Sheffield Teaching Hospitals NHS
NHS Foundation Trust

STUDY TITLE

A Pilot Study of the Use of 129Xe and 1H MRI to measure the Modulation of Eosinophil-Related inflammation by Mepolizumab in COPD

Lay Title: A study using lung imaging to see if an asthma drug works to reduce inflammation in COPD.

Study acronym: SUMMER

Clinical study protocol

RESEARCH REFERENCE NUMBERS

Sponsor reference: STH21067

ClinicalTrials.gov: NCT05138250

Protocol version: 5.0 19 April 2024

EudraCT 2021-002901-84

MHRA CTA 21304/0276/001-0001

IRAS no: 1003843

SPONSOR DETAILS

Sponsor: Sheffield Teaching Hospitals NHS Foundation Trust

This protocol has regard for the NHS Health Research Authority guidance and order of content

PROTOCOL SIGNATURE PAGE

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

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

I also confirm that I will make the findings of the trial publically 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.

For and on behalf of the Trial Sponsor:

Signature:

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Date:
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Name (please print):

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Position:
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Chief Investigator:

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

Name: (please print):

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I. KEY TRIAL CONTACTS

Chief Investigator	Dr Rod Lawson Brearley Outpatients Department Northern General Hospital Barnsley Road Drive, Sheffield S5 7AU
University MRI department	Prof Jim Wild
Trial Coordinator	Dr Stephen Kirby-Smith
Trial Administrator	Jenny Rodgers/Leanne Armstrong
Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust Clinical Research and Innovation Office D Floor, Royal Hallamshire Hospital
Funder	GSK
Clinical Research Facility	Sheffield Clinical Research Facility

	Centre for Biomedical Research Northern General Hospital Barnsley Road Drive, Sheffield S5 7AU
Pharmacy Contact	Kim Ryalls Pharmacy Department Northern General Hospital Herries Road, Sheffield S5 7AU

CONTENTS

II. List of abbreviations

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

ADC	Apparent diffusion coefficient
AE	Adverse Event
AECOPD	Acute Exacerbation of COPD
AR	Adverse Reaction
AS	Area of Reactance
CA	Competent Authority
CAT	COPD Assessment Test
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disorder
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CV	Coefficient of variation of signal intensity
DCE	Dynamic Contrast Enhanced
DLCO	Carbon Monoxide Diffusing Capacity

DSUR	Development Safety Update Report
EudraCT	European Clinical Trials Database
EXACT-PRO	EXAcerbation of Chronic Pulmonary Disease Tool – Patient Reported Outcome
FEF 25-75	Forced Expiratory Floe at 25-75%
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in one second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HRQoL	Health-related quality of life
HP	Hyperpolarised
ICF	Informed Consent Form
ICS	Inhaled corticosteroid
IMP	Investigational Medicinal Product
ISF	Investigator Site File (This forms part of the TMF)
K_{trans}	volume transfer coefficient of contrast agent between the vascular plasma space and the extravascular extracellular

	space
LABA	Long acting beta$_2$ agonist
LAMA	Long acting muscarinic antagonist
Lm_D	diffusive length scale
M_0	proton spin density
MA	Marketing Authorisation
MDI	Metered Dose Inhaler
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MTT	mean transit time
NHS R&D	National Health Service Research & Development
NICE	The National Institute for Health and Care Excellence
NIMP	Non-Investigational Medicinal Product
NSF	Nephrogenic Systemic Fibrosis
PBF	pulmonary blood flow
PBV	pulmonary blood volume
PI	Principal Investigator

PIC	Participant Identification Centre
PIS	Participant Information Sheet
PREFUL	Phase-Resolved Functional Lung
PRO	Patient Reported Outcome
R5-20	Resistance at 5 Hz minus 20 Hz
RAST	Radioallergosorbent Test
RBC/gas	Red blood cell to gas ratio
RBC/TP	Red blood cell to tissue and plasma ratio
REC	Research Ethics Committee
RV	Residual Volume
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SpO2	Oxygen Saturation
STH	Sheffield Teaching Hospitals
SUSAR	Suspected Unexpected Serious Adverse Reaction

T_1	Longitudinal relaxation time
TLC	Total Lung Capacity
TMF	Trial Master File
TMG	Trial Management Group
TP/gas	Tissue and plasma/gas
V_e	Extravascular extracellular space per unit volume of tissue
VQ	Ventilation Perfusion
VQ-intersect	Intersect between ventilation and perfusion
X5	Respiratory reactance at 5Hz
XeMRI	Xenon MRI
%PV	Percentage Perfused Lung Volume
%VV	Percentage Ventilated Lung Volume

III. Trial summary

Trial Title	A pilot study of the use of 129Xe and 1H MRI to measure the modulation of eosinophilic inflammation by mepolizumab in COPD
Study Acronym	SUMMER
Local Reference number	STH21067
Clinical Phase	III
Trial Design	Open label, multi-dose observational pilot study
Trial Participants	Patients with eosinophilic COPD
Planned Sample Size	32 participants
Treatment duration	3-12 months, patients recruited after April 2024 will complete the study at assessment visit 2
Follow up duration	3-12 months (concurrent with treatment duration)
Planned Trial Period	April 2022 – June 2025.

	Objectives	Outcome Measures
Co-Primary end points	To measure the effect of anti-eosinophil therapy on lung ventilation in COPD over 12 weeks, using XeMRI	The within subject change in percentage ventilated volume of lung (%VV) assessed by XeMRI from baseline to 12 weeks of treatment with mepolizumab.
	To measure the effect of anti-eosinophil therapy on alveolar thickness (as an index of pulmonary inflammation) in COPD over 12 weeks using XeMRI	The within participant change in TP/gas (a measure of alveolar thickness, as an index of pulmonary inflammation) assessed by XeMRI from baseline to 12 weeks of treatment with mepolizumab.
Secondary end points	To compare MRI derived measures of lung ventilation, perfusion and inflammation at 12 weeks with variation in a key clinical outcome (total exacerbation frequency) over 52 weeks	Comparison of change in MRI metrics from baseline to 12 weeks in groups with a) low or b) high total 52 week exacerbation (groups defined by median split of total exacerbations over 52 weeks assessed by EXACT-Pro)
	To measure the effect of anti-eosinophil therapy in COPD over 12 weeks, using other XeMRI	Change in MRI indices of ventilation, perfusion and inflammation (see text) - CV,

	and MRI indices of lung ventilation, perfusion and inflammation	RBC/TP, RBC/gas, ADC, LmD, Ve, Ktrans, PBV, PBF, MTT, VQ-intersect, T1, M0 from baseline to 12 weeks
Tertiary endpoints	To measure the effect of anti-eosinophil therapy in COPD over 52 weeks, using XeMRI indices of lung ventilation, perfusion and inflammation, and to determine if effects seen after 12 weeks persist for 52 weeks	Change in MRI indices of ventilation, perfusion and inflammation (see text) - %VV, CV, RBC/TP, TP/gas, RBC/gas, ADC, LmD, Ve, Ktrans, PBV, PBF, MTT, VQ-intersect, T1, M0 at 52 weeks compared to baseline and 12 weeks
	To compare MRI derived measures of lung ventilation, perfusion and inflammation with changes in physiological measurements	Correlation of changes in physiological measures (see text) and MRI measures of lung function and inflammation (see text) at 12 weeks
	To determine if changes in indices of lung ventilation, perfusion and inflammation derived from physiological and MRI parameters are related to initial eosinophilic inflammation	Change in physiological and MRI determined measures of ventilation, perfusion and inflammation at 12 weeks from baseline will be correlated with; a) Baseline peripheral blood eosinophil count

		b) Baseline FeNO c) Change of peripheral blood eosinophil count from baseline to 12 weeks d) Change in FeNO from baseline to 12 weeks. Similar correlation will be carried out for data obtained at 52 weeks rather than 12 weeks.
Exploratory end points	To compare MRI derived measures of lung ventilation, perfusion and inflammation at 12 weeks with a key clinical outcome (moderate to severe exacerbation frequency) over 52 weeks	Comparison of change in MRI metrics from baseline to 12 weeks in groups with a) low or b) high total 52 week exacerbation. Groups defined by median split of total moderate to severe exacerbations over 52 weeks, see section 3.8
	To assess the overall impact of mepolizumab treatment on HRQoL in COPD over time, and assess how this relates to impact on pulmonary function assessed by physiology and XeMRI	Comparison of change of CAT from baseline to 12 and 52 weeks within participants compare to changes in measures of lung function by physiology and MRI.

		Comparison of changes in physiological and MRI derived parameters at 12 weeks in groups with either high and low improvement of CAT at 52 weeks (determined by median split)
	To compare measures of lung function assessed by XeMRI and DCE perfusion MRI with PREFUL MRI measures.	PREFUL %VV and PREFUL %PV will be correlated with XeMRI and proton MRI determined measures of lung function at all time points
Investigational Medicinal Product(s)	Mepolizumab (Nucala™)	
Formulation, Dose, Route of Administration	100 mg, subcutaneous injection via pre-filled syringe, once every 4 weeks	

IV. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
GSK	£989,774.00

V. ROLE OF TRIAL SPONSOR AND FUNDER

The sponsor, Sheffield Teaching Hospitals NHS Foundation Trust, will contribute to study design and arrangements before approving the protocol and associated study documents. The sponsor will handle site initiation, monitoring and close-out. They will also provide pharmacy support to the study. The Sheffield Clinical Research Facility, jointly supported by Sheffield Teaching Hospitals and the University of Sheffield, will provide facilities and staff for study conduct. Sheffield Teaching Hospitals will continue to provide routine and urgent medical care for trial participants according to routine clinical indications.

The funder, GSK, reviewed and approved an application for this study, and will provide monetary resources to complete it.

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

The Trial Management Group will consist of Dr Rod Lawson (Chief investigator, respiratory physician), Prof. Jim Wild (co-investigator, Professor of MR Imaging), Dr Helen Marshall (co-investigator and Research Staff Scientist in MR Imaging), Dr Paul Hughes (MR scientist), Dr Guilhem Collier (MR Scientist), Dr Stephen Kirby-Smith (trial research fellow) , plus physiologists including Laurie Smith, secretarial staff and departmental research co-coordinator as required. Meetings will be quorate with at least 3 of the named individuals present. They will meet at least 2 monthly for the duration of the trial. They will be responsible for day to day trial planning, development and institution, and subsequent data analysis. Reports will be prepared as appropriate for regulatory purposes. They will carry out regular reviews of recruitment, any protocol deviations or adverse events, or practical problems resulting from study procedures and will take appropriate actions. A record of meetings will be maintained. They will be responsible for data analysis, and the dissemination of results by way of presentations and meetings and submission of academic papers.

As this is a single centre open label observational trial with multi-disciplinary representation in the trial management group, it is not proposed to have a separate data monitoring and ethics committee, or a separate scientific committee.

VII. PROTOCOL CONTRIBUTORS

The proposed project from an internationally leading team builds on previous collaborative work with GSK in the development (Hughes et al. 2018; Hughes et al. 2019; Hughes et al. 2015) (PhD Studentship STU100037614 and Post-Doctoral Fellowship BIDS3000032592) and clinical evaluation (Marshall et al. 2012; Stewart et al. 2015) of lung imaging biomarkers for the assessment of COPD.

Dr Rod Lawson-Clinical aspects and overview

Prof Jim Wild-Imaging scientific aspects

Dr Helen Marshall-Imaging scientific aspects and data analysis

Dr Laurie Smith – Research Physiologist, scientific aspects and analysis of lung function assessments

Dr Lisa Watson-Research logistics and regulatory requirements

Dr Erica Wallis-critically reviewed the protocol on behalf of the sponsor

Dr Stephen Kirby-Smith – Contribution to Clinical aspects

VIII. KEY WORDS:

COPD

Eosinophil

Mepolizumab

Inert gas MRI

Lung physiology

1. BACKGROUND

1.1 CLINICAL BACKGROUND

Traditionally, COPD and asthma have been regarded as lung diseases with different underlying inflammatory mechanisms; in terms of granulocytes, the former involving neutrophils, the latter involving eosinophils (Lawson 2018). However, it has become apparent that there is a distinct overlap in inflammatory mechanisms found in the two diseases, with eosinophilic inflammation playing an important role in COPD. This has led to modification of the GOLD worldwide guidelines for the treatment of COPD (Singh et al. 2019).

The mainstay of treatment of eosinophil inflammation is glucocorticoids. However, in severe disease their efficacy may be limited, and their use is associated with a range of severe side effects. IL-5 is a cytokine contributing to eosinophil differentiation, recruitment, maturation, activation and degranulation, and hence provides an appealing target for anti-inflammatory strategies in airway disease. Mepolizumab is a monoclonal antibody which neutralises circulating IL-5 (in contrast to benralizumab which blocks the IL-5 receptor) (Narendra and Hanania 2019).

Both mepolizumab and benralizumab are now licenced for use in the UK for patients with eosinophilic asthma, with specific guidance for eligible patients (NICE 2017, 2019). However, they are yet to be approved for use in COPD where there is some contradictory evidence.

Pavord (Pavord 2018) identifies particular problems with developing new treatments for COPD including:

1. Heterogeneity in patterns of airway inflammation
2. Airflow limitation may be due to ‘burnt out’ disease no longer amenable to disease modification
3. Heterogeneity in exacerbations

Thus there is a need for sensitive methods to study the effects of new therapies on inflammation and its resulting lung pathophysiology in vivo in COPD. In particular, most drugs are used to target the clinically relevant endpoint of exacerbations, but study of these must be long term, as they are relatively rare events. In addition, they are downstream endpoints that are the resultant effect of not only intrinsic disease but also external factors such as infection or air pollution. The heterogeneity of this interaction makes interpretation of mechanistic actions and outcomes challenging. There is a need for more precise non-invasive measurement of mechanistic effects that can be used as surrogate markers in clinical development and treatment monitoring.

1.2 IMAGING BACKGROUND

Our team at the University of Sheffield and Sheffield Teaching Hospitals NHS Trust have developed novel functional lung imaging techniques to assess changes in lung ventilation, perfusion, gas exchange and endothelial permeability using hyperpolarised xenon and contrast enhanced proton MRI. In collaboration with clinical colleagues the department of academic radiology have evaluated these techniques' sensitivity to regional changes in lung function in asthma and COPD, and clinicians are using these techniques to support assessment of patients in routine clinical practice. Our evolving clinical experience indicates that pulmonary MRI provides additional insights into the extent and severity of airways disease that can be useful in guiding of treatment. We believe that these techniques may be useful in assessing in vivo inflammation in addition to ventilation, perfusion and gas exchange (see below) and that this provides the prospect of non-invasive mechanistic studies of drug action in man, offering the prospect of being useful in drug development. Furthermore, as many novel treatments are expensive and require correct targeting for maximal efficacy and cost effectiveness, there is the prospect that such imaging modalities could be useful in patient selection for specific treatments. In such a personalised approach the costs of scanning to measure within patient response would be mitigated by the decrease in drug use in circumstances where its efficacy is poor.

The aim of the proposed pilot study will be to evaluate a host of functional MR imaging techniques to assess the effects of mepolizumab on regional lung pathophysiology by comparing indices measured before, and 12 weeks and 52 weeks after a 4 weekly doses of mepolizumab.

1.3 TREATMENT OPTIONS

As noted, though both mepolizumab and benralizumab are now licensed for use in participants with eosinophilic asthma in the UK and are approved by NICE (NICE 2017, 2019) there is some contradictory evidence for their use in COPD and they are yet to be licensed for this indication. Pavord (Pavord 2018) reviews the METREX and METEO studies of mepolizumab as add on treatment in COPD compared to placebo. Over a year there was a 15 to 20% decrease in exacerbation rate, of borderline significance because of the relatively low event rate and other factors noted above, as well as correction for multiple comparisons. Notably there was a greater effect in a subpopulation with higher baseline eosinophil counts, as expected.

Criner et al (Criner et al. 2019) describe the GALATHEA and TERRANOVA trials of benralizumab as add on therapy in COPD versus placebo. Despite participants having slightly higher baseline eosinophil counts than METREX and METEO and being larger studies, no significant effect on the rate of exacerbation was found. Recent post hoc analyses of these studies has suggested that there is a greater chance of response in those with baseline eosinophils > 0.5, poorer lung function, greater reversibility and three or more exacerbations per year (Criner et al. 2020).

As noted, mepolizumab and benralizumab are each anti-IL5 antibodies and a similar effect might be predicted. The former acts against circulating IL-5, whereas the latter blocks its receptor. The latter's blocking action is rapid and complete and it is surprising that similar efficacy on COPD exacerbations was

not demonstrated. This may be a genuine difference, or may represent the methodological differences described above, and there is a need for further studies to clarify this.

Mepolizumab is currently licensed in the UK as an 'add on treatment for severe refractory asthma' adults, adolescents and children aged 6 years and older. It is not currently licensed for COPD of any severity. In clinical practice mepolizumab has been found to be well tolerated. A 'real world' study showed that 14% of patients had a treatment-related adverse event, <1% had a serious adverse event and no deaths were reported in 368 participants treated over 2 years in a global observational survey (Harrison et al. 2020).

The SmPC applicable in August 2021 draws attention to the need to exclude helminthic disease before treatment. This would be rare in UK practice and in this study would be likely to be detected by an unusually high eosinophil count, as well as clinical history at screening.

In asthma, significant numbers are treated with oral steroids and their reduction following clinical benefit due to mepolizumab may uncover secondary adrenal suppression. Participants on long term oral steroids will not be recruited to the current study. Allergic reactions of varying degrees of severity have been observed, requiring standard treatments. In this study participants will have an hour of direct observation after medication administration as anaphylaxis (though rare) has been reported. Beyond these considerations, special precautions ae not advised; in particular there is no need to adjust dose for age or organ failure, and no significant interaction with other drugs. There is limited human data on pregnancy and breastfeeding but low levels are excreted in milk and detrimental effects on pregnancy have not been found in animal studies. Nevertheless this study will advise participants to avoid pregnancy, and should pregnancy occur they will be withdrawn from the study.

Common side effects in registration studies include respiratory and other infections, nasal congestion, abdominal pain, eczema, back pain, but these are usually not severe.

Participants will be warned that local injection site reactions are common, but self-limiting.

Doses up to 15 times the therapeutic dose have not been found to be toxic.

There is no specific requirement for ongoing safety monitoring when using mepolizumab in patients with asthma. However, participants in this study are expected to be on average be older and have more co-morbidity than those in registration studies for asthma or in clinical practice, so haematological and biochemical monitoring will be carried out during the study, together with urinalysis.

Participants will also receive Gadovist injections on assessment visits. This may be associated with allergic reactions. It may be associated with the rare syndrome of nephrogenic systemic fibrosis in those with poor renal function. It will be given with safety checks in line with clinical SOPs at Sheffield Teaching Hospital NHS Foundation Trust and manufacturer's guidelines.

1.4 THE USE OF MR IMAGING IN LUNG DISEASE ASSESSMENT

Hyperpolarised (HP) gas MRI, in which patients inhale either helium-3 or xenon-129 that has been hyperpolarised before administration, can provide detailed three-dimensional images of the ventilated lung airspaces. As MRI can be safely repeated, longitudinal studies to examine time courses of change are also feasible.

129Xe ventilation imaging is extremely sensitive to obstructive lung disease, with increased ventilation defects and heterogeneity in patients with chronic obstructive lung disease (COPD) (Kirby et al. 2012) and patients with asthma (Svenningsen et al. 2013; Ebner et al. 2017) when compared to healthy volunteers. Regions of decreased or no ventilation, described as ventilation defects, are related to areas of airway obstruction and air trapping (Fain et al. 2008).

Ventilation defects are associated with eosinophil count (Altes et al. 2016; Mummy et al. 2018; Svenningsen et al. 2018), neutrophil count (Fain et al. 2008), fractional exhaled nitric oxide (FeNO) (Svenningsen et al. 2014; Ebner et al. 2017), and increased exacerbations requiring hospitalisation in patients with COPD (Kirby et al. 2014) and asthma (Mummy et al. 2018).

HP gas MRI has been used to assess ventilation response to bronchodilator in COPD (Kirby et al. 2011) and asthma (Altes et al. 2001; Svenningsen et al. 2013; Horn et al. 2017; Svenningsen et al. 2018), and the effect of leukotriene receptor inhibitor montelukast in mitigating exercise-induced bronchoconstriction (Kruger et al. 2014). Treatment response mapping (Horn et al. 2017), which visualises and quantifies regional differences in ventilation, can provide a more sensitive metric of ventilation response to therapy than conventional analyses (see image appendix).

A case report using dupilumab (an IL-4 blocker) confirms that changes in ventilation defects occurred in ventilation MR images in an asthmatic participant after treatment (Svenningsen et al. 2019), further confirming the promise of MR imaging for monitoring functional response to human monoclonal antibodies, though the more extensive measures enumerated here were not utilised. Contrast enhanced proton perfusion MRI, using an injected gadolinium contrast agent, allows assessment of first-pass pulmonary perfusion (Ohno et al. 2007) and is sensitive to reduced microvascular blood flow in patients with COPD (Hueper et al. 2015). Imaging over a longer period tracks the leakage of contrast agent from the capillaries to the extravascular parenchymal space to assess capillary wall permeability that may change with inflammation (Naish et al. 2009). Ventilation and perfusion MRI can be used alongside each other to

characterise regional gas exchange and the response of VQ matching to therapy (Marshall et al. 2014). Surrogate maps of ventilation and perfusion can also be obtained using free-breathing proton MRI, without the use of a contrast agent, to investigate VQ matching (Voskrebenzev et al. 2018).

Dissolved phase 129Xe MRI studies the small proportion of inhaled 129Xe that dissolves into the lung tissue and blood. Monitoring this process can provide information about gas exchange. The ratio of red blood cell to tissue signal measured in this way is decreased in COPD (Qing, Mugler, et al. 2014), and dissolved-phase 129Xe MR has also been shown to distinguish healthy smokers from age-matched controls (Ruppert et al. 2019).

Proton T_1 mapping is affected by changes in tissue water content. Lung T_1 values are lower in patients with COPD (Alamidi et al. 2016) and asthma (Renne et al. 2015) compared to healthy controls. Lung T_1 has been shown to increase after segmental allergen challenge in patients with asthma, and to correlate with percentage of eosinophils in bronchoalveolar lavage fluid in these participants (Renne et al. 2015).

1.5 STUDY DESIGN

We propose therefore to study the changes in the above MRI parameters compared to base line at 12 and 52 weeks after the first dose of mepolizumab, which will be given at a dose of 100mg s/c dose every 4 weeks for a year. Particpants recruited after April 2024 will only be studied at the 12 week, primary endpoint, timepoint, see section 7.12. Maximal peripheral blood eosinophil suppression is seen 2 to 4 week post dose (Tsukamoto et al. 2016). The first time point will thus represent a time point at which the peripheral blood eosinophil count will have been well suppressed for around 10 weeks, and it may be expected that eosinophil dependent inflammatory changes will already have been impacted, and may be detected by MRI. The later time point will allow measurement of long term maintenance of such changes with correlation with long term clinical outcomes.

The co-primary outcome will be average of the change from baseline in ventilated volume at 12 weeks, i.e. (VV% time 12 weeks minus VV% baseline)/n, the average of within participant change) and the average change from baseline in measured alveolar thickness as an index of inflammation, ie (TP/gas time 12 weeks minus TP/gas baseline)/n.

The main secondary outcomes will be comparison of changes in primary outcome measures at 12 weeks in participants stratified by low and high exacerbation rates. These groups will be determined by median split of participants depending on their total exacerbations over the 12 month study period. The hypothesis is that those with greatest response in terms of ventilated volume or TP/gas will also have greatest reduction in exacerbation frequency. The median split allows stratification by aggregated exacerbation number for maximum power with no prior assumption of a particular threshold. Early detection at 12 weeks of a change that proved to anticipate the clinical treatment response over a year could suggest great utility in drug development and clinical use.

Further secondary outcomes will be the within participant change from baseline to 12 weeks in a variety of measures of ventilation, perfusion and inflammation; CV, RBC/TP, RBC/gas, ADC, LmD, Ve, Ktrans, PBV, PBF, MTT, VQ-intersect, T1, M0. Changes in these outcomes at 12 weeks will also be compared in low and high exacerbation groups as defined above. It is possible that an anti-inflammatory signal relevant to reduction of exacerbation frequency could be found which is independent of effects on airflow obstruction or is compartmentalised. Hence, each parameter will be tested for a difference between median-split low and high exacerbation groups.

A number of tertiary endpoints will be addressed. MRI indices of lung ventilation, perfusion and inflammation will be measured at 52 weeks to assess whether changes from baseline to 12 weeks are maintained over 52 weeks.

Change in MRI parameters will be correlated with changes in physiological parameters at 12 weeks to provide mechanistic inference. Likewise, changes in MRI and physiological parameters will be correlated with baseline measure of eosinophilic inflammation, and baseline to 12 week changes in eosinophilic inflammation, as reflected by peripheral blood eosinophil count and FeNO.

Exploratory outcomes will include analysis of changes by median split of exacerbations in similar to fashion to that described above, but including only moderate to severe exacerbations. The study is unlikely to be adequately powered to address this clearly, but an exploratory analysis is included for comparison with many trials of COPD treatment that address this. Likewise, changes in health related quality of life from baseline to 12 and 52 weeks as reflected in CAT score will be correlated with changes in MRI and physiologically derived changes in lung function. Finally, XeMRI and DCE perfusion MRI measures will be correlated with those derived from PREFUL at all timepoints as an exploration of the techniques relative sensitivity to change.

Thus, in this pilot study we expect to be able to non-invasively demonstrate eosinophil dependent changes in indices of regional pulmonary pathophysiology using MRI. By comparing these with standard physiological outcomes and clinical data we aim to understand their relevance, and provide some mechanistic support. This has the potential to be utilised in drug development where early and accurate measures of change may hasten the process. This also has the potential to be used clinically for early identification of treatment responders for a personalised therapeutic approach.

2. RATIONALE

We hypothesise that by its anti-eosinophilic action mepolizumab will decrease airways inflammation in COPD patients with peripheral blood eosinophil counts of over 0.3cells·μL^{-1}, and that this can be detected non-invasively by XeMRI. We hypothesise that the group having a higher number of total exacerbations during a year of treatment will have less change in Xe MRI parameters after 12 weeks of that year, compared to a group having fewer exacerbations.

2.1 ASSESSMENT AND MANAGEMENT OF RISK

During this study mepolizumab will be used to treat COPD, a condition for which it is not currently licensed. (It is licensed for used in asthma in the UK, and is used widely according to NICE guidelines). Safety will be the first priority at all times.

The table below shows side effects in registry trials that were more common than with placebo.

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

Hypersensitivity reactions (e.g. anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA, per its labelling for licensed indications.

Although centres treating asthma clinically have introduced home administration of mepolizumab after initial dosing and appropriate patient education, as this study uses the medication off licence it will be administered in a clinical setting by experienced staff with full resuscitation facilities available to clinical NHS standards should the need arise.

Pulmonary function testing will use routine clinical methods that are very unlikely to produce side effects. Procedures will reflect those used in the NHS clinical laboratories at the research site.

MRI-related adverse events are highly unlikely. Jim Wild holds MHRA approval as a qualified person for the manufacture of xenon for MR imaging. Xenon may produce dizziness, light-headedness and nausea, lasting less than a minute, with no long-term sequelae and evidence suggests it is well tolerated in healthy participants and participants with lung disease (Driehuys et al. 2012). These published observations are in keeping with our local experience. Side effects of the contrast agent injection may include mild headache, nausea and localized cold sensation at the site of injection. Rarely low blood pressure and light-headedness occurs which can be treated immediately with a drip (intravenous fluid). Very rarely (less than one in one thousand), participants are allergic to the contrast agent. These effects are most commonly hives and itchy eyes, but more severe reactions have been reported, which result in shortness of breath. There have been several reports of patients developing nephrogenic systemic fibrosis (NSF), after intravascular MRI contrast agents containing gadolinium. NSF is a very rare but potentially serious and life-threatening condition. However, no cases of NSF have been reported in patients with normal renal function and Gadovist (gadobutrol) is categorised as a “low risk agent”, unless there is severe renal impairment. We will test all patients for renal dysfunction (eGFR less than 30ml/min) and will not expose any participants at risk of NSF to Gadovist. These patients will only complete the xenon and non-contrast proton MR imaging.

The department in which the MRI is carried out is utilised for a variety of clinical studies, with full access to emergency resuscitation facilities to an NHS clinical standard.

Participants will be asked to withhold bronchodilators for specified intervals before assessment visits to allow pre- and post- bronchodilator measures to be made. This approach common to many studies in COPD will effectively mean participants are asked to defer morning long acting bronchodilators until after the assessments, and not to take short acting ‘rescue’ treatments from the night before. During the assessments participants will be given a bronchodilator so the period without treatment will be brief and it is highly unlikely that this will be detrimental above and beyond a brief and temporary and modest period of increased breathlessness. However, participants who find this unacceptable at the time will be allowed to take their short acting ‘rescue’ treatment and if the participant is willing and the investigator agrees it is safe to do so they may proceed with the study assessment with the omission of pre-bronchodilator measurements.

Women of childbearing potential will be asked to ensure they avoid pregnancy during the study by using highly effective contraception. Pregnancy testing will occur at all visits for premenopausal females. This is primarily to avoid the risk of administration of intravenous contrast agents during pregnancy. There is no data on their safety during human pregnancy, though in high dose they may cause harmful effects in animals. MRI scans are not known to have adverse effects in pregnancy but we will avoid research imaging on principle as a non-essential procedure. Mepolizumab itself has not been shown to be harmful in animal pregnancies and in limited data appears safe in human pregnancy, so though participants advised to avoid pregnancy whilst on treatment and asked to use highly effective contraception throughout the course of the study. In the event of a positive pregnancy test (as a study safety procedure, or during clinical care during the time course of the research) the participant will be withdrawn from the study. No further assessment or treatment visits will occur.

Pharmacovigilance will take place as described in section 9.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 CO-PRIMARY OBJECTIVES

To measure the effect of anti-eosinophil therapy on lung ventilation in participants with eosinophilic COPD over 12 weeks, using XeMRI indices of lung function change.

To measure the effect of anti-eosinophil therapy on lung inflammation, using change in XeMRI index linked to alveolar interstitial thickness (and hence lung inflammation).

3.2 SECONDARY OBJECTIVES

To assess whether there is a relationship between primary outcome measures and the total number of exacerbations over 12 months of anti-eosinophil treatment.

To assess measure the effect of anti-eosinophil therapy on a variety of MRI derived measures of lung ventilation, perfusion and inflammation over 12 weeks, and assess whether there is a relationship between these and the total number of exacerbations over 12 months of anti-eosinophil treatment.

3.3 TERTIARY OBJECTIVES

To assess whether the effects of anti-eosinophil therapy at 12 weeks compare to baseline persist at 52 weeks, using MRI indices of ventilation, perfusion and lung inflammation.

To assess whether MRI changes in lung perfusion, ventilation and inflammation at 12 weeks correlate with changes in lung physiological measures, and indices of eosinophil inflammation.

To determine if changes in indices of lung ventilation, perfusion and inflammation derived from physiological and MRI parameters are related to initial eosinophilic inflammation.

3.4 EXPLORATORY OBJECTIVES

To assess measure the effect of anti-eosinophil therapy on a variety of MRI derived measures of lung ventilation, perfusion and inflammation over 12 weeks, and assess whether there is a relationship between these and the number of moderate and severe exacerbations over 12 months of anti-eosinophil treatment.

To assess the effect of anti-eosinophil therapy on quality of life over 12 and 52 weeks and correlate this with changes in MRI and physiologically derived measure of changes in lung function.

To compare the performance of PREFUL with XeMRI and DCE perfusion MRI derived measures lung ventilation and perfusion at baseline, and their sensitivity to change at 12 and 52 weeks.

3.5 PRIMARY ENDPOINT/OUTCOME

The primary outcomes will be the within participant change in:

- Lung ventilation from baseline to 12 weeks of treatment with mepolizumab (assessed as percentage ventilated volume of lung (%VV) measured by XeMRI).
- Lung inflammation from baseline to 12 weeks of treatment with mepolizumab (assessed as 129Xe IDEAL tissue-plasma to gas ratio (TP/gas)

3.6 SECONDARY ENDPOINTS/OUTCOMES

Participants will be divided into high and low exacerbation groups by median split of total number of exacerbations per participant (measured by EXACT-PRO). These symptom-based exacerbations will be defined as a sustained worsening of EXACT daily scores above baseline (≥ 9 points) for 3 consecutive days or 12 or more points for 2 consecutive days (Leidy et al, 2011). Each of the primary outcome measurements will then be compared for low and high exacerbation groups.

A number of further measures of lung ventilation, perfusion and inflammation will be analysed. For each, the average within participant change from baseline to 12 weeks will be measured. They will then be split into low and high exacerbation groups as above, and each outcome measure then compared for low and high exacerbation groups.

Short term change in MRI indices of ventilation, perfusion and inflammation at 12 weeks of treatment (compared to baseline), using each of the following measures:

Ventilation from XeMRI

- Coefficient of variation of signal intensity (CV), a measure of ventilation heterogeneity
- Treatment response mapping, to visualise and quantitate changes in ventilation (as (Horn et al. 2017))

Gas exchange and acinar structure from XeMRI

- Red blood cell to tissue and plasma (RBC/TP) ratio, RBC/gas ratio from 129Xe IDEAL imaging (as (Qing, Ruppert, et al. 2014))
- Apparent diffusion coefficient (ADC) and diffusive length scale (LmD) from 129Xe diffusion-weighted imaging (as (Chan et al. 2018)).

Indices of perfusion, lung inflammation and ventilation from proton MRI

- Extravascular extracellular space per unit volume of tissue (Ve) and the volume transfer coefficient (Ktrans) of contrast agent between the vascular plasma space and Ve, from delayed enhancement perfusion imaging (as (Naish et al. 2009))
- Pulmonary blood volume, pulmonary blood flow and mean transit time, from dynamic contrast enhanced first pass perfusion imaging (as (Ohno et al. 2007))

- Longitudinal relaxation time (T1) and proton spin density (M0), both affected by changes in tissue water content, from gradient echo sequences with variable flip angles (as (Naish et al. 2009))
- Ventilation-perfusion intersect from ventilation/perfusion maps and ventilation/perfusion histogram analysis, to assess gas exchange (as (Marshall et al. 2014))

Total exacerbation number in each participant will be determined from electronic diary records (EXACT-PRO). Analysis will be carried out to see if XeMRI indices of change in lung function and inflammation after 12 weeks of mepolizumab therapy correlate with total exacerbations over 52 weeks of mepolizumab therapy by dividing the study group by median split for total exacerbation frequency over 52 weeks and comparing changes in XeMRI parameters at 12 weeks for the 52 week low and high total exacerbation groups.

3.7 TERTIARY ENDPOINTS

- MRI derived indices of lung ventilation, perfusion and inflammation enumerated as being measured at 12 weeks as defined above in sections 3.5 and 3.6 will also be measured at 52, both being compared to baseline. Changes of MRI derived indices of lung ventilation, perfusion and inflammation will be correlated with changes in the following measures of pulmonary physiology from baseline to 12 and 52 weeks to see if any changes detected at 12 weeks persist to 52 weeks;
  FEV1, FVC, FEF 25-75 from spirometry
  FRC, RV, TLC from plethysmography, diffusing capacity for carbon monoxide, and R5-20, AS and X5 from oscillometry
- Changes in lung MRI variables and physiological measures from baseline to 12 and 52 weeks will be correlated with baseline eosinophil inflammation as measured by each of peripheral blood eosinophil count and FeNO, and with treatment induced changes in eosinophil inflammation at 12 weeks as measured by within participant changes in each of peripheral blood eosinophil count and FeNO.

3.8 EXPLORATORY ENDPOINTS/OUTCOMES

The number of moderate and severe exacerbations in each participant will be determined from patient recollection at visits, recording whether they have taken any medication for an exacerbation in their e-diary and confirmed by access to medical records. Moderate exacerbations are defined as those requiring oral treatment with steroids and/or antibiotics, and severe exacerbations as those requiring hospital admission. Analysis will be carried out to see if XeMRI

indices of change in lung function and inflammation after 12 weeks of mepolizumab therapy correlate with number of moderate to severe exacerbations over 52 weeks of mepolizumab therapy by dividing the study group by median split for total exacerbation frequency over 52 weeks and comparing changes in XeMRI parameters at 12 weeks for the 52 week low and high moderate and severe exacerbation groups. (Measurement of moderate and severe exacerbations rather than total exacerbations is considered an exploratory outcome as the number of events encountered are unlikely to be sufficient to allow adequate power for a definitive outcome. However, these will be collected alongside total exacerbations and also reported as this is a standard outcome measure in clinical trials in COPD. Total exacerbations are included as a secondary outcome as their far greater number allow greater power).

Data on exacerbations will be collected from the screening visit, however the number of exacerbations from the first administration of IMP until the end of the treatment period will be used in the analysis.

With similar methodology utilised to derive high and low exacerbation frequency groups using median split, groups will be derived with high or low improvement of health related quality of life groups based on change in COPD Assessment Test (CAT) score at 52 weeks. MRI derived indices at 12 weeks of treatment with mepolizumab will be compared in those with high or low change in CAT. The changes of CAT score from baseline to 12 and to 52 weeks will also be correlated with change in MRI and physiological measures from baseline to each time point.

PREFUL derived measures of lung function (Voskrebenzev et al. 2018) will be correlated with XeMRI and DCE perfusion MRI measures and relevant pulmonary function parameters:

- PREFUL percentage ventilated lung volume (PREFUL %VV), a surrogate measure of lung ventilation, will be correlated with XeMRI %VV.
- PREFUL percentage perfused lung volume (PREFUL %PV), a surrogate measure of lung perfusion, will be correlated with DCE perfusion MRI %PV.

Indices from XeMRI are more established and better validated than PREFUL measures. However, the technique requires more dedicated equipment and more expense. PREFUL is included as an exploratory outcome to measure its relative sensitivity to change compared to XeMRI and DCE perfusion MRI.

3.9 TABLE OF ENDPOINTS/OUTCOMES

Co-Primary end points	To measure the effect of anti-eosinophil therapy on lung	The within participant change in percentage ventilated volume of

	ventilation in COPD over 12 weeks, using XeMRI function.	lung (%VV) assessed by XeMRI from baseline to 12 weeks of treatment with mepolizumab.
	To measure the effect of anti-eosinophil therapy on alveolar thickness (as an index of pulmonary inflammation) in COPD over 12 weeks using XeMRI	The within participant change in TP/gas (a measure of alveolar thickness, as an index of pulmonary inflammation) assessed by XeMRI from baseline to 12 weeks of treatment with mepolizumab.
Secondary end points	To compare changes in MRI derived measures of lung ventilation, perfusion and inflammation at 12 weeks with variation in a key clinical outcome (total exacerbation frequency) over 52 weeks	Comparison of change in MRI metrics from baseline to 12 weeks in groups with a) low or b) high total 52 week exacerbation (groups defined by median split of total exacerbations over 52 weeks assessed by EXACT-PRO)
	To measure the effect of anti-eosinophil therapy in COPD over 12 weeks, using other XeMRI and MRI indices of lung ventilation, perfusion and inflammation	Change in MRI indices of ventilation, perfusion and inflammation (see text) - CV, RBC/TP, RBC/gas, ADC, LmD, Ve, Ktrans, PBV, PBF, MTT,

		VQ-intersect, T1, M0 from baseline to 12 weeks
Tertiary endpoints	To measure the effect of anti-eosinophil therapy in COPD over 52 weeks, using XeMRI indices of lung ventilation, perfusion and inflammation, and to determine if effects seen after 12 weeks persist for 52 weeks	Change in MRI indices of ventilation, perfusion and inflammation (see text) - %VV, CV, RBC/TP, TP/gas, RBC/gas, ADC, LmD, Ve, Ktrans, PBV, PBF, MTT, VQ-intersect, T1, M0 at 52 weeks compared to baseline and 12 weeks
	To compare MRI derived measures of lung ventilation, perfusion and inflammation with changes in physiological measurements	Correlation of changes in physiological measures (see text) and MRI measures of lung function and inflammation (see text) at 12 weeks
	To determine if changes in indices of lung ventilation, perfusion and inflammation derived from physiological and MRI parameters are related to initial eosinophilic inflammation	Change in physiological and MRI determined measures of ventilation, perfusion and inflammation at 12 weeks from baseline will be correlated with; Baseline peripheral blood eosinophil count

		Baseline FeNO Change of peripheral blood eosinophil count from baseline to 12 weeks Change in FeNO from baseline to 12 weeks. Similar correlation will be carried out for data obtained at 52 weeks rather than 12 weeks.
Exploratory end points	To compare MRI derived measures of lung ventilation, perfusion and inflammation at 12 weeks with a key clinical outcome (moderate to severe exacerbation frequency) over 52 weeks	Comparison of change in MRI metrics from baseline to 12 weeks in groups with a) low or b) high total 52 week exacerbation. Groups defined by median split of total moderate to severe exacerbations over 52 weeks, see section 3.8.
	To assess the overall impact of mepolizumab treatment on HRQoL in COPD over time, and assess how this relates to impact on pulmonary function	Comparison of change of CAT from baseline to 12 and 52 weeks within participants compare to changes in measures of lung function by physiology and MRI.

	assessed by physiology and XeMRI	Comparison of changes in physiological and MRI derived parameters at 12 weeks in groups with either high and low improvement of CAT at 52 weeks (determined by median split)
	To compare measures of lung function assessed by XeMRI and DCE perfusion MRI with PREFUL MRI measures.	PREFUL %VV and PREFUL %PV will be correlated with XeMRI and proton MRI determined measures of lung function at all time points

4. TRIAL DESIGN

The trial is an open label, descriptive pilot study using advanced MRI techniques to demonstrate physiological and pathological changes from baseline during acute and chronic treatment of COPD by mepolizumab, in participants with eosinophilic disease at baseline.

32 participants with COPD will be enrolled in this study. 100mg mepolizumab will be administered to patients at 4 weekly research visits over the course of 1 year. During their time in the study participants will be asked to attend 15 visits in total. A screening visit, 3 assessment visits, one at baseline, 12 weeks and 52 weeks and 11 treatment/safety visits. After 30th April 2024 enrolled participants will complete visits up to assessment 2 and will complete the study at this point, contributing data to the primary endpoint timepoint. See section 7.12. The assessment visits will involve lung function testing and MRI scans as

well as a full clinical examination and blood tests. The treatment/safety visits will comprise of a review of safety bloods, and AEs, collection of diary information and administration of mepolizumab.

The study aims to show whether MRI is able to detect changes during treatment with the goal of:

A) Allowing better functional understanding to aid further drug development
B) To afford better targeting of treatment to participants likely to benefit, with improved cost-benefit

5. TRIAL SETTING

The study is a single centre study to take place at the Sheffield Teaching Hospital NHS Foundation Trust, with collaboration between the NHS Respiratory Department and the University of Sheffield. Recruitment will be via both the hospital and primary care PICs. The facility has a world class imaging facility which to date is the only hospital in the UK to make XeMRI available to clinical patients, following a long history of development of this and similar technology, including clinical studies in COPD as well as other lung disease.

The hospital is an acute hospital admitting patients with COPD and running multiple specialist outpatient clinics for COPD from where patients will be considered for recruitment. In addition local primary care networks will be used to provide PIC sites for further participants.

6. PARTICIPANT ELIGIBILITY CRITERIA

6.1 INCLUSION CRITERIA

- Diagnosis of COPD as determined by a post bronchodilator FEV1/FVC <70% and an FEV1 of between 20 and 80% at screening visit
- Treatment with inhaled triple therapy (at least the equivalent of a licensed triple therapy combination of long acting beta 2 agonist, long acting anti-muscarinic and corticosteroid) at constant dose for at least 12 weeks before screening visit. Treatment with roflumilast, theophyillines and macrolides will be permitted so long as they were introduced at stable dose > 12 weeks prior to screening visit. (If maintenance drug dosing has not been with stable dosages for 12 weeks the screening visit may be rescheduled until this is achieved: see sections 7.3 and 7.9)
- At least 2 acute exacerbations of COPD (AECOPD) requiring treatment with oral steroids and/or antibiotics in the last 12 months, or 1 acute AECOPD requiring hospital admission in the last 12 months.
- At least one eosinophil count of $>0.3x10^9$ cells/L in the 12 months prior to or at screening

- Age over 18 years

6.2 EXCLUSION CRITERIA

- Contraindication to MRI scanning as per the UoS MRI unit screening form.
- Inability to give informed consent or comply with study procedures
- Hypersensitivity to mepolizumab or its excipients
- Untreated helminthic infection
- Exacerbation of COPD requiring treatment with oral steroids and/or antibiotics within 4 weeks of screening. A repeat screening visit may be scheduled in order to achieve this criterion. The participant will be required to successfully complete all screening procedures at the rescheduled visit, including that for exacerbation-free stability. See sections 7.3 and 7.9
- SpO2 <90% on room air at screening
- Clear history of childhood and/or current asthma
- Past history of lung surgery
- Other significant lung disease
- Long term oral steroid treatment
- NYHA class 3 or 4, where the functional limitation from heart disease is greater than that from COPD, or uncompensated heart failure
- Chronic liver disease (Any elevation of ALT above twice the upper limit of normal at screening. Lower levels of abnormality are permitted after investigator review if felt not to compromise safety)
- Malignancy unless treated and disease free for 5 years
- Conditions causing significant immunosuppression
- Active infection with blood borne viruses (including hepatitis A and B and HIV)
- Other significant medical condition compromising participant safety or fidelity of study.
- Pregnant or breast feeding
- Of childbearing potential and not willing to use highly effective methods of contraception during the course of the study and for 100 days post last dose of mepolizumab (see section 6.3).
- Participants who have received an investigational drug within 30 days of first dose, or within 5 drug half-lives of the investigational drug, whichever is longer

6.3 PREGNANCY

Women of childbearing potential will be asked to avoid pregnancy for the duration of the study and for 100 days after last administration of mepolizumab by the use of highly effective contraception, here defined:

A. Highly Effective Methods That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
  Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.

B. Highly Effective Methods That Are User Dependent Failure rate of <1% per year when used consistently and correctly.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation.
  - oral
  - injectable
- Sexual abstinence
  Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

7. TRIAL PROCEDURES

7.1 RECRUITMENT

Recruitment will be via the following routes:

- Specialist COPD clinics run by Dr. Lawson and team at Sheffield Teaching Hospital NHS Foundation Trust
- Patients seen by the respiratory team at Sheffield Teaching Hospital NHS Foundation Trust either as inpatients or in general clinics
- Patients seen by the community COPD teams, and the community pulmonary rehabilitation teams in Sheffield.
- Patients identified by PICs in Sheffield and surrounding areas
- Patients identified from the respiratory research database of Sheffield Teaching Hospital NHS Foundation Trust
- By public advertisement
- Via the NIHR Be Part of Research Volunteer Service

Patients thought by clinicians of STHFT and associated community teams to be likely to fulfil appropriate inclusion and exclusion criteria will be approached, and asked if they might consider taking part in the study. Should they agree to consider this their contact details will be forwarded to the coordinator for this trial, who will send a summary patient leaflet and full patient information sheet to the patient. They will be invited to contact the coordinator if interested. If they do not make contact within 2 weeks, they will be contacted once to check the patient's wishes. Participants who declare an interest after reading the PIS will be invited to a screening visit.

At PICs, clinical databases will be searched using a simplified tool based on inclusion and exclusion criteria to select those who might be suitable for the study. These patients will be sent a summary patient information leaflet and full patient information sheet with a letter from their responsible clinician at the PIC site informing the patient that a research study is being carried out at the hospital, and inviting them to volunteer by contacting the trial coordinator.

We also plan to advertise the study via the Be Part of Research Volunteer service (BPOVRS). The purpose of the BPORVS is to allow members of the public to become volunteers by creating an account, specifying the areas of research that they are interested in and give consent to be contacted by the Be Part of

Research team. Those who consent will receive information about BPORVS, in particular to alert them to specific BPORVS registered studies that they may be interested in, based on their volunteered details and study specific eligibility criteria, using an online self-registration service. The register is open to those that live in the UK, are over 18 and have an email address.

At the time of registration, volunteers are made aware that they are not signing up to take part in a specific health study when they join this register and that they will only be signposted to studies that have NIHR funding or are listed on the NIHR CRN Portfolio. If the volunteer is interested in the study there will be a link in the email to take them to the study team (e.g. website, pre-screener) where they will move into the study teams screening process and consenting process if they take part in the study.

The Be Part of Research Volunteer Service is funded by the Department of Health and Social Care and delivered by the National Institute for Health and Care Research (NIHR) in conjunction with Public Health Agency, Research & Development, Northern Ireland, NHS Scotland and Health and Care Research Wales.

Further information on the Be Part of Research Volunteer Service is available here: https://bepartofresearch.nihr.ac.uk/volunteer-service/researchers

Those responding to public adverts will be sent a PIS, and asked to contact the coordinator if interested in participating in the study after reading this. If interested, a brief telephone screening tool will be used to check their likely suitability. Verbal consent will sought to review potential eligibility by access of the patient's Summary Care Record, STH hospital medical record and laboratory results, or if not accessible to access this from their GP or hospital. Verbal consent form will be used to record this process. If a participant appears suitable they will be invited to a screening visit.

All patients contacting the study coordinator with a view to inclusion in the trial will be asked to provide verbal consent to access NHS summary care records, and to provide age/gender/ethnicity. Verbal consent will be recorded on a pre-screening CRF along with participant details. The summary care record will be printed for use as source data for pre-screening. This will be scrutinized to ensure a diagnosis of COPD has been recorded, and that the potential participant is treated with a licensed triple therapy for COPD. Frequency of exacerbation will be inferred from the summary care record by scrutinizing antibiotics and steroids prescribed in the last year, together with ICE results reporting to ensure the requirement for two exacerbations needing treatment or one hospital admission are met. ICE will also be checked to access existing eosinophil counts and ensure where counts are available one is >0.3 in the last year. The SCR will also be used to exclude those with known asthma, chronic liver disease, previous lung surgery, taking immunosupressants, or who are HIV positive, or have other conditions that would be likely to exclude them. The remainder will be judged likely to be suitable and invited for a screening visit should they agree to volunteer. This data will be recorded on the pre-screening CRF with a record will kept of the decision as to whether they are suitable or not, and if they agree to participate or not, in each case with the reason recorded.

Where the eosinophil count criteria is not already met, either because no blood tests have been completed within the last year or a recent count is narrowly under the threshold, and the clinical team believe the candidate may meet this inclusion criteria, the team will invite the participant to have an additional blood test prior to the full screening visit. This will ensure only candidates who are likely to be eligible need attend for this longer screening visit. We will ask participants for verbal consent to have this additional blood test. Depending on participant preference, participants may attend the drive through phlebotomy service, or they may attend the clinical research facility for a short appointment to have their bloods taken. If participants are eligible based on their blood results and care record review, they will be invited for a full screening visit.

7.2 PARTICIPANT IDENTIFICATION

Participants will be identified as above. In most cases screening and invitation will in the first instance be by the usual clinical team. In the case of PIC sites, this will again hold true, with the screening of patients and issuing of invitations by the usual clinical team.

The Sheffield Teaching Hospitals Respiratory Research Database (STH16261, REC ref 18/YH/0383) holds data with prior consent for access for research studies and will be used to identify potential participants based on diagnosis, previous pulmonary function and historical peripheral blood eosinophil counts.

Open invitation via adverts will also be used. These will be offered for display in hospitals and primary care settings, and other community locations, as wall posters and flyers.

The trial bookings will be coordinated via the NIHR Clinical Research Facility, a joint body of Sheffield Teaching Hospital NHS Foundation Trust and the University of Sheffield. Fully trained reception staff will be able to take initial calls and expressions of interest. A simple screening questionnaire will then allow selection of potential participants likely to fulfil inclusion and exclusion criteria. This will be reviewed by a medical practitioner from the research team who is also a member of the respiratory clinical team. If the potential participant is already known to the respiratory clinical team at the Northern General Hospital their clinical record will be checked to ensure there is no contraindication to trial recruitment, and if the potential participant is felt appropriate a screening visit will be scheduled.

As noted above, demographics and reasons patients decline the study, or who are declined as unsuitable, will be kept in anonymised form on secure computers in the Clinical Research Facility.

7.3 SCREENING VISIT (VISIT 1 – DAY -28- -7)

Informed consent (see section 7.4) will be obtained prior to any study related procedures. Patients will be asked to consent to access to all historical pathology results held on STH electronic systems for the purposes of this research, and to access to the summary care record and hospital electronic records at one year after the study, or until resolution of any possible study related adverse event.

At the screening visit a full clinical history will be obtained, in particular focusing on diagnosis of COPD, exclusion of asthma and other diseases, and any condition likely to compromise safety or study fidelity. Smoking history and treatment history will be recorded. If a history of exacerbation within the 4 weeks is obtained, the screening visit will be rescheduled until an exacerbation free period of at least 4 weeks has elapsed. If there is a further exacerbation the study visit may be deferred for a second time, but the visit may only be rescheduled twice in total; if the participant then fails to meet the criterion for stability they will be withdrawn.

If maintenance treatment including clinically licensed inhaled triple therapy with LABA/LAMA/ICS, has not been stable for 12 weeks the screening visit may be rescheduled to a time when this will have been achieved. Where roflumilast and/or a long term macrolide and/or theophyllines are used in addition, if their dosage has not been stable for 12 weeks then the screening visit will be deferred to a time when this will have been achieved. The study visit may be rescheduled a maximum of 2 times to allow for COPD baseline therapy (LABA/LAMA/ICS and/or any additional therapies such as roflumilast/long term macrolide/theophyllines) to become stable for 12 weeks.

Participants will also be asked about their prior involvement in clinical trials. If a participant has been involved in a study where an IMP has been taken recently, the study visits will be arranged so that at 30days, or 5 halflives of the previous IMP, whichever is longer, have passed before the baseline visit of this study. The screening visit may be rearranged once for this reason to allow the study timelines to be met.

A full clinical examination will be carried out, focusing on the respiratory system. However, examination will include vital signs (pulse, blood pressure, respiratory rate, oxygen saturation on air and temperature), general appearance/neck/lymph glands, cardiovascular system, abdomen, and central nervous system for baseline safety reasons.

Salbutamol 400mcg via MDI and spacer will be administered, in preparation for post –bronchodilator spirometry 15 minutes later

Blood will be taken for full blood count, urea and electrolytes, liver function tests, calcium profile, CRP and screen for blood born viruses. The latter will included tests for hepatitis B surface antigen and hepatitis C antibody, and combined test for HIV antibody and antigen.

Other assessments at the screening visit areas follows:

- Post-bronchodilator spirometry and pulse oximetry on air will be carried out to ensure inclusion criteria are met.

- An ECG for safety purposes, as a baseline.
- Urinalysis for safety purposes, as a baseline.
- A pregnancy test will be carried out in women of childbearing potential. If positive, the participant will be withdrawn. Woman of child bearing potential with a negative pregnancy test will be asked to use highly effective contraception from the time of first treatment to 100 days after last treatment with mepolizumab. See section 6.3 for details.

Participants will be instructed in the use of an electronic diary to ensure the ability to utilise this during the study. They will be asked to commence completing the diary daily for the duration of the study, which will record data for EXACT-PRO quantitation of exacerbation frequency.

This is uses a 14-item PRO used to quantify and measure exacerbations of COPD with standardized definitions of exacerbation, exacerbation severity, and exacerbation duration (Leidy et al 2011).

This is being used under academic licence from the EXACT-PRO consortium.

At the screening visit participants will be trained on diary usage and will be issued with their own electronic device and an instruction sheet. Participants will be asked to complete the diary daily, in the evening, for the duration of the study. The study team will be able to view whether a participant has completed the diary via a data portal. This information will be stored with participant ID as an identifier only (no personal identifiable information will be stored), this data will also integrate with our research database. Over the duration of the study the research team will monitor compliance to the diary. If a participant has a period of non-compliance the study team will contact the participant to offer support and re-train as necessary, Compliance to the diary will be assessed at a minimum of at each study visit.

Data recorded between the screening visit and the baseline visit will include a final 7 days as baseline data for calculation of baseline symptom score as defined by the EXACT handbook. An additional data will be considered practice data.

The MRI checklist safety screening questionnaire will be carried out. Failure to comply with this will result in withdrawal from the study, unless acquisition of further information (eg MRI compliance of an implant) can be gathered before the baseline visit, with satisfactory response.

If inclusion and exclusion criteria are complied with, participants will be invited to attend a Baseline visit, Assessment 1 (see section **Error! Reference source not found.**). A letter of gratitude will be sent to participants who do not meet eligibility, thanking them for their interest in research. Patients may also request a letter from the study that they can choose to give to their employer, requesting their support to attend research visits during their working week. The letter will express gratitude to the employer for support they give to research and outline the participants anticipated visit dates.

Participants who initially fail screening, may be re-invited for the screening visit should it become known that they subsequently meet the required eligibility eg. a raised eosinophil count, or subsequently meet required exacerbation criteria.

7.4 CONSENT

All participants will receive a patient information sheet if invited to consider the trial by their clinical team in secondary care, or if invited to consider this following identification at a PIC, or after contacting the study coordinator if responding to adverts. They will be given a minimum of 24 hours to consider this before any screening visit is scheduled.

At the screening visit no procedure will be undertaken until the full process of informed consent has been completed. A medically qualified member of the study team with up to date GCP certification will carry out the consent process, first confirming with the participant that they have read and understood the PIS; failure to have done so will be considered to invalidate the process of consent and the screening visit rescheduled to allow this to happen with a period of at least 24 hours for reflection.

They will give a synopsis of the trial. It will be emphasised that this is a research study and is voluntary. Participation does not affect usual clinical care, and consent can be withdrawn at any stage without being required to give a reason. The possible risks of participation will be explained.

The participant will then be given an unlimited amount of time to ask questions and seek clarification, before giving written consent, with the medical practitioner carrying out the consent process signing to confirm this has taken place as per local protocols.

7.4.1 ADDITIONAL CONSENT PROVISIONS

Participants will be asked to give consent for their anonymised data to be used for future research, this is optional.

Any participant becoming pregnant during the course of the study will be asked to consent for follow up to determine the outcome for the mother and child.

Any participant withdrawing from the trial will be asked to consider consent to any or all of the following:

- to be contacted at sufficient time after administration of last study drug to ascertain any side adverse events

- access medical records for two years
- for their de-identified data to be shared with other researchers
- to be contacted about future research studies

They will also be asked if they wish to receive a trial summary in due course.

7.4.2 HIGHLY EFFECTIVE CONTRACEPTION

Woman of child bearing potential with a negative pregnancy test will be asked to use highly effective contraception from the time of first treatment to 100 days after last treatment with mepolizumab, see section 6.3.

7.4.3 ELECTRONIC PATIENT DIARY (EXACT-PRO)

The participant will be issued with a handheld electronic device which will be used by the participant to complete the EXAcerbations of Chronic pulmonary disease Tool (EXACT) patient-reported outcome (PRO) daily diary and asked to complete this daily from screening visit until study completion. Baseline data will be collected in the 7 days prior to the first assessment visit. Adherence to the EXACT-PRO will be monitored and the study team alerted if a participant has had a period of non-compliance. The study team will then attempt to contact the participant to troubleshoot any potential issues with diary compliance. In some cases, where a participant is unable to complete the electronic diary for a short period (e.g. hospital admission), or if the electronic system is unavailable for any reason, we may issue a paper version of the EXACT-PRO for completion during this period.

7.5 TRIAL ASSESSMENTS

7.5.1 VISIT 2 (ASSESSMENT VISIT 1 – DAY 0)

The baseline visit will be planned to occur between 7 days and 4 weeks following the screening visit, unless deferred per protocol because of exacerbations.

Prior to the baseline visit, safety bloods from the screening visit will be reviewed to ensure no exclusion criteria have been breached. (Full blood count, biochemical profile, screen for blood borne viruses). Participants with positive screens for active infection with blood borne viruses will be withdrawn, and referred for clinical attention as appropriate. Participants with any blood parameter outside the laboratory normal range will have their clinic history and records reviewed; being withdrawn unless the investigator confirms safety is not compromised.

Participants will be contacted by phone a few days prior to their scheduled baseline visit to check stability since screening, that is, freedom from acute exacerbation, and to confirm the appointment for the baseline assessment visit. If an exacerbation requiring oral treatment has occurred since the screening visit, the baseline visit will be abandoned and rescheduled so that at least 4 weeks (and no more than 6 weeks) have elapsed since the exacerbation commenced. If there is further exacerbation requiring oral treatment between the original baseline visit and the rescheduled visit, the baseline visit will be similarly rescheduled once, to between 4 and 6 weeks from the exacerbation commencement. If there is a further exacerbation before the second rescheduled baseline visit the baseline visit will be rescheduled a second time. If there is a further exacerbation the participant will be withdrawn from the study, i.e. the visit will be rescheduled a maximum of two times.

On the day of the baseline assessment, participants will attend having withheld short acting bronchodilators for at least 12 hours and long acting bronchodilators for at least 24 hours. If the patient has needed to take their bronchodilator within this time frame this will be recorded and the pre bronchodilator spirometry will be omitted.

At the baseline visit the following assessments and eligibility/safety checks will be completed:

- Data from screening will be reviewed to ensure eligibility.
- The clinical history will be reviewed and a clinical examination carried out to detect changes from the previous visit. Any changes will be noted and reviewed; if a change compromising safety is found the participant will be withdrawn from the study. Any significant change from screening visit will be considered an AE and evaluated and recorded appropriately. If since the telephone check there has been an exacerbation requiring treatment the assessment visit will be abandoned, and rescheduled as above.
- Conmeds (concomitant non-study medications) will be recorded.

- Compliance with the electronic diary will be reviewed (see section 7.4.3).
- A pregnancy test will be carried out if appropriate (all women of childbearing potential). If positive the participant will be withdrawn from the study.
- The MRI screening questionnaire will be rechecked.

At this point, a medically qualified member of the study team will review all results of screening. If these are deemed satisfactory and there is no significant clinical change from screening visit, the participant will be declared eligible and the baseline assessment visit will continue; this being the first day of the trial.. If there is a resolvable clinical concern which prevents the assessments being performed at this visit then the visit will be rescheduled once for this reason, per investigator discretion. If the visit is to go ahead as planned the following assessments will then be completed:

- Pre-bronchodilator spirometry will be carried out.
- Participants will then inhale 400mcg of salbutamol via MDI and spacer.
- The CAT will be completed by the participant.
- SpO2 on air recorded. If the SpO2 on air is <90% the research visit will be terminated and the visit deferred as if the patient had suffered an exacerbation.
- Clinical assessment will be carried out and treatment given as clinically indicated.
- 20 minutes after the bronchodilator was administered post bronchodilator spirometry will be carried out.
- Blood will be taken for FBC, IgE, RAST to common aero-antigens, aspergillus precipitins and RAST, for baseline demographic/descriptive purposes.
- If sputum can be produced at any stage during the visit a sample will be sent for culture.
- The participant will directly undergo MRI scans as per MRI protocol. Xenon MRI must be completed as a minimum for the participant to remain in the study. Other scans may be omitted as per details below.
- Vital signs (pulse, blood pressure, respiratory rate, oxygen saturation on air and temperature) will be recorded prior to mepolizumab administration.
- 100 mg of mepolizumab will be administered subcutaneously
- Participants will be observed for adverse events for 1 hour afterwards, with vital signs (as above) measured after 15 and 60 minutes in a clinical environment with full resuscitation facilities available.
- During this observation period participants will proceed to have further lung function testing, the timing of each assessment will be recorded. The lung function testing comprises:
    - oscillometry
    - fractional exhaled nitric oxide (FeNO) measurement,
    - gas transfer, and

- plethysmography.

These assessments will be carried out in the above order where possible.

The tests will be performed according to published UK ARTP lung function guidelines and the ERS technical documents. Should the participant be unable to complete any of the lung function manoeuvres this will be recorded as a protocol non-compliance. Participants must be able to complete the Xenon MRI sequences to remain in the study, however the contrast and/or proton scans may be omitted if the participant is not able to tolerate these or they cannot safely be carried out. If this is not possible, the participant will be withdrawn from the study.

7.5.2 VISIT 5 (COMBINED ASSESMENT VISIT 2/TREATMENT VISIT 4; 84+/- 5 DAYS) AND VISIT 15 (ASSESSMENT VISIT 3; 364+/-10 DAYS)

Participants will be contacted by phone a few days prior to their scheduled assessment visit to check stability since their previous visit, that is, freedom from acute exacerbation, and to confirm the appointment for their assessment visit. If an exacerbation requiring oral treatment has occurred since the previous visit, the assessment visit will be rescheduled so that at least 4 weeks (and no more than 6 weeks) have elapsed since the exacerbation commenced and a treatment visit will take place in its place (visit 5 only, for visit 15 the visit will simply be rescheduled). If the participant is too unwell to attend, data relating to the exacerbation, AEs and con-meds will be collected over the phone where possible. If appropriate compliance to the diary will be checked and the participant will be asked to complete the CAT over the phone. If IMP is not given at two consecutive visits, treatment will be withdrawn and the participant will continue for assessment only, if the participant agrees. If a further exacerbation occurs before the rescheduled assessment visit, the visit may be rescheduled one further time as above.

Patients will attend having withheld short acting bronchodilators for at least 12 hours and long-acting bronchodilators for at least 24 hours. If the patient has needed to take their bronchodilator within this time frame this will be recorded and the pre bronchodilator spirometry will be omitted.

The following assessments will be completed to ensure continued eligibility and that the participant is safe to continue with the study visit:

- Conmeds will be recorded, with any changes from previous visits noted.
- Compliance with the electronic diary will be reviewed (see section 7.4.3)
- Exacerbations will be reviewed. A pregnancy test will be carried out if appropriate (all women of childbearing potential). If positive the participant will be withdrawn from the study, the pregnancy will be reported and followed up as per section 9.6.
- If at any time during the visit sputum can be produced a sample will be sent for culture.
- An ECG will be performed
- Patients will give a urine sample for urinalysis.

- The clinical history, including review of recent blood results, will be reviewed and a clinical examination carried out to detect changes from the previous visit by a medically qualified member of the study team.
- The MRI screening questionnaire will be re-administered.

Should there be an exacerbation requiring treatment in the preceding 4 weeks before visit 5, the assessment visit will be deferred per section 7.9, and the visit will instead be treated as a treatment visit (with dosing with mepolizumab determined as per criteria in section 7.5.3 and 7.9). Should there be an exacerbation requiring treatment before visit 15, the assessment visit will be deferred 4 to 5 weeks, and again if necessary until there has been a 4 week period before the assessment period without an exacerbation requiring treatment, to a maximum of 2 deferrals (3 scheduled visits in total), per section 7.9.

Any other changes will be noted and reviewed; if a change compromising safety of the assessments the assessments may be deferred per section 7.9, but if likely to endure then the participant will be withdrawn from the study. If potentially remediable, the assessment visit will be deferred in the same way as if an exacerbation had occurred, so for visit 5 becomes a treatment visit identical to visit 4, and the assessment carried out at visit 6, with one further deferral possible. Any significant change from the previous visit will be considered an AE and evaluated and recorded appropriately. If the GFR has fallen below 30 ml/min/1.73 m2, the participant will continue in the study if deemed by the investigator safe to do so, with the exception that Gadovist will not be administered, and scans requiring its administration will be omitted (see section 7.9).

Once the medical practitioner has determined it is appropriate to continue with study assessments, the following assessments will be completed:

1. Pre-bronchodilator spirometry will be carried out. Participants will then inhale 400mcg of salbutamol via MDI and spacer.
2. The CAT will be completed by the participant
3. SpO2 on air will be recorded. If the SpO2 on air is <90% the assessment will be deemed unsafe. The protocol assessments will not be undertaken. Instead, a clinical assessment will be carried out and treatment given as clinically indicated. The assessment visit will be replaced by a treatment visit, per section 7.10.
4. 20 minutes after the bronchodilator was administered post bronchodilator spirometry will be carried out.
5. Blood will be taken for a full blood count.
6. The participant will directly undergo MRI scans as per the MRI protocol. Xenon MRI must be completed as a minimum, however the contrast and/or proton scans may be omitted if the participant is not able to tolerate these or they cannot safely be carried out.
7. Vital signs (pulse, blood pressure, respiratory rate, oxygen saturation on air and temperature) will be recorded prior to mepolizumab administration.
8. 100 mg of mepolizumab will be administered subcutaneously at study visit 5 (to make this combined assessment visit 2 and treatment visit 4), but not at the completion visit, study visit 15 which is an assessment visit only.

9. Participants will be observed for adverse events for 1 hour afterwards, with vital signs (as above) measured after 15 and 60 minutes in a clinical environment with full resuscitation facilities available. During this observation period participants will proceed to have further lung function testing. The timing of each assessment will be recorded. The lung function testing comprises:
    - oscillometry
    - fractional exhaled nitric oxide (FeNO) measurement,
    - gas transfer, and
    - plethysmography

    These assessments will be carried out in the above order where possible.

7.5.3 VISITS 3, 4,–6-14 - TREATMENT VISITS 2, 3, 5-13 (DAYS 28+/-5, 56+/-5, 112+/-5, 140+/-5, 168+/-5, 196+/5, 224+/5, 252+/-5, 280+/-5, , 308+/-5, 336+/-5)

Patients will attend having taken their normal medication at home.

A history will be taken to ensure clinical stability since the preceding visit. Any adverse events elicited will be recorded and reported appropriately, with clinical action and follow up as appropriate. If the investigator judges these may compromise safety due to study drug or procedures the participant will be withdrawn from the study, unless likely to resolve by the next study visit; in this case mepolizumab will be withheld at investigator discretion on the visit in question, pending re-assessment at the next visit. The visit will take place without administration of mepolizumab or associated period of observation, If the safety of assessments is compromised the participant will be withdrawn from the study entirely. If the safety of mepolizumab administration but not assessments is compromised, participants will be asked to continue with assessment visits as planned and compliance with the electronic diary will be reviewed (see section 7.4.3).

If intercurrent illness entirely prevents the participant from attending for a treatment visit, they will be contacted by telephone for appropriate safety monitoring, recording, and reporting at the time of the planned visit, in an *ad hoc* fashion, responding to patient need. Participants will be asked to continue to maintain electronic diaries if possible. The visit will otherwise be abandoned, with the next visit to take place per protocol as planned. If the following visit is an assessment visit at which prior U&E are required for safety purposes, *ad hoc* arrangements will be made for this. Should this prove impossible, then the next assessment visit may go ahead, but without injection of Gadovist or MRI sequences reliant on this.

Mepolizumab will not be withheld at two successive visits; should this be necessary the participant will be withdrawn from further treatment, but may be invited to continue assessment visits per protocol if safe to do so (see section 7.9 and).

If the participant is deemed safe to continue the following further assessments will be carried out:

- A pregnancy test will be carried out if appropriate (all women of childbearing potential). If positive the participant will be withdrawn from the study, the pregnancy will be reported and followed up as per section 9.6.
- Blood will be taken for a full blood count with differentials (to monitor efficacy of mepolizumab).
    - On visits 4 and 14 U&E, LFT and CRP will be measured to ensure safety, particularly for the administration of Gadovist at the following visit.
- Vital signs (pulse, blood pressure, respiratory rate, oxygen saturation on air and temperature) will be recorded.
- Mepolizumab 100mg will be administered subcutaneously.
- Participants will be observed for adverse events for 1 hour afterwards, with vital signs (as above) measured after 15 and 60 minutes in a clinical environment with full resuscitation facilities available.

7.5.4 PARTICIPANTS ATTENDING FOR ASSESSMENT VISITS ONLY

Where a participant has been unable to receive IMP for two consecutive visits they will be kept in the study for assessments only if they are willing. In this case, treatment visits may be replaced with telephone calls to reduce the number of times a participant needs to attend clinic unnecessarily. During the treatment visit replacement telephone call the participant's compliance to the ediary will be checked, they will be asked about any AEs, and changes to con-meds. Pregnancy tests and blood tests will be omitted and only completed at the next assessment visit. On visits when measurement of U&E were due as a safety check in readiness for the following visit, an ad hoc arrangement to obtain this sample in time for the assessment visit will be made where possible; if this is not possible then the assessment visit will go ahead but without the administration of Gadovist or MRI sequences that use this. Where a participant attends for safety bloods, a blood sample for FBC analysis will also be obtained.

7.6 PAYMENT

Participants will be reimbursed for time and disruption/inconvenience due to the study to the amount of £50 per completed MRI assessment visit (3 visits). Travel expenses will be reimbursed for all visits.

7.7 LONG TERM FOLLOW-UP ASSESSMENTS

On the screening visit consent will be sought for review of participant's primary care summary care record and hospital electronic patient records and other medical records to verify the exacerbation history and other clinical details for the following two years. The extended consent will be sought to allow further exploratory analyses to be carried out post hoc without the requirement for re-consent.

Study medication will not continue beyond the study, with the last dose being given at visit 14 as mepolizumab is yet to be licenced for COPD in the UK. They will be advised to continue treatments for COPD according to relevant clinical guidelines. An abstract of the research physiological measures and records of exacerbation will however be attached to patient records for general reference, and to guide decisions on access to mepolizumab should it be licenced for use in COPD in the future.

Participants will be telephoned 28 to 35 days after study completion to check for any late adverse events, and to ensure any patient concerns following medication change at study completion are addressed.

In the event that SAEs occur participants will be followed up until complete data is obtained as defined in section 9.3.

7.8 QUALITATIVE ASSESSMENTS

The COPD Assessment Test (CAT) will be used to measure health related quality of life through the study, this will be completed at assessment visits.

7.9 WITHDRAWAL AND RESCHEDULING CRITERIA

Complex criteria are necessary for stability and to allow appropriate rescheduling. This study hopes to address baseline inflammation, in addition to lung structure and function. However, the target group of participants are by definition those who may be unstable. The study addresses the theme of using targeted anti-inflammatory to reduce exacerbation frequency, and thus participants are selected as those with a propensity to exacerbate. However, during exacerbation, the baseline inflammatory signal will be overshadowed by an acute inflammatory response. Thus, a balance must be struck between timely study per protocol whilst avoiding intercurrent acute inflammation. The protocol emphasises, in particular, good stability at baseline.

For purposes of assessment of stability, an 'exacerbation' here refers to a moderate-to-severe exacerbation requiring oral treatment with steroids and/or antibiotics and is regarded as lasting for the duration of that treatment.

Participants may withdraw their consent to the study at any stage. Should they do so they will be asked to volunteer a reason, but not required to do so. Should they withdraw consent to study related procedures they will be asked (but not required) to consent to continued access to their medical records to assess outcomes.

Participants developing serious adverse events thought to be related to study medication will be withdrawn from further treatment with study drug. If withdrawn for this reason, the participants will be invited to complete assessment visits per protocol and continue to complete their electronic diary.

Participants will be withdrawn from the study (all study visits) if other adverse events are felt to compromise safety within the trial, particularly if the change in condition means they no longer pass study exclusion criteria.

Participants too unstable to meet timing criteria for study visits will be withdrawn from the study, as per protocol criteria.

Participants withdrawn from or who withdraw themselves from the study will continue to have AE and SAE for weeks after last study related procedure, or 8 weeks after last mepolizumab administration, whichever is the greater. ARs/SARs and SUSARs will be recorded until 8 weeks after last mepolizumab administration. Where possible a supplementary telephone call will be carried out to elicit this information unless consent for this is refused.

Mepolizumab administration visits may be carried out at the discretion of the investigator in the event of mild inter-current illness thought to be unrelated to the study drug. In the event of more severe inter-current illness (defined as requiring a change in systemic treatment at the scheduled time of study visit) the investigator may determine that mepolizumab administration is precluded. Drug administration and associated observation period will be cancelled. The next visit will take place at the usual time after baseline. If the participant cannot attend the Clinical Research Facility due to intercurrent illness, arrangements will be made to collect the patient's diary for download, with other study information collected by telephone rather than face to face. On visits when measurement of U&E were due as a safety check in readiness for the following visit, an ad hoc arrangement to obtain this sample in time for the assessment visit will be made where possible; if this is not possible then the assessment visit will go ahead but without the administration of Gadovist or MRI sequences that use this.

Visit 2 (baseline) and visit 15 (completion) visits will be deferred until clinically stable and free of exacerbations requiring treatment for 4 weeks in order to avoid acute inflammatory changes; they will be rescheduled a maximum of twice. If the participant is still not stable, they will be withdrawn from the study. If the period of instability occurs prior to visit 5 (12 weeks), the assessment visit will be put back to the time of visit 6 or visit 7, whichever first follows a 4-week period of stability. Visit 5 (and visit 6 if the assessment visit is further deferred) will follow the schedule for a treatment visit, with limitations detailed above.

Visit	Criteria to be satisfied	Allowance of criteria not satisfied	Further allowance
Visit 1 (screening)	4 weeks since beginning of last exacerbation requiring treatment	Reschedule until at least 4 weeks since beginning of last treatment	Reschedule maximum of twice for this reason
Visit 1 (screening)	Stable treatment with licenced triple therapy for COPD (LAMA/LABA/ICS) and any additional therapies (roflumilast/long term macrolide/theophyllines) for at least 12 weeks	Reschedule until 12 weeks of stable background therapy treatment complete	Reschedule maximum of twice for this reason once
Visit 1 (screening)	Participant has not recently taken another IMP. That is first dosing visit of mepolizumab will be 30days or 5 half-lives of previous IMP, whichever is longer, from last dose of previous IMP	Reschedule once until this criteria can be met with study timelines.	

Visit 2 (baseline)	Stable since screening (free of exacerbation requiring oral treatment for 4 weeks)	Reschedule to 4 to 6 weeks since beginning of last exacerbation	Reschedule maximum of twice.
Visit 5 (Assessment)	4 weeks since beginning of last exacerbation requiring treatment	If exacerbation within last 4 weeks, carry out assessment visit at the anticipated time of visit 6; replace visit 5 with treatment visit identical to visit 4	If exacerbation within last 4 weeks before assessment visit deferred to visit 6, carry out assessment visit at the anticipated time of visit 7; replace visit 6 with treatment visit identical to visit 4. If exacerbation within 4 weeks of assessment visit rescheduled to time of visit 7, withdraw from study
Visit	**Criteria to be satisfied**	**Allowance of criteria not satisfied**	**Further allowance**
Visit 5 (Assessment)	No intercurrent condition making assessment procedures unsafe (including SpO2<90% on	If potential for resolution, carry out assessment visit at the anticipated time of visit 6; replace visit 5 with	If intercurrent condition making assessment procedures unsafe at assessment visit rescheduled to time of visit

	air) (but see below if eGFR only deemed unsafe)	treatment visit identical to visit 4. If no deemed potential for improvement at initially scheduled or at rescheduled assessment visits then, withdraw from study	6, replace visit 6 with treatment visit identical to visit 4, and reschedule assessment visit to time of visit 7 (but see below if eGFR only deemed unsafe) If assessment procedures unsafe at visit 7, withdraw from study
Visit 5 (Assessment)	eGFR above 30 ml/min/1.73 m2	If only stability criterion breached is eGFR then proceed with assessment visit, omitting Gadovist injections and MRI sequences reliant on using this	If at assessment visit rescheduled to time of visit 6 the only criterion breached is eGFR then proceed with assessment visit, omitting Gadovist injections and MRI sequences reliant on using this
Visits 3-4, 6-14	Free of intercurrent disease or exacerbation	At investigator discretion; if mild intercurrent illness, proceed with visit and	If mepolizumab withheld for clinical reasons on two successive scheduled

(Treatment visits)		mepolizumab administration. If severe, then cancel mepolizumab administration and associated observation. If participant unable to attend in person, telephone collection of data, with ad hoc arrangements to collect e-diary information and take U&E, CRP and LFT if required for following visit. If potential for resolution continue with study schedule thereafter (If mepolizumab withheld and no potential for resolution, continue in study for assessment only, including e-diary; withdraw from treatment)	study visits then participant will be removed from treatment, and continue in study for assessment only, including e-diary.
Visit	**Criteria to be satisfied**	**Allowance of criteria not satisfied**	**Further allowance**

Visit 15 (Assessment 2)	4 weeks since beginning of last exacerbation requiring treatment	If exacerbation within last 4 weeks, defer until 4 to 5 weeks since beginning of last exacerbation	If exacerbation within last 4 weeks before rescheduled visit, then reschedule again for 4 to 5 weeks later. Reschedule a maximum of twice.
Visit 15 (Assessment 2)	No intercurrent condition making assessment procedures unsafe (including SpO2<90% on air) (but see below if eGFR only deemed unsafe)	If assessment unsafe but deemed potential for improvement then defer 4 to 5 weeks	Defer maximum of 2 times (ie schedule 3 times in total)
Visit 15 (Assessment 2)	eGFR above 30 ml/min/1.73 m2	If only stability criterion breached is eGFR then proceed with assessment visit, omitting Gadovist injections and MRI sequences reliant on using this.	

NB in all cases AE/SAE will be collected to 4 weeks after the last study related procedure, or 56 days post last dose of mepolizumab, whichever is the longer.

ARs/SARs and SUSARs will be collected until 8 weeks after the last dose of mepolizumab was administered.

7.10 STORAGE AND ANALYSIS OF CLINICAL SAMPLES

No clinical samples will be stored.

Blood samples will be analysed by agreement in NHS clinical laboratories following their usual clinical procedures and protocols

7.11 END OF TRIAL

The study aims to recruit 32 participants. The trial will be considered to have been completed after the last participant has completed their final assessment visit and the subsequent follow up telephone call 4 weeks later. Alternatively, if safety or recruitment problems mandate an early termination of the study by agreement with the study sponsors, the study will be considered complete after the last study related procedure and follow up has been completed.

7.12 PARTICIPANTS RECRUITED AFTER 30TH APRIL 2024/AM08 APPROVED

Participants recruited after 30TH April 2024 and AM08 is approved will only complete the study to assessment 2, the primary end point timepoint. All visits until this point will be identical to the full study. Assessment 2 may be rescheduled a maximum of twice, as per section 7.9. That is to say they may have assessment 2 at visit 5, 6 or 7, with treatment visits replacing the missed assessment visits if possible. At assessment 2, the participant will complete the visit as normal, however will not receive a dose of mepolizumab at this visit. The participant will be followed up with a safety call 28-35 days later.

7.13 SCHEDULE OF ACTIVITIES

	1	2	3	4	5	6[3]	7[3]	8[3]	9[3]	10[3]	11[3]	12[3]	13[3]	14[3]	15[3]	16[4]
	Screening	Assessment[1] (baseline)	Treatment 2	Treatment 3	Assessment 2 and Treatment 4	Treatment 5	Treatment 6	Treatment 7	Treatment 8	Treatment 9	Treatment 10	Treatment 11	Treatment 12	Treatment 13	Assessment[3] (completion)	Telephone call
Time (days)	-28–7	0	28+/-5	56+/-5	84+/-5	112+/-5	140+/-5	168+/-5	196+/-5	224+/-5	252+/-5	280+/-5	308+/-5	336+/-5	364+/-10	28 to 35 days after last study visit
Phone call to check for exacerbations/inter-current illness and confirm appointment 1-3 days prior to visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Review screening bloods	x[1]	x[1]														
Ensure stability		x														
Informed consent	x															
Review of inclusion and exclusion criteria	x	x														
Review Blood tests from previous visit		x			x										x	
Review possible AEs		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Record/review conmeds and exacerbations	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Full clinical history and examination	x															

	1	2	3	4	5	6[3]	7[3]	8[3]	9[3]	10[3]	11[3]	12[3]	13[3]	14[3]	15[3]	16[4]
Clinical history and examination review (change from last history and examination)		x			x										x	
FBC,	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Calcium Profile	x															
U&E, LFT, CRP	x			x										x		
Blood for BBV	x															
IgE		x														
RAST aero-antigens, Aspergillous preciptins and RAST		x														
Pregnancy test if woman of childbearing potential – nurse	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECG	x				x										x	
Urinalysis	x				x										x	
Instruction on electronic diary use – nurse	x															
Review electronic diary completion (and retraining if required)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Collection of sputum for MC&S (if available)		x			x										x	

	1	2	3	4	5	6[3]	7[3]	8[3]	9[3]	10[3]	11[3]	12[3]	13[3]	14[3]	15[3]	16[4]
Post bd spirometry (400mcg salbutamol via MDI and spacer)	x															
Pre and post bd spirometry 400mcg salbutamol via MDI and spacer)		x			x										x	
FeNO		x			x										x	
Gas transfer, oscillometry, plethysmography		x			x										x	
CAT		x			x										x	
MRI scans[2]		x			x										x	
Record vital signs (pre mepolizumab dose); (pulse, blood pressure, respiratory rate, oxygen saturation on air and temperature)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Administer mepolizumab 100mg sc; Observe for 1 hour and record vital signs after one hour and any possible drug reaction in this time (15 and 60 minutes post)		x	x	x	x[5]	x	x	x	x	x	x	x	x	x		

1. Screening bloods will be reviewed as soon as available after the screening visit to confirm whether baseline visit should be scheduled. They will be double checked at the baseline visit.
2. MRI scanning protocol must include xenon scan as a minimum. If participants are unable to tolerate proton scan and/or contrast scan is unsafe due to kidney function they may remain in the study with these scans omitted.
3. Visits after assessment visit 2 will be omitted for patients recruited after 30st April 2024 see section 7.12
4. For patients recruited after 30th April 2024, the follow up safety visit will occur 28-35 days after their assessment 2, see section 7.12
5. For patients recruited after 30th April 2024, drug will not be administered at assessment 2, this will be their final study visit, see section 7.12

Baseline = assessment visit 1 and treatment visit 1

Abbreviations: FBC = full blood count, U&E = urea and electrolytes, LFT = liver function tests, CRP = c-reactive protein, IgE = immunoglobulin E, RAST = rapid annotation using subsystem technology, BBV = blood borne virus, ECG = electrocardiogram, MDI = metered dose inhaler, FeNO = exhaled nitric oxide, CAT = COPD assessment test, sc = subcutaneous, bd = bronchodilator.

8. TRIAL TREATMENTS

8.1 NAME AND DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Mepolizumab, 100mg subcutaneous injection from prefilled syringe, (Nucala, GSK) administered every 4 weeks for a maximum of 13 doses in total. Mepolizumab is a humanised anti-interleukin-5 (anti-IL-5) monoclonal antibody; it reduces the production and survival of eosinophils.

8.2 REGULATORY STATUS OF THE DRUG

Mepolizumab is licensed as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older.

In the UK, it is licensed to use in accordance with NICE guidelines, which state:

Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if:

- the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and
- the person has agreed to and followed the optimised standard treatment plan and
- has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or
- has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months and
- the company provides the drug with the discount agreed in the patient access scheme. https://www.nice.org.uk/guidance/ta431/chapter/1-Recommendations

The commercially produced product, Nucala, manufactured by GSK will be used in its commercial formulation and presentation, bearing marketing authorisation (EU/1/15/1043/003 pre-filled individual syringes).

8.3 PRODUCT CHARACTERISTICS

The Reference Safety Information will consist of the approved SmPC for commercial Nucala (mepolizumab) produced for asthma treatment.

A copy will of the approved SmPC for use as RSI will be kept in the trial management file.

The study team will check for updates to these documents at regular intervals throughout the development and conduct of the study, and will review and file these as needed. If an update to the reference safety information is involved, the revised SmPC will be submitted and approved as a substantial amendment before the revised SmPC is filed as the new reference safety information for the trial for the assessment of expectedness of adverse events.

8.4 DRUG STORAGE AND SUPPLY

Nucala (100mg/ml 1ml pre-filled Safety Syringes) will be obtained by commercial supply from GSK specifically for this trial, supplied as individual items. The Investigator or delegates will maintain accurate records of receipt of all drug supplies used in this study including lot numbers and dates of receipt. In addition, accurate records will be kept regarding when and how much drug is dispensed and used by each participant in the study. Reasons for departure from the expected dispensing regimen will also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all drugs will be reconciled and returned to the Manufacturer or destroyed according to applicable regulations or at the discretion of the Sponsor.

The drug will be stored within the Northern General Hospital Pharmacy in accordance with manufacturer's instructions. Before each visit a medically trained member of the study team will sign a study specific prescription form for each individual dose of IMP recording study number, participant number, visit number, and date. The drug will be held in the Pharmacy department ready to be collected once safety procedures are completed and signed off. At the study visit the medical practitioner will confirm that the participant is eligible to receive the IMP and will record this on the case report form prior to collection of the study drug from Pharmacy and administration of drug by the study team. IMP will not be collected from pharmacy or administered without this sign off. Successful administration of the IMP to the patient will also be recorded on the case report forms. After IMP administration used syringes will be disposed of locally at the Clinical Research Facility in accordance with Clinical Research Facility and hospital policy. Any malfunction will be noted as a device incident (See section 9.13 and the device will be kept for possible inspection by GSK). Other drug packaging will be also destroyed locally, with accountability relying on the written records described. If the IMP is not administered at the study visit for any reason it will be returned to pharmacy for destruction.

Storage in the pharmacy will be in a refrigerator maintained at 2-8 degrees centigrade. The storage environment within the pharmacy at the Northern General Hospital is automatically and continually monitored to ensure correct temperature with a daily check of records for the last 24 hours to ensure no unacceptable temperature excursion has occurred. It will be stored in the original carton in order to protect from light. The sponsor will be notified if stored mepolizumab has suffered a temperature excursion outside the acceptable range and IMP will be quarantined until review by GSK. The research team will be notified that the IMP is in quarantine and updated as necessary.

Should a temperature excursion outside the quoted range be suspected prior to delivery or on storage, the GSK LOC Quality Team will be contacted by email at syy65883@gsk.com. They will carry out an investigation and determine whether or not it is appropriate to release and use the product.

Following transfer to the Clinical Research Facility the syringe of mepolizumab will remain packaged and will be kept at 2-8^{o} in a continually monitored temperature controlled environment before being allowed to warm to room temperature for at least 30minutes before administration. It will be used within 8 hours of removal from refrigeration.

As the IMP is prescribed and dispensed one dose at a time and administered by the study team on the same day, accountability can be assessed by confirmation of administration of the dose at the study visit.

The used syringe will be disposed of locally in the Clinical Research Facility according to department protocols, unless there is a device failure. Should this occur this will be recorded using the appropriate form and the syringe will be retained for inspection by GSK, being returned to them or disposed of with their approval.

8.5 PREPARATION AND LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCT

Nucala will be obtained by agreement from GSK in the standard format marketed for use in eosinophilic asthma. The packaging will not be modified but the supply will be labelled with an Annex 13 compliant label marking it "for clinical trials use only" on arrival.

8.6 DOSAGE SCHEDULES

100mg of Nucala will be administered subcutaneously from the supplied pre-filled syringe at study visits 2 to 14, ie. every 4 weeks for one year, by an appropriately qualified member of the research team. Participants recruited after April 2024 will receive 3-5 doses of mepolizumab, see section 7.12. A medically qualified member of the

study team will prescribe the treatment dose at each treatment visit on a study specific prescription, allowing its administration at the study visit following safety checking. The medically supervised member of the study team supervising the research study visit will then review eligibility and safety criteria to confirm administration should go ahead, signing a written record that is part of the case report forms to allow this. The drug will be transferred from pharmacy to the Clinical Research Facility once safety checking has occurred and the IMP will then be administered to the patient.

8.7 DOSAGE MODIFICATIONS

All doses administered will be the same for all participants at all time-points.

In the event of inter-current illness the Nucala may be given on schedule if the inter-current illness is mild. If the inter-current illness is more severe, the dose may be withheld for safety reasons at the discretion of the investigator (see section 7.9). This accords with general clinical practice when using this product for its licensed indication of treating severe eosinophilic asthma.

8.8 KNOWN DRUG REACTIONS AND INTERACTION WITH OTHER THERAPIES

There are no known interactions with other medications, with the exception of other drugs specifically targeting eosinophil number. None of these are licensed for use in COPD.

8.9 CONCOMITANT MEDICATION

All participants will be required to be on a stable dose of ‘triple therapy’ for COPD for at least 12 weeks before the screening visit , i.e. a licensed combination of inhaled medications including a long acting beta 2 agonist, a long acting anti-muscarinic, and an inhaled corticosteroid. Macrolides, PDE4 inhibitors and theophyllines will also be allowed so long as their dosage has been stable for 12 weeks before the screening visit.

Other medications will be allowed according to usual clinical indications, without restriction for study purposes.

8.10 TRIAL RESTRICTIONS

Whilst there are no known adverse consequences of receiving mepolizumab during pregnancy, trial participants will be advised not to embark on pregnancy during the course of the study. There is evidence in monkeys the mepolizumab may cross the placenta, and the limited data in humans means that avoiding mepolizumab during pregnancy is recommended as a precaution. Those of childbearing potential will be required to use a highly effective method of contraception, as detailed in section 6.3.

On assessment days (study visits 2, 5 and 15) participants will be asked to withhold short acting bronchodilators for 8 hours and long-acting bronchodilators for at least 24 hours, as described in the protocol, until study assessments for that day are complete.

8.11 ASSESSMENT OF COMPLIANCE WITH TREATMENT

Treatment will be directly administered by an appropriately qualified member of the study team, with observation for an hour afterwards for safety reasons. Thus, no additional assessment of compliance is required.

8.12 NON INVESTIGATIONAL MEDICINAL PRODUCT (NIMP)

Salbutamol, a bronchodilator, is used for spirometry reversibility assessment and is a NIMP in this study. Salbutamol will be dispensed from STH Pharmacy via requisition accompanied by a treatment card for the study participant. The salbutamol will be stored in the clinical research facility designated drug cupboard and prescribed on the patient's treatment card (study specific drug Kardex) by a medically qualified study investigator. Salbutamol will not be labeled with any trial specific labels. Drug accountability records will be held in the site file to document the administration of salbutamol to study participants.

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.
Adverse Reaction (AR)	An 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 etiology 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 • requires inpatient hospitalisation or prolongation of existing hospitalisation • 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious 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 Reaction (SUSAR)	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: • version of the smPC for Mepolizumab approved as RSI.
Medical Device Incident	A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health. Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

9.2. OPERATIONAL DEFINITIONS FOR (S)AES

All AEs will be recorded in the CRF.

An important trial endpoint will be acute exacerbations of COPD. They will thus not be recorded as AEs or SAEs, but will be recorded separately. Mild exacerbations will be identified and recorded by change in daily symptom score (EXACT-PRO) (Leidi et al 2011). Moderate (those requiring oral treatment) and severe (those requiring hospital admission) will be separately recorded from patient recollection and with reference to clinical records, with date of onset, date of resolution, details of treatment and record of severity.

Mepolizumab (Nucala) is licensed, and with a well-established safety record in asthma.

All SAEs, other than those excluded from adverse event reporting as outlined above due to them being trial endpoints, will be reported to the study sponsors via the STH SAE report form. This report will be made within 24 hours of the investigators becoming aware of the SAE.

9.3. RECORDING AND REPORTING OF SAES, SARS AND SUSARS

Any AE or SAE occurring from the time of consent to 4 weeks after the last study assessment visit (visit 15) will be recorded. If the participant leaves the study at an earlier time point the final follow up call will take place 28 days after their last study related procedure or 56 days after last mepolizumab administration, whichever is the greater. A final telephone call (study visit 16) will be made to each participant to ensure all AE are captured. Exacerbations of COPD will not be considered AEs and will not be reported as such (see 9.2) and will be recorded separately as study endpoints.

ARs/SARs and SUSARs will be recorded from the first dose of mepolizumab given at study visit 2 until the final telephone call (study visit 16) or 56 days after last mepolizumab administration if discontinued early.

Reporting of all AEs and AR will continue even if a participant withdraws consent to the study, where such events can be discovered by the investigator, until 28 days after last study related procedure or 56 days after last mepolizumab administration respectively.

All SAEs / SUSARs will be recorded in the CRF and the medical notes. Reportable events will be recorded on the STH SAE form and emailed to the Sponsor within 24 hours of the research staff becoming aware of the event.

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

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

These must be recorded on the Sheffield Teaching Hospitals NHS Foundation Trust SAE reporting Form and emailed to the Sponsor's dedicated email address for this purpose within 24 hours of the research staff becoming aware of the event.

Any change of condition or other follow-up information will be emailed 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 (including judgement of causality) has been reached.

All SAEs assigned by the investigator or delegate as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be participant 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.

In addition, any pregnancy occurring within 16 weeks of last IMP dose will be followed up; see section 9.6

9.4. RESPONSIBILITIES

SAEs will be evaluated by the sponsor and investigator team with regard to ongoing safety implications. If there are ongoing safety implications for the trial then these will be addressed via urgent safety measure, substantial amendment or termination of the trial.

Duties will be as below:

Investigator/Medically qualified delegate

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and whether the event/reaction was expected using the version of the SmPC for treatment of asthma that has been approved as Reference Safety Information approved for the trial.
2. 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.
3. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was expected (in line with the Reference Safety Information).
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
6. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).
7. Notifying study team of SUSARs that occur within the trial.
8. The CI shall report all SAEs and medical device incidents arising during the Study in Study Participants exposed to the GSK IMP(s) and/or use of GSK medical device(s) (as defined by the Protocol), to GSK using copies of the original Case Report Form pages and within 24 hours of first becoming aware of the event, regardless of Investigator causality assessments against GSK IMP(s).
9. The CI will report pregnancy information on any participant who becomes pregnant while participating in the study to GSK using copies of the original Case Report Form pages and within two weeks of first becoming aware of the pregnancy. So long as they give consent, the participant will also be followed to determine the outcome of the pregnancy (including any premature termination of the pregnancy). Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be requested by GSK no longer than 6 to eight 8 weeks following the estimated delivery date

Sponsor

1. Collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.

3. Checking for (annually) and notifying CI of updates to the Reference Safety Information for the trial.
4. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

9.5.NOTIFICATION OF DEATHS

All deaths, including deaths deemed unrelated to the IMP, will be reported to the sponsor as an SAE. The report will be made to the sponsor by email within 24 hours of the event becoming known to the study team, with a review with any further information that becomes available within one week as per SAE/SUSAR reporting process.

9.6.PREGNANCY REPORTING

There are no known or expected hazards due to pregnancy during treatment with mepolizumab. Pregnancy will therefore not be considered an AE per se. However, participants becoming pregnant during the course of the trial will be withdrawn entirely from the study. The pregnancy will be reported to the sponsors within 24 hours of the pregnancy becoming known to the study team, this will also be reported to GSK. The pregnant participant will be followed up to term, and the outcome of participant and baby ascertained and recorded.

- The investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study and up to 16 weeks after the last dose of study intervention.
- Information will be recorded on the appropriate form and submitted to Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

9.7.OVERDOSE

Mepolizumab has been administered in doses of up to fifteen times the therapeutic dose to be administered. This has not resulted in adverse consequences, in line with expectation. Drug will be administered directly by the study team from pre-filled syringes and thus overdosage is highly unlikely. Were an incorrect dose to be administered this will be recorded and the sponsors informed. However, no additional monitoring will be carried out in addition to usual safety monitoring, and the participant will continue in the trial.

9.10 REPORTING URGENT SAFETY MEASURES

In the event that the CI and/or the sponsor consider urgent safety measures are required, the MHRA will be notified within 3 days.

9.11 THE TYPE AND DURATION OF THE FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE REACTIONS.

AEs and ARs will be recorded until a final telephone call 4 weeks after the final study procedure (visit 16). Participants suffering an AE or AR will be followed up until the AE or AR resolves or reaches resolution, defined as one of:

- Resolution to baseline health status
- Resolution but with sequelae
- Death

Follow up will also continue until causality is established. If necessary they will receive care as an inpatient or outpatient at Sheffield Teaching Hospital NHS Foundation Trust for diagnosis, monitoring and treatment, or directly by the study team as appropriate. Clinical records will be accessed to allow informed evaluation of the AR or AE.

9.12 DEVELOPMENT SAFETY UPDATE REPORTS

The CI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or as necessary, to the Competent Authority (MHRA in the UK), where relevant the Research Ethics Committee and the sponsor.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended

9.13 MEDICAL DEVICE INCIDENTS: DEFINITION AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study, i.e. pre-filled syringes. A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.

- A serious deterioration in state of health can include any of the following:
- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Any device incident fitting the above definition will be reported to GSK within 24 hours of awareness.

10. STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

This is a pilot study so no power calculation is possible/appropriate.

Previous hyperpolarised gas MRI studies have observed significant increases in VV% after:

- salbutamol inhalation in 14 patients with COPD (Kirby et al. 2011)
- salbutamol inhalation in 7 patients with asthma (Svenningsen et al. 2013)
- anti-T2 therapy in 10 prednisone-dependent patients with asthma (Svenningsen et al. 2020)

The aim will be to recruit 32 patients, expecting 6 to drop out due to exacerbations; leaving 26 studied (i.e. a total sample size of 32 patients is needed to account for a 19% drop out rate). For end points including a median split of data this will then leave 13 each in low and high groups. To increase the number of participants reaching the primary endpoint timepoint, we will continue to recruit participants after 30th April 2024, however these participants will only be followed up until assessment visit 2. See section 7.12.

10.2 PLANNED RECRUITMENT RATE

The aim will be to recruit 32 patients. The expected consent rate will be 1 patient per week with an expected screen fail rate averaging around 40% (significantly lower in those recruited directly from COPD clinics run by members of the study team, but higher in those responding to adverts or recruited from PIC sites). Patients will take part in the study for a planned duration of 60 weeks from the screening visit to the final telephone call. This may increase to a maximum of 72 from the time of the screening visit if there are maximum visit deferrals due to instability.

Patients will be recruited from the Sheffield Teaching Hospitals NHS FT COPD service which has patients from across South Yorkshire. Links with local primary care / GP practices will also aid recruitment, acting as PICs, and by advertisement.

10.3 STATISTICAL ANALYSIS PLAN

Statistical analysis will be performed using GraphPad Prism. All data will be assessed for normality and treated accordingly.

10.4 SUMMARY OF BASELINE DATA AND FLOW OF PATIENTS

This is not a randomised control trial so assessment of the baseline comparability of randomised groups will not take place. Baseline demographic data, and physiological measurements and measurements will be full presented as mean +/- SD or median and interquartile range as appropriate.

10.5 PRIMARY OUTCOME ANALYSIS

The co-primary endpoints will be the ventilated volume (%VV) at 12 weeks compared to the ventilated volume (%VV) at baseline and TP/gas at 12 weeks compared to TP/gas at baseline.

The 129Xe ventilation images will be segmented to measure the ventilated volume of the lungs (VV) and the co-registered proton images will be segmented to measure the total lung volume (TLV). The percentage ventilated lung volume (%VV) will be calculated as VV/TLV x 100. Segmentation will be performed using a custom-built graphical user interface based upon (Hughes et al. 2018). This has been demonstrated to improve inter-observer variability compared with basic methods and more consistent results compared to alternatives.

TP/gas will be calculated from 129Xe IDEAL images as outlined in (Collier et al. 2021).

All participants with ventilation imaging at baseline and 12 weeks or 129Xe IDEAL imaging at baseline and 12 weeks who received at least 2 of 3 doses of mepolizumab prior to the 12 week assessment will be included in the analysis. Paired t-tests or Wilcoxon matched-pairs signed rank tests will be used to assess statistical significance between %VV at baseline and %VV at 12 weeks and between TP/gas at baseline and TP/gas at 12 weeks.

10.6 SECONDARY OUTCOME ANALYSIS

Participants will be stratified into low and high exacerbation frequency groups by median split of per participants total number of exacerbations during the whole study year. Wherever median split of data is performed, any values equal to the median value will be included in the low group. To test the hypothesis that a large change from baseline to 12 weeks in MRI parameters predicts treatment efficacy (that is fewer subsequent exacerbations) over a year, changes in each MRI metric from baseline to 12 weeks in the higher exacerbation group will be compared to those in the lower exacerbation group using an unpaired t-test or a Mann-Whitney test.

Differences between all other MRI metrics at baseline (assessment 1) and 12 weeks (assessment 2) will be assessed using paired t-tests or Wilcoxon matched-pairs signed rank tests.

10.6.1 TERTIARY OUTCOME ANALYSIS

Differences between all MRI metrics at baseline (assessment 1), 12 weeks (assessment 2) and 52 weeks (assessment 3) will be assessed using repeated-measures one-way ANOVA tests or Friedman tests.

The Spearman or Pearson correlations between changes of physiological measures and changes of MRI measures between baseline and 12 weeks will be calculated, for the intervals of baseline to 12 weeks (assessment 2).

For 12 week and for 52 week time points, the Spearman or Pearson correlations between the change in each physiological and MRI metric and:

- baseline periopheral blood eosinophil count
- baseline FeNO
- change in peripheral blood eosinophil count
- change in FFeNO

will be calculated.

10.6.2 EXPLORATORY OUTCOME ANALYSIS

Participants will be stratified into low and high moderate-to-severe exacerbation frequency groups by utilising median split of participants by total number of moderate to severe exacerbations during the study year. Changes in each parameter from baseline to 12 weeks in the higher moderate to severe exacerbation group will be compared to those in the lower moderate to severe exacerbation group using an unpaired a Mann-Whitney test.

Participants will be stratified into groups with low and high improvement in health related quality of life by median split of per participant change in CAT score from baseline to final assessment at 52 weeks. To test the hypothesis that a large change from baseline to 12 weeks in MRI parameters predicts treatment efficacy (better quality of life) over a year, changes in each MRI metric from baseline to 12 weeks in the higher HRQoL improvement group will be compared to those in the lower group using an unpaired Mann-Whitney test.

Changes in baseline to 12 weeks, and baseline to 52 weeks, in CAT score will be correlated at each time point with changes in MRI derived and physiology derived endpoints, using Spearman or Pearson correlations.

The correlation of PREFUL-derived ventilation (%VV) and perfusion (%PV) metrics with the equivalent metrics from xenon ventilation and dynamic contrast enhanced perfusion MRI will also be performed.

10.7 SUBGROUP ANALYSES

Participants will be stratified into low and high exacerbation frequency groups by median split of participants by total number of exacerbations during the study year. To test the hypothesis that a large change from baseline at 12 weeks reflects treatment efficacy (that is fewer subsequent exacerbations), changes in each parameter from baseline to 12 weeks in the higher exacerbation group will be compared to those in the lower exacerbation group using an unpaired t-test or a Mann-Whitney test.

10.8 ADJUSTED ANALYSIS

There is no intention to perform adjusted analyses.

10.9 INTERIM ANALYSIS AND CRITERIA FOR THE PREMATURE TERMINATION OF THE TRIAL

As this is a pilot study and not a randomised control trail there is no intention to perform an interim analysis and there are no statistical criteria for stopping the trial.

10.10 PARTICIPANT POPULATION

All patients who receive mepolizumab at least 2 of 3 doses of mepolizumab will be included in 12 week analyses, and all those receiving at least 10 of 12 doses over 52 weeks will be included in the 52 week analysis (per protocol analysis).

10.11 PROCEDURE(S) TO ACCOUNT FOR MISSING OR SPURIOUS DATA

If data are missing the reason(s) for the missing data will be recorded on the case report form. If data essential for a given analysis are missing the affected patient will be removed from that analysis. The affected patient will still be included in independent analyses for other outcome measures. There are no plans to estimate missing outcome data. Where used the median split allocation to groups is relatively resistant to missing data, which affects each group by redistributing the remaining values between groups. This method is used as there is no a priori data to suggest a particular threshold of interest and makes no prior assumptions.

10.12 OTHER STATISTICAL CONSIDERATIONS.

There are no other statistical considerations.

10.13 ECONOMIC EVALUATION

An economic evaluation will not be undertaken.

11. DATA MANAGEMENT

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management, including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

Study participants will be assigned a unique ID number at screening to identify them throughout the study, and to link all of their clinical information on the study database and on any paper case report forms. Any correspondence between CTRU and participating centres about individual participants should reference this number instead of identifiable data.

11.1 DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION

Participant data will be collected by study staff as described in the Delegation Log.

Data will be entered on the study database from source documents (paper data collection forms). The source documents will differentiate data transcribed from the medical notes (e.g. safety bloods) and what is collected during the study visit within the paper data collection forms. The study database will be designed to capture all clinical data in a suitable format for statistical analysis.

11.2 DATA HANDLING AND RECORD KEEPING

Paper CRFs will bear the unique ID number rather than identifiable participant details such as name.

Case report forms will be designed and produced by the Sheffield CTRU, Chief investigator and trial team. The final version will be approved by key study personnel including the Data Manager, CI, Clinical Trials Manager, Statistician and Sponsor representative.

The study staff will enter data into the study database. Validation rules will be defined within Prospect, and automated validation reports will regularly check the data against these rules: discrepancies will be generated for the research team to look into. These will be investigated and resolved within the system. All data entries and corrections will be logged with the person, date and time captured within the electronic audit trail.

Imaging data will be anonymised and stored on secure computing systems at the University of Sheffield.

All data will be handled in accordance with the appropriate regulations.

11.3 ACCESS TO DATA

The study database will reside on Prospect, Sheffield CTRU's in-house data management system. Prospect uses industry standard techniques to provide security, including password hashing and encryption of data transmission using SSL/TLS. Access to the system is controlled by usernames and passwords, and comprehensive privilege management ensures that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data.

Imaging data will be accessed via secure University of Sheffield systems with permissions granted only to those carrying out analysis on these data.

Participant confidentiality will be respected at all times. No contact details will be entered on the database. All data will be identifiable by ID number and no direct identifiers will be transferred from the database to the statistician. All data will be stored and processed in accordance with the General Data Protection Regulation (GDPR).

11.4 ARCHIVING

Archiving will be authorised by the Sponsor following submission of the end of trial report. The sponsor will archive all study documents through existing SOPs and external contracts for a minimum of 15 years after the end of the study, as per local protocols. Destruction of essential documents will require authorisation from the Sponsor. The trial database will be kept by the investigators for at least 15 years, at which point storage arrangements will be reviewed, in electronic format on University of Sheffield file storage systems.

This will be stated in the PIS.

11.5 MONITORING, AUDIT & INSPECTION

- A Trial Monitoring Plan will be developed and agreed by the Sponsor based on the trial risk assessment, which may include on-site monitoring. This will be dependent on a documented risk assessment of the trial by the Sponsor.
- It is anticipated that monitoring audits will take place after the first participant first visit and last participant last visit.
- The monitoring plan will be kept in the trial master file.
- The monitoring personnel will be determined by the Sponsor.
- The processes reviewed will include participant enrolment, consent, eligibility, adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection.
- Monitoring will be performed through site visit to review original documentation.
- The investigators will host the site visits.
- The Chief Investigator and the Trial Management Team will conduct on-going monitoring of trial conduct, in particular to ensure integrity of primary source data.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1 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 and GP information letters.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the amendment and HRA amendment approval is received. Amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at the site.

All correspondence with the REC, MHRA and HRA will be retained in the Trial Master File. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

It is the Chief Investigator's responsibility to produce the annual reports as required and the Chief Investigator will notify the REC of the end of the trial. If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

12.2 PEER REVIEW

This study design was reviewed and approved in accordance with Sponsor Independent Scientific Review SOP. The statistical aspects of the study were independently reviewed by the Sponsor Statistical clinic led by the University of Sheffield Statistics Unit.

12.3 PUBLIC AND PATIENT INVOLVEMENT

The Clinical Research and Innovation Office's online PPI panel were involved in reviewing key participant facing documents. The Sheffield based Breatheasy charitable support group for those suffering from lung disease and their supporters has a history of patient involvement in both research and in clinic service evaluation and improvement. They have supplied volunteers to review patient facing documents.

12.4 REGULATORY COMPLIANCE

- The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA, Favourable REC opinion and Confirmation of Capacity and Capability (CCC) is received from the research site. PICs will not be activated until CCC has been issued the site.
- The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.
- No ionising radiation will be used during this study.

12.5 PROTOCOL COMPLIANCE

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations must be adequately documented on the relevant Sponsor-provided forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur will require immediate action

and could potentially be classified as a serious breach, at the discretion of the Sponsor.

12.6 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR THE PROTOCOL

A “serious breach” is a breach which is likely to effect to a significant degree –

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

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase

The Sponsor will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

12.7 DATA PROTECTION AND PATIENT CONFIDENTIALITY

All investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles.

Personal information will be collected by the investigators, kept secure within a room in the Clinical Research Facility that is kept locked and alarmed out-of-hours, and will be maintained by the staff of the Clinical Research Facility.

The study database will reside on Prospect, Sheffield CTRU’s in-house data management system. Prospect uses industry standard techniques to provide security, including password hashing and encryption of data transmission using SSL/TLS. Access to the system is controlled by usernames and passwords, and comprehensive privilege management ensures that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data.

Monitoring visits will take place at site to avoid any data breaches. Transmission of information relating to safety eg. SAE reports will occur by secure NHS email channels. Any sharing of data with collaborators will be anonymised.

Study source documents will be kept for a minimum of 15 years as per Sponsor protocols. The data custodian will be the CI.

12.8 FINANCIAL AND OTHER COMPETING INTERESTS

The Chief Investigator’s salary for time devoted to this research project will be covered by commercial contract with GSK. He has previously similar support from Novartis for joint research. He has worked on commercial research contracted via the NHS and Sheffield University from Pfizer, Astra Zeneca and Boehringer Ingelheim. He has received educational grants from GSK, Boehringer, Astra Zeneca and GSK. These companies have also paid expenses for educational events he has organised or at which he has spoken. He holds no direct financial interests in these or other relevant companies or institutions.

12.9 INDEMNITY

This is an NHS-sponsored research trial. If an individual suffers negligent harm as a result of participating in the trial, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an ex-gratia payment may be considered in the event of a claim.

12.10 AMENDMENTS

Any changes to the protocol or study documentation will be assessed by the Sponsor to determine the necessary approvals to be obtained (MHRA, HRA and/or REC). The Sponsor will then approve the amendment when the necessary approvals have been granted according to the sponsor's green light process.

12.11 POST TRIAL CARE

Research participants will return to standard of care at the end of the study. An abstract of pulmonary function tests and progress during the trial will be added to participant's clinical notes.

12.12 ACCESS TO THE FINAL TRIAL DATASET

The investigators identified on the delegation log will have access to the full dataset, at the discretion of the CI. Summary data will be shared with the funder (GSK). Data will not be shared with any commercial organisation other than GSK (or GSK's nominees) during the study or for a period of five (5) years from the date of completion of the Study without the prior written consent of GSK.

13. DISSEMINIATION POLICY

13.1 DISSEMINATION POLICY

- The data arising from the trial will be owned by STH, MRI scan data will be owned by UoS.
- On completion of the trial, the data will be analysed and tabulated and a Final Trial Report prepared.
- The trial report will be accessible via the EudraCT system, and on request from the CI. It will also be published in one or more portions in peer reviewed medical journal/s.
- The CI will retain the sole right to publish any of the trial data.
- The Sheffield NIHR Clinical Research Facility will be acknowledged within any publications but will not have review/publication rights of the data from the trial.
- Participants will be able to obtain a short summary of the results by letter on request.
- It will not be possible for the participant to specifically request results from the investigators.
- The disclosure of the trial protocol, full trial report, anonymised participant level dataset, and statistical code for generating the results may be made available to interested parties at the discretion of the CI, not before 1 year after study completion.

13.2 AUTHORSHIP ELIGIBILITY GUIDELINES AND ANY INTENDED USE OF PROFESSIONAL WRITERS

Individuals who contribute significantly to the development, conduct and writing up of the study will be offered authorship of the final trial report. Individually-named authors will meet the authorship criteria of The International Committee of Medical Journal Editors. No professional medical writers will be involved in the preparation of reports or publications.

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15. APPENDIX 1 – AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
AM01	1.1	9th March 2022	Lisa Watson	i) inconsistencies in the procedures around rescheduling visits and withdrawing patients where they experience exacerbations, inter-current illnesses or are unable to attend study visits have been corrected/clarified. A section to clarify what happens where a participant becomes "assessment only" has been added ii) The typographical error in the units for eosinophil counts in the inclusion criteria has been corrected iii) The number of hours that patients must withdraw their short acting bronchodilator has been corrected from 12 to 8 hours. iii) It has been clarified when paper diaries will be used. iv) spelling errors have been corrected throughout. v) Laurie Smith has been added as a protocol contributor and Stephen Kirby-Smith as the named research fellow.
AM02	2.0	30th August 2022	S Kirby-Smith	Document language changed from US English to UK English and various typographical errors corrected. Eosinophil inclusion criteria clarified to make it clear that esosinophil countcompleted on day of screening is accepted, as intended. 7.1 - Patients responding to public adverts will be sent PIS, and asked for verbal consent using a tool for the purpose of checking eligibility to participate, their record will be reviewed against inclusion & exclusion criteria. This will avoid a wasted

				visit for those who are unlikely to meet the criteria. These patients may live further afield, and this information may not be available unless requested at their GP. 7.3 Added letter given to patient to give to employer at patients choice. The letter will not identify the patients medical condition, or study title to maintain confidentiality. 7.3 - Added letter of gratitude for participants not meeting eligibility at screening/pre-screening, 7.3 - Added clause for re-invite should in the future a participant meets eligibility, for participants who previously fail screening who 7.5.2 - Visit 15 rescheduling error, inconsistent number of defferals with section 7.5.4 - CAT score is completed at visit 2, visit 5 and visit 15, this does not need to be completed at phone calls that replace treatment visits. This now matches visit schedule section 7.12 7.9. Corrected to 2 deferrals (i.e. maximum of 3 visits) 7.12 Schedule of activities updated to reflect calcium profile required at screening visit.
AM03	2.1	12/10/2022	S Kirby-Smith	6.1 Clarification of inclusion criteria “inhaled licensed triple therapy” to include those on equivalent combination of licensed triple therapy. This will therefore include patients on generic inhalers at equivalent doses, or those who take the combination but with a higher inhaled corticosteroid dose. Must still have constant dosing and achieve 12 week stability. 7.12 Schedule of activities to have a separate section for IgE level instead of being included with the RAST test. These tests are taken in different blood bottles

				using different laboratory labels. Separate row will help avoid the test being missed.
AM04	3.0	06/04/2023	L Watson	Section 2.1 clarifying that individuals with poor kidney function will not complete contrast MRI scans. Section 6.2 exclusion criteria. Update to excl criterion #1 Participants should only be excluded based on MRI screening form outcome. The rationale for this is that those with poor kidney function, but who are otherwise well enough to participate in the trial, may be included but will not receive Gadolinium contrast and will only complete non-contrast scans. Exclusion criterion #11 relating to eGFR measurement has been removed. This only relates to the safety of the contrast scan, which will be omitted, rather than other aspects of the study. Section 7.1 Recruitment has been updated to allow potential participants who have not had a recent blood test to give verbal consent to have an additional blood test as an additional screening visit. This will streamline our screening visits and prevent people who may fail on eosinophil count from having to complete all the other screening assessments. Section 7.5.1, 7.5.2. and additional footnote in section 7.12. Clarification on which MRI sequences must be completed and which may be omitted as above.
AM07	4.0	07/12/2023	L Watson	Section 7.1 Recruitment pathway has been updated to allow for recruitment via the Be Part of Research Volunteer service (BPOVRS).
AM08	5.0	Xx/04/2024	L Watson	Participants recruited to after 30th April 2024/AM08 approved will only be followed

				up to assessment visit 2. Addition of section 7.12 to cover details.