paragraph included to describe the linking of outcomes of this trial with environmental exposure listed in the optional section of the Informed Consent Form. The PIS has also been amended to reflect this as it was removed in error during the response to the Provisional Opinion. • Appendix 1 Schedule of procedures – reinstatement of safety blood samples from visits 5&6, 8&9, 11&12 that were removed in error in Protocol version 3.0 (17/10/2019) as part of the response to Provisional Opinion. These have been reinstated to correct the inconsistency with the body text (Section 7.7.3).
5	5.1	27th April 2020	Nafisa Boota	Changes made in response to point raised by HRA as part of Substantial Amendment 02 • Long trial title: initiated 'during' hospitalisation changed to initiated 'following' hospitalisation on pages 1, 3 and 10. • Section 3.1 Primary objective: initiated 'during' hospitalisation changed to initiated 'following' hospitalisation

				• Section 4.0 Trial Design: started 'during' their index admission to hospital changed to started 'following' their index admission to hospital
6	6.0	21st June 2021	Nafisa Boota	• Section 9.2 - SAEs will be reported following first administration of IMP/placebo rather than following consent. Section 9.1 – clarification provided on events that are clinical outcomes. Section 9.3 – the causality and relatedness assessment may be performed by the PI or a suitably trained delegate (does not require an unblinded doctor). Section 9.4 - clarification provided on notification of deaths. • Section 6.1 and trial summary table: > has been changed to ≥ for the following inclusion criterion: '4. Smoking pack years ≥ 10 years'. • Section 7.7.1 & Appendix 1 - the current (exacerbated state) eMRC score is to be collected at visit 1 in addition to their baseline eMRC score (stable state). • Sections 7.7, 7.8 & Appendix 1 – Clarification that trial assessments (e.g. Quality of Life/Symptoms Assessments) may be completed remotely by telephone consultation, where possible, and when necessary. • Section 7.10 – Pandemic guidance section added. • Sections 3.4.3 and 7.9 – corrections confirming DNA for analysis will only be taken from blood samples at week 0; RNA analysis will occur on blood samples taken at weeks 0, 4, 8, 12, 24, 36, 48. • Section 7.9 - correction to confirm blood tests for Trop I and BNP blood are not stored for the purposes of the study and are either used or destroyed during the testing process. • Section 13.5 - protocol deviations are not required for instances where a participant is unable to produce a sample or for assessments omitted due to a pandemic. • Section 7.7.4 - participants that have discontinued treatment early (prior to visit 12) will be invited back to hospital for visit 13 assessments.

7	7.0	26/10/2022	Hannah Gilbert	• Removal of COVID-19 omitted procedures:
				  ○ Faecal sample
				  ○ Post-BD (FEV1/FVC) Spirometry
				  ○ Oscillometry
				  ○ Breath volatile organic compounds
				  ○ **Induced** sputum samples
				  ○ Throat swab (viral PCR)
				  ○ Nasal epithelial sampling
				• Clarification that only spontaneous sputum samples are collected as part of standard care
				• Update to study timelines (recruitment, total study duration) in line with funding extension
				• Update to wording around indemnity (section 13.10) per Sponsor's request
				• Update to statistician information

8	8.0	06/02/2023	Hannah Gilbert	• Truncated follow-up for participant recruitment from April 2023 added to protocol and all applicable sections (schedule of events, etc.) amended to reflect new follow-up schedule • Visit 13 also named Final Follow-up for those in the truncated follow-up phase of the trial; patients recruited from April 2023 to September 2023 will be consented to a truncated follow-up model, whereby last patient last visit will remain the same. This will result in participants consented in April to have up to the 44-week follow-up, those in May will have up to the 40-week follow-up, and so on. Patients will be dosed for a minimum of 24 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 4 weeks ± 7 days of final dosing visit.
9	8.1	11/07/2023	Hannah Gilbert	• Truncated follow-up has been moved to start from July 2023 instead of the original April 2023, therefore all dates in the protocol and truncated f/u summary and main PIS have been amended to reflect this. Truncated follow-up will be

				participants consented from July 2023 to December 2023. • Correction to dosing and follow-up timelines – as participants are dosed at the baseline visit, dosing will occur for a minimum of 20 weeks (6 doses, the first at baseline) and followed-up for a minimum of 24 weeks (final follow-up 4 weeks +/- 7 days after last dosing visit). Amount of time for truncated follow-up model remains the same as approved in protocol v8.0, number of weeks is just a correction to accurately reflect the truncation.
10	9.0	12/09/2023	Hannah Gilbert	• Addition of new pre-filled syringe IMP and matched placebo to study IMP and dosing for participants dosed from 01 March 2024 onwards.
11	9.1	10/05/2024	Ghazala Waheed, Cassey Brookes, Hannah Gilbert, Hamish McAuley	• Updated outcome wording to align with trial SAP – outcomes are the same, however the wording around index hospital admission has changed to 'Time to discharge from randomisation'. Accelerometry data moved to exploratory outcome measure. • Updated analysis sections throughout to include the use of historic spirometry data collected as part of routine clinical care and a WHO Clinical Progression Scale for baseline characteristics. • Addition of statement in Pandemic section 7.10 to include details of historical or contemporaneous spirometry data collection for descriptive characterisation.