CLINICAL STUDY PROTOCOL

[Logo to be included]

Full Study Title:	**Treating severe paediatric asthma; a randomised controlled trial of mepolizumab and omalizumab**
Short Study title / Acronym:	TREAT
Product:	mepolizumab, omalizumab
Development Phase:	Phase IV
Sponsor:	Imperial College London
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This protocol describes the TREAT trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling participants for the first time are advised to contact the Trial Coordination centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination centre (ICTU).

This trial 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 the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

ACT	Asthma Control Test
AE	Adverse Event
AESI	Adverse Event of Special Interest
CACE	Complier-Adjusted Causal Effect
CASI	Composite Asthma Severity Index
C-ACT	Childhood Asthma Control Test
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CTA	Clinical Trial Authorisation
DMEC	Data Monitoring and Ethics Committee
EMA	European Medicines Agency
EPX	Eosinophil Peroxidase
FeNO	Fractional Concentration of exhaled Nitric Oxide
GMP	Good Manufacturing Practice
HRA	Health Research Authority
DA	Difficult Asthma
ICS	Inhaled corticosteroids
ICTU	Imperial Clinical Trials Unit
IQR	Interquartile Range
ITT	Intention to Treat
MCMC	Markov Chain Monte Carlo
NI	Non-inferiority
OCS	Oral Glucocorticoids
PAQLQ	Paediatric Asthma Qualify of Life Questionnaire
PICU	Paediatric Intensive Care Unit
PP	Per Protocol
PSA	Problematic Severe Asthma
RDA	Refractory Difficult Asthma
REC	Research Ethics Committee
SAE	Serious Adverse Event

STRA	Severe Therapy Resistant Asthma
TMG	Trial Management Group
TSC	Trial Steering Committee

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1. BACKGROUND

1.1 The problem to be addressed

Over 1 million children in the UK are diagnosed with asthma. Although the majority of school-aged children (>95%) with asthma have mild to moderate disease which can be controlled with relatively low and safe doses of maintenance inhaled corticosteroids (ICS), there is a minority who have persistent poor control and/or frequent asthma attacks despite maximal prescribed maintenance therapy. This group, with problematic severe asthma are a significant clinical challenge as they have marked morbidity[1] utilise more than 50% of all healthcare resources for asthma[2,3] and are at increased risk of asthma death[4]. Improving control and reducing risk for children with problematic severe asthma is therefore an urgent unmet clinical need[5].

1.1.1 Identification of children with true severe therapy resistant asthma (STRA)

Problematic severe asthma is an umbrella term used to describe all children aged 6-16 years with on-going asthma symptoms or frequent asthma attacks despite maximal conventional treatments[6]. Of these, there is a sub-group in whom persistent symptoms result from a failure of basic asthma management, and are termed “Difficult Asthma” (DA). These children do not need add-on therapies to improve control, but require interventions that will help to address and optimize basic management, such as adherence. However, there remains a group of children who have a confirmed asthma diagnosis and persistent poor control despite maximal therapy after the basics of management have been addressed. This minority have true severe therapy resistant asthma (STRA)[7-9]. The most common reason for a failed response to prescribed therapy, and inappropriate escalation of treatment, is poor adherence to maintenance ICS[10,11]. Systematic literature reviews have identified a mean level of adherence to ICS of only 22–63%[12], with even lower adherence in at-risk populations, including 20–33.9% in children[13]. Adherence monitoring is recommended particularly for patients with severe asthma because of the associated high morbidity and mortality, and is now a recommendation included in the British Thoracic Society Guidelines for the management of asthma[14].

Therefore, prior to escalation of therapy, it is essential that adherence to maintenance therapy is objectively assessed in all children with problematic severe asthma in order to identify those with poor adherence and poor control, for whom improved adherence to ICS, rather than therapy escalation is the desired intervention. Currently, there is marked variation in adherence assessment between centres in the UK. Most centres undertake an assessment of prescription uptake for maintenance ICS over the last 12 months to estimate adherence. However, this does not provide a reliable evaluation of actual medication used. Indeed, home visits have demonstrated stock piling of inhalers that remain unused[15]. The use of objective, real-time measures to monitor adherence can overcome the limitations of using prescription checks alone[16]. Electronic monitoring devices which can be attached to the ICS inhaler and provide objective, reliable, and precise data, on the time and date of administration of each dose, are considered the current gold standard to assess adherence[14]. We have shown approximately 58% of all children with problematic severe asthma have poor adherence (<80%) to maintenance therapy when monitored using electronic devices. Intervention studies that have used electronic monitoring with audio-visual reminder functions have shown significantly improved adherence in children given an electronic monitor compared to controls[17]. This programme will be the first to ensure STRA is only diagnosed in children that have persistent poor asthma control after they have been

shown to have satisfactory adherence (taking ICS ≥80% of monitoring period)[8] to maintenance therapy using electronic monitoring.

1.1.2 The challenge of managing children with Refractory Difficult Asthma

It is recognised that there is a sub-group of children with problematic severe asthma who have poor control because of persistent poor adherence despite maximal efforts to encourage adherence. This group are termed Refractory Difficult Asthma (Refractory DA)[18,19] and are a significant clinical concern. The 2014 UK National Review of Asthma Deaths has shown 39% of asthma deaths were in patients with severe asthma, of whom >60% had Refractory DA[4]. Current guidelines do not make any recommendations for add-on therapies in this very high risk group.

1.1.3 The pathophysiology of paediatric STRA

As a group, children with STRA have reversible airflow obstruction, significant airway eosinophilia and marked structural changes of the airway wall (airway remodelling)[20,21]. Of note, the airway eosinophilia persists despite high dose maintenance steroid therapy. In contrast to adults, children with STRA do not have an increase in tissue mast cells or airway neutrophils[20,22]. A very consistent feature of paediatric STRA is the presence of severe sensitisation to multiple aero-allergens, and those with concomitant food allergy appear to have the most severe disease[9,20]. Although the overall phenotype of paediatric STRA is allergen driven and would therefore suggest a T helper 2 (Th2) mediated disease, airway Th2 cytokines including interleukin (IL)-5 and IL-13 are difficult to detect and levels are variable between patients[20,23,24]. Paediatric STRA is therefore a markedly heterogeneous disease, characterized by clinical, pathological and physiological diversity[20,25-27]. It is important to obtain a picture of the airway pathology for each child to help determine a molecular phenotype and identify optimal targeted therapies. In contrast to adults with Th2 mediated disease, at present, there are no reliable non-invasive biomarkers that allow an assessment of phenotype in children. The gold standard for an assessment of lower airway pathology is therefore to undertake a flexible bronchoscopy and obtain samples including broncho-alveolar lavage and endobronchial biopsies for phenotypic assessments and also to exclude upper airway structural abnormalities that might be contributing to poor symptom control[7,28]. This can be done safely at specialist centres[29].

1.2 Treatments for STRA

1.2.1 Omalizumab: the add-on therapy currently available at all centres for paediatric severe asthma

One of only two licenced add-on therapies ("biologic") for children with severe asthma is omalizumab, a therapeutic humanized monoclonal antibody specific for IgE. Its mechanism of action is neutralisation of circulating free IgE, which leads to reduction in the quantity of cell-bound IgE, downregulation of high-affinity IgE receptors, and, eventually, prevention of mediator release from effector cells[30]. While omalizumab therapy has been associated with an overall reduction of asthma attacks and health-care utilization[31], the quality of available evidence in children under 12 years of age remains very low[9] and non-response is common. A systematic review of placebo-controlled trials of omalizumab as add-on therapy in children aged 6-18 years could only include 3 trials and a total of 1381 participants[32]. Treatment with omalizumab was associated with fewer asthma exacerbations in comparison with placebo, (number needed to treat = 7). This effect was independent of the length of the treatment[32].

1.2.2 Limitations of omalizumab in paediatric STRA

Although overall omalizumab is beneficial in paediatric moderate-severe asthma, there are several limitations to its use. 1. Benefit has only been shown for a single outcome measure; reduction in exacerbations, there was no improvement in lung function[32]. 2. None of the children included in clinical trials of omalizumab to date have undergone prior objective monitoring for ICS adherence. 3. Current criteria for its use are based on serum IgE levels between 30-1500 IU/ml, even though there is evidence for efficacy in asthmatic adults with higher and lower IgE levels[33,34] and safety in children with other allergic conditions with higher IgE levels[35,36]. These IgE criteria significantly limit its use because approximately 15% of children with STRA have IgE levels >1500 IU/ml, driven by other concurrent allergic diseases (eczema, food allergies) and approximately 10% <30IU/ml[20]. There are no clinical predictors as to which children will respond to omalizumab (about 30-50% have a poor clinical response to a trial of treatment). There is therefore a need to identify predictors of clinical benefit from omalizumab for children with STRA to allow stratification of patients to decide the optimal add-on therapy for each child. In addition, the serum IgE range within which omalizumab can currently be prescribed, and has been derived from studies in adults, needs to be confirmed or otherwise in children.

1.2.3 Mepolizumab in paediatric STRA

Increasingly, phenotype-directed therapies, specifically therapies that target eosinophilic inflammation, are emerging for use in adult severe asthma[37]. One of these, mepolizumab, was licenced for use in children aged 6 years and over in Europe in August 2018, but neither its efficacy nor mechanism of action in paediatric severe asthma populations known. Given the differences between paediatric and adult STRA (above) it is not safe to extrapolate findings from adult studies into children.

The fundamental inflammatory phenotype in most paediatric STRA is a steroid resistant airway eosinophilia[20,38,39]. Despite this, few studies that have targeted airway eosinophils have been undertaken in children with severe asthma. Disappointingly, one paediatric study that compared the effect of titrating maintenance inhaled steroid therapy according to sputum eosinophils, or to clinical guidelines and symptoms based management, showed no benefit of the eosinophil guided strategy in reducing exacerbations in severe asthma[40]. This was in contrast to a prior study undertaken in adults[41]. There are several explanations for this; firstly, paediatric STRA is associated with a steroid resistant eosinophilia, thus titration of steroid dose is unlikely to be effective, and secondly, it is known that *numbers* of airway eosinophils may vary in children over time independently of clinical status[42]. In addition, adolescents in clinical asthma remission have evidence of tissue eosinophilia[43]. However, the functional or activation status of eosinophils may be more important in determining effector responses than numbers alone[44]. Eosinophil peroxidase (EPX) can be measured as a marker of eosinophil numbers and/or degranulation and can be used to reflect eosinophil activation[45]. A significant advantage over other eosinophil granule proteins such as eosinophilic cationic protein is that EPX is eosinophil-specific and is not elevated in patients with more neutrophilic conditions[46]. Moreover, our preliminary data shows higher levels of EPX in sputum from children with STRA compared to those with Difficult Asthma.

Mepolizumab is a humanized monoclonal antibody against IL-5 which is a cytokine involved in the maturation, recruitment and activation of eosinophils. The effect on eosinophil activation makes this an attractive target for paediatric STRA. It has been licenced for use

as an add-on treatment in adult severe eosinophilic asthma for several years[8]. The first large scale clinical trial to show benefit was the DREAM study in 13 countries that included 621 patients in which mepolizumab significantly reduced the rate of clinically relevant asthma attacks[47]. Subsequently, it has been shown that adding mepolizumab for those dependent on oral glucocorticoids (OCS) for asthma control, enabled the daily OCS dose to be significantly reduced[48]. Although children aged >12 years were eligible for inclusion in the trials that have been undertaken, only a very small number were included (Prof Ian Pavord, personal communication to SS), thus preventing an assessment of efficacy in children. However, no differences in adverse effects were observed in the adolescent group enrolled in the phase 3 trial compared to the overall population[47]. A clinical trial studying the pharmacological properties of subcutaneous administration of mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma has been undertaken to determine safety and optimal dose in younger children. The results of this study have been published[49] and the correct dose of mepolizumab in this age group has been defined. Safety has been demonstrated in children aged >6 years with eosinophilic oesophagitis[50] and the dose for asthma was based on this.

Given the pathophysiology of paediatric STRA and the potential for benefit from a therapy that targets airway eosinophils and atopy, it is hypothesised that mepolizumab will provide similar clinical benefit compared to omalizumab in children with STRA and Refractory DA.

1.3 Benefits and risks

1.3.1 Benefits

- The benefits of our study include the development of a unified, national approach to the management of children with STRA which includes an extended run-in period of objective adherence monitoring of maintenance therapy to accurately identify and exclude those with Difficult Asthma. Despite electronic monitoring and a further period of enhanced monitoring some children may remain with poor adherence; defined as 'Refractory Difficult Asthma'. These patients are at particularly high risk of asthma death[4] and will thus be included in the intervention study; they have not previously been assessed (see Figure 1).
- A significant additional benefit is the investigation of the clinical efficacy and mechanism of action of mepolizumab in paediatric STRA and Refractory DA. The efficacy of this drug has not been tested to date in children that have been accurately clinically and pathologically phenotyped, and thus we will be able to answer whether a therapy that targets eosinophils will be as beneficial in children as omalizumab, which targets IgE.
- The larger benefits to society include improved control of asthma in paediatric patients with severe disease. These patients currently utilise 50% of all healthcare resources for asthma; therefore, although drug costs are high, they will not amount to more than the cost of recurrent hospitalisations for acute attacks. A recent meta-analysis of adult studies has shown mepolizumab approximately halved hospitalisations or emergency department visits in patients with severe eosinophilic asthma[51]. Moreover, both drugs are administered by healthcare professionals by subcutaneous injections thus ensuring adherence to therapy. This trial will also address the significant clinical unmet need of children who die of asthma, specifically those with Refractory DA.

1.3.2 Risks

- ***Clinical flexible bronchoscopy:*** The bronchoscopy is undertaken clinically at all centres. It involves a general anaesthetic but the safety of the procedure, when undertaken during stable disease and in a specialist centre, is established. It is a clinically indicated procedure in STRA. Moreover, all of the procedures that will be undertaken during the bronchoscopy, including broncho-alveolar lavage, endobronchial brushings and biopsy, all have proven safety when taken for research or for clinical purposes[29,52,53].
- ***Safety of the interventional drugs:*** Omalizumab has proven safety in children and is therefore unlikely to result in undue risk. The safety of mepolizumab has been shown in children ≥12 years, and safety in those aged between 6 and 11 years has been evaluated by the manufacturer. We have been informed that the results of the safety and dosing study will be shared with us prior to us undertaking our trial. We will therefore finalise the dose in collaboration with the manufacturer. A previous study of mepolizumab in children aged 2-17 years in eosinophilic oesophagitis, did not report any serious adverse events associated with the drug[54].
- ***Trial design and duration:*** The trial design involves 2 or 4 weekly visits. This is a requirement of the interventions, which have to be given subcutaneously in hospital. This would be the same if the drugs were being used clinically. We have done our best to optimise the trial design to limit the duration, however, a 52 week intervention is needed to fully assess drug efficacy using asthma exacerbations as the primary outcome measure.
- ***Differences in drug administration regimens:*** This proposal includes two biologics with different administration regimens. The dose and frequency of omalizumab administration is determined by the child's weight and serum IgE level and means that children may need between 1 and 4 injections either 2 or 4 weekly. Mepolizumab is only administered as a single injection 4 weekly. After discussion with our Patient and Public Involvement (PPI) groups, it became apparent that children and families would be very reluctant to participate in a trial that involves placebo injections over 52 weeks. We have therefore decided to undertake a pragmatic, open label trial. This will allow us to optimise recruitment and retain children in the trial for the full duration. The primary outcome is objective (≥3 day course of oral steroids, prescribed by a healthcare professional or admission to hospital) which is unlikely to be affected by the open label design.

1.3.3 Rationale for this study

Risk factors for childhood asthma death include severe atopy, persistent eosinophilia and median prescription pick up less than 50% expected[4], all of which are central to the pathophysiology of paediatric STRA and Refractory DA. These children have a markedly impaired quality of life, and the economic burden is significant, driven by costs from hospital visits, admissions, medications, missed school days and parental days off work. Critically, there is a significant life-long impact of childhood severe asthma on lung health. Both clinical and lung function outcomes in adult life are strongly determined by asthma severity in childhood, and severe asthmatic children have a 32-fold higher risk of developing chronic obstructive pulmonary disease (COPD)[55] . Early life interventions to minimise exacerbations and consequent lung function deficits are therefore essential. At present, it is uncertain how many children have STRA and Refractory DA and need expensive biologics, our preliminary data suggest it is approximately 45% of all with problematic severe asthma[17]. In order to undertake planning of healthcare resources, it is essential that we accurately identify those children with refractory disease.

1.3.4 Unmet need in the management of paediatric STRA and Refractory DA

1. Efficacy of therapeutic agents that reduce eosinophilic inflammation (Mepolizumab)

Trials of the efficacy of monoclonal antibodies that target IL-5 have not been undertaken in children with STRA, but given the prevalence of airway eosinophilia and the potential impact of anti-IL-5 antibody on eosinophil function, this is an obvious avenue to pursue. There has been one recent open-label trial in children that has reported long-term safety and dosing, but decisions about efficacy cannot be made from that trial as it was not designed to assess efficacy[49,56]. We will investigate whether mepolizumab is as effective as omalizumab in reducing asthma attacks in children with STRA and Refractory DA, and we will determine its mechanism of action in children. We hypothesise that mepolizumab will provide similar clinical benefit to omalizumab in children with STRA and Refractory DA by reducing eosinophil activation status assessed by change in eosinophil peroxidase levels in sputum and blood.

2. Stratification of patients to identify who will respond to an add-on therapeutic

Currently, all children with paediatric severe asthma who are eligible for omalizumab are given a 16 week clinical trial and those that have a clinical response (improvement in symptom control and quality of life scores) continue. Beyond the licensing and NICE criteria (extrapolated from adult studies), there is no application of specific selection criteria to decide which children should have a clinical trial of omalizumab. Given a) the marked clinical phenotypic heterogeneity of paediatric STRA, b) we do not distinguish STRA from Refractory DA prior to prescribing omalizumab, c) ≈ 30% of children are ineligible for omalizumab because of a serum IgE outside current licence indications, and c) at least a further 30% have a failed clinical response, it is apparent that we need to determine an optimal serum IgE range for children. This is a significant unmet need that has been recognised which to date has been ignored for children. We now want to examine whether omalizumab is beneficial in children with an IgE outside the recommended range and whether blood eosinophils can be used to determine response to mepolizumab.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To determine whether mepolizumab is as efficacious as omalizumab in reducing asthma attacks in children with STRA and Refractory DA.

2.2 Secondary objectives

1. To determine whether efficacy of omalizumab is determined by serum IgE
2. To determine whether efficacy of mepolizumab is determined by blood eosinophils
3. To identify children with STRA and Refractory DA that require biologics by implementing a run-in period of electronic adherence monitoring
4. Explore the relationship between the rate of asthma attacks in children receiving omalizumab and serum IgE.
5. Explore the relationship between the rate of asthma attacks and blood eosinophils and serum and sputum eosinophil peroxidase levels in children receiving mepolizumab.

2.3 Exploratory objectives

1. Identify a paediatric STRA and Refractory DA molecular phenotype using transcriptomic analysis and detailed assessments of inflammatory mediators of lower airway samples

2.4 Primary outcome

52-week asthma exacerbation rate; defined as the number of asthma attacks requiring high dose oral steroids for 3 or more days or admission to hospital.

2.5 Secondary outcomes

1. Composite asthma severity index (CASI)[57] at weeks 4, 16, 52
2. Paediatric asthma quality of life questionnaire (PAQLQ) score (4 weekly)
3. Lung function (FEV_1, bronchodilator reversibility) 4 weekly
4. Exhaled nitric oxide – 4 weekly
5. Asthma control test (ACT) score – 4 weekly
6. Inhaled corticosteroid dose – 4 weekly
7. Sputum inflammatory cell count and eosinophil peroxidase – at weeks 4, 16, 52
8. Patient burden (number of visits and injections, a patient assessed visual analogue scale)

2.6 Exploratory outcomes

1. Identification of an epithelial gene signature for STRA and Refractory DA using transcriptomics analysis of bronchial epithelial cells.
2. Identification of an inflammatory mediator or gene signature from bronchoalveolar lavage, induced sputum or bronchial epithelial brushings that predicts clinical response to omalizumab or mepolizumab.
3. Identification of single nucleotide polymorphisms (SNPs) from whole blood genotyping that predict response to either omalizumab or mepolizumab
4. Defining the mechanism of action of mepolizumab by assessing the impact on blood and sputum eosinophil numbers and activation status before and at weeks 4, 16, 52 after randomisation
5. Understanding the impact of omalizumab and mepolizumab on the nasal and lower airway microbiome

2.7 Summary Table of Objectives and Outcomes

Table 1. Objectives and outcomes

Objectives	Outcomes	Timepoint(s) of evaluation of this Outcome
Primary objective To determine whether mepolizumab is as efficacious as omalizumab in reducing asthma attacks	**Primary outcome** Number of asthma attacks by 52 weeks (> 3 day course of high dose oral steroids)	52 weeks

in children with STRA and Refractory DA.		
Secondary objectives 1. To determine whether efficacy of omalizumab is determined by serum IgE 2. To determine whether efficacy of mepolizumab is determined by blood eosinophils 3. To identify children with STRA and Refractory DA that require biologics by implementing a run-in period of electronic adherence monitoring 4. Explore the relationship between the rate of asthma attacks in children receiving omalizumab and serum IgE. 5. Explore the relationship between the rate of asthma attacks and blood eosinophils and serum and sputum eosinophil peroxidase levels in children receiving mepolizumab.	**Secondary outcomes** 1. Composite asthma severity index (CASI) at weeks 4, 16, 52 2. Paediatric asthma quality of life questionnaire (PAQLQ) score (4 weekly) 3. Lung function (FEV_1, bronchodilator reversibility) 4 weekly 4. Exhaled nitric oxide – 4 weekly 5. Asthma control test (ACT) score – 4 weekly 6. Inhaled corticosteroid dose – 4 weekly 7. Sputum inflammatory cell count and eosinophil peroxidase at weeks 4, 16, 52 8. Patient burden (number of visits and injections, a patient assessed visual analogue scale)	
Identify a paediatric STRA and Refractory DA molecular phenotype using transcriptomic analysis and detailed assessments of inflammatory mediators of lower airway samples	1. Transcriptomics analysis of bronchial epithelial cells. 2. Identification of an inflammatory mediator or gene signature from bronchoalveolar lavage, induced sputum or bronchial epithelial brushings that predicts clinical response to omalizumab or mepolizumab.	

	3. Identification of single nucleotide polymorphisms (SNPs) from whole blood genotyping that predict response to either omalizumab or mepolizumab 4. Defining the mechanism of action of mepolizumab by assessing the impact on blood and sputum eosinophil numbers and activation status before and at weeks 4, 16, 52 after randomisation 5. Understanding the impact of omalizumab and mepolizumab on the nasal and lower airway microbiome	

3. STUDY DESIGN

This study will be performed at 11 investigational sites in the UK. Patients will be randomised to one of 2 treatments, as shown in Table 2. Omalizumab or mepolizumab will be administered in hospital every 2 to 4 weeks for 52 weeks.

3.1 Design

A multi-centre, parallel arm, randomised, controlled, non-inferiority trial of mepolizumab and omalizumab with a run-in to identify STRA and Refractory DA.

3.2 Treatment Regimens

Recruited eligible participants will be randomised (1:1) to either omalizumab or mepolizumab. Omalizumab administration is determined by the patient's weight and serum IgE level and means that patients may need between 1 and 4 subcutaneous injections either 2 or 4 weekly for 52 weeks. Mepolizumab is administered as a single injection 4 weekly.

Table 2: Summary of treatment groups

Treatment arm	Number of patients	Treatment
1	75	Omalizumab 75 to 600mg ever 2-4 weeks
2	75	Mepolizumab 40mg (6-11yrs) or 100mg (≥12 yrs) every 4 weeks
Total number of subjects	150	

4. TRIAL FLOW CHART

Figure 1. Extended run-in with adherence monitoring to identify children with severe therapy resistant asthma (STRA) and Refractory Difficult Asthma (Refractory DA)

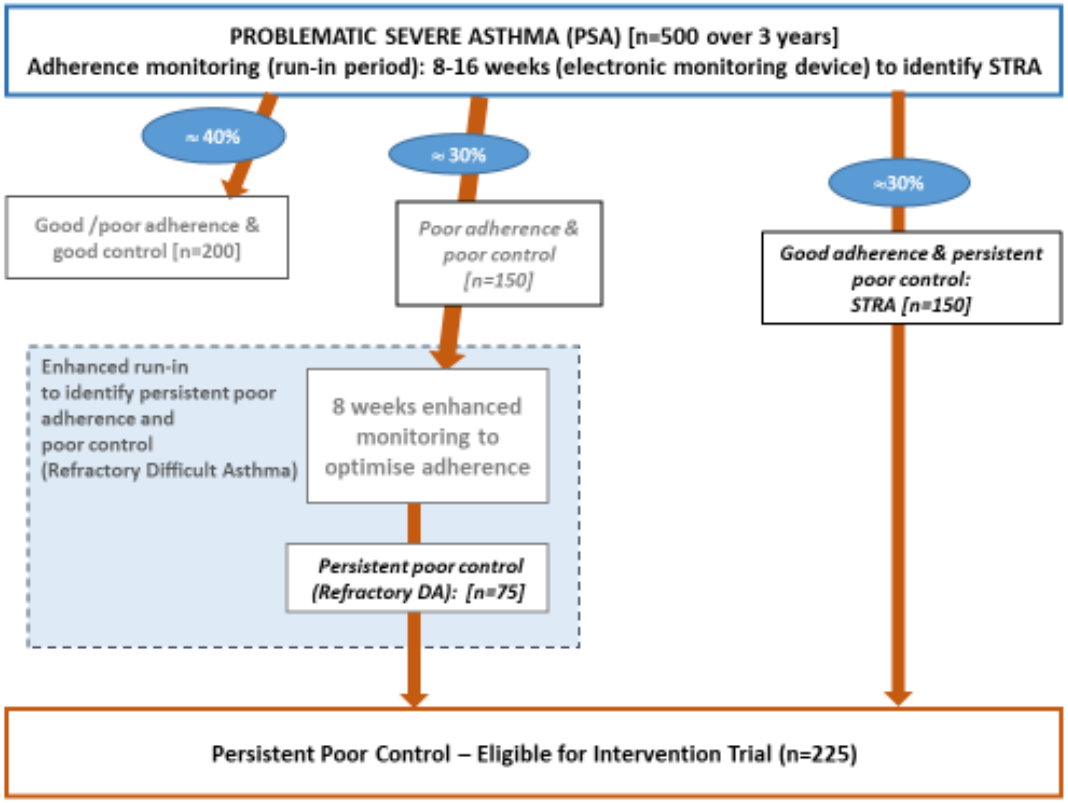
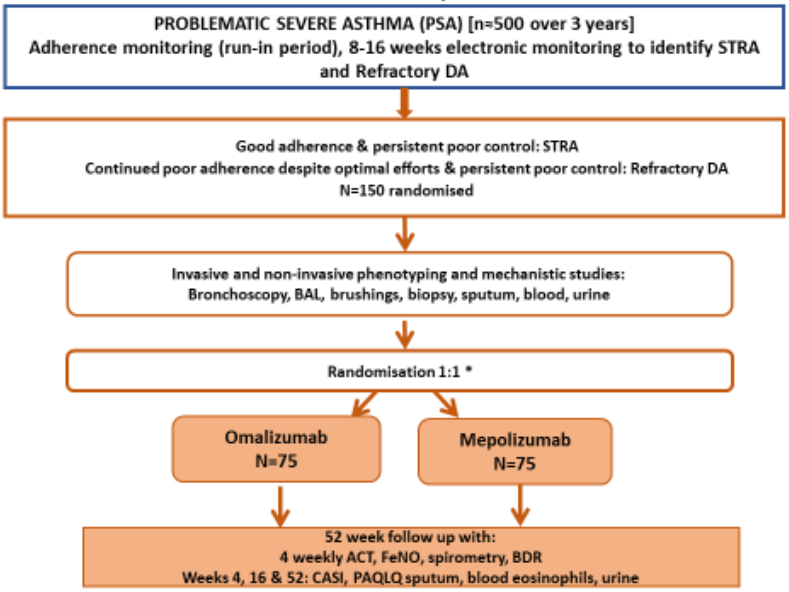


Figure 2. Trial design flow chart: A non-inferiority trial to determine whether mepolizumab is as effective as omalizumab in paediatric severe asthma



Primary outcome: Number of asthma attacks by 52 weeks (≥ 3 day course of high dose oral steroids)
Secondary outcomes: composite asthma severity index (CASI), lung function, inflammation, quality of life
* **Randomisation** (minimisation) stratified by blood eosinophils (</> 300), IgG(< 30, 30-1500, > 1500), STRA/Refractory DA

5. PARTICIPANT ENTRY

5.1 Study Population

Children with severe asthma will be recruited from eleven specialist paediatric severe asthma centres in the UK.

5.2 Inclusion criteria for run-in phase

1. Written informed consent
2. Children aged 6 – 16 years
3. Female patients capable of becoming pregnant* must agree to use hormonal contraception, intrauterine device, intrauterine hormone-releasing system, or to complete abstinence** for the duration of the trial and up to 100 days after the last dose of IMP.
4. Confirmed diagnosis of asthma***
5. Poor asthma control**** despite being prescribed high dose therapy*****[8]

** Females capable of becoming pregnant are defined as: fertile, following menarche and until unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.*

***Complete abstinence (defined as refraining from heterosexual intercourse) must be in line with the preferred and usual lifestyle of the participant. Barrier contraception, periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods), withdrawal and progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action are not acceptable methods of contraception.*

*****Confirmation of asthma diagnosis, one or more of:**

- Airway hyper-responsiveness confirmed by direct or indirect challenge
- Documented bronchodilator reversibility (≥12%)
- Recorded evidence of spontaneous variation in FEV1 (≥12%) or peak flow (≥20%) in the past year

******Definition of poor control, at least 1 of the following:**

- Recurrent severe asthma attacks in the past year (≥4 per year if on high dose inhaled corticosteroids OR ≥2 per year of on maintenance oral corticosteroids) requiring either hospital admission or high dose OCS for at least 3 days)
- A single PICU admission in the past year

*******Definition of high dose therapy, either of:**

- Maintenance inhaled corticosteroids (budesonide ≥800μg/day or fluticasone ≥500μg/day) or equivalent (as defined in the BTS/SIGN guidelines 2016) plus a long acting β2 agonist plus montelukast (or previous failed trial) or trial of other add on therapy such as theophylline
- Maintenance daily or alternate day oral corticosteroids

Adherence to inhaled corticosteroids to be assessed during run-in:
All participants will undertake a period of adherence monitoring using electronic monitoring devices following enrolment in the study.

- Those with ongoing poor control (ACT / cACT<20) and monitored adherence of ≥80% will be eligible for intervention study.
- Those with >/=1 attack (defined as 3 days of high dose OCS or hospital admission) and monitored adherence of ≥80% at the end of this period will be eligible for the intervention study.
- Those with on-going poor control and monitored adherence of <80% will enter a period of enhanced monitoring.

5.3 Inclusion criteria for RCT phase

1. Written informed consent
2. Children aged 6-17 years
3. Confirmed diagnosis of asthma with:
   i) Persistent poor control*/ >/= 1 attack after adherence assessment with ≥80% adherence during run-in (STRA) **OR**
   ii) Persistent poor control* and poor adherence despite optimal efforts to improve adherence, including enhanced monitoring (Refractory DA)

***Persistent poor control defined as at least one of the following:**

- Control Test (ACT) or Childhood Asthma Control Test (cACT) score of <20
- ≥1 severe attack requiring either hospital admission or high dose oral corticosteroids for at least 3 days during the adherence monitoring period

5.4 Exclusion criteria for run-in and RCT phase

1. As a result of medical interview, physical examination or screening investigation the physician responsible considers the child unfit for the study or has a risk of non-compliance with study procedures.
2. Hypersensitivity to Omalizumab or Mepolizumab or to any of the excipients.
3. The child has a history of drug or other allergy, which, in the opinion of the responsible physician, contra-indicates their participation.
4. Participant is female who is pregnant, lactating or within 6 weeks post-partum or breast feeding.
5. The child has participated within 3 months in a study using a new molecular entity, another study investigating drugs or in a study with invasive procedures.
6. Significant alternative diagnoses that may mimic or complicate asthma, in particular dysfunctional breathing, panic attacks, and overt psychosocial problems (if these are thought to be the major problem rather than in addition to severe asthma)
7. Significant other primary pulmonary disorders in particular cystic fibrosis, or interstitial lung disease
8. Diagnosis of chronic inflammatory diseases other than asthma (e.g. inflammatory bowel disease)

6. PROCEDURES AND MEASUREMENTS

6.1 Identification and recruitment of patients

Patients will be identified and recruited at 11 Specialist Paediatric Severe Asthma Centres within the UK. Identification of potential eligible children may also occur at Patient Identification Centres (PICs) located close to the specialist paediatric centres.

The trial will be registered on the National Institute of Health Research (NIHR) Clinical Research Network (CRN) Portfolio, enabling eligibility for National Health Service (NHS) service support costs and interaction with the UK Clinical Research Facilities and the Study Support Service.

6.2 Visit Schedule

Visit	Screening	Baseline adherence monitoring[1] (N = 500)	Follow up adherence monitoring visit[2] (N= 500)	Bronchoscopy visit[3] (N=150)	Randomised controlled trial (N=150; 75 vs 75)													
Visit number	1	2	3	4	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Time	Day 1	0 – 28 days post screening	3 - 4 mnths post baseline	Within 1 month of visit 3	Wk 0 / Baseline	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52 / End of study
Window		min 0d / max 28d (post visit 1)	min 91d / max 122d (post visit 2)	min 0d / max 30d (post visit 3)	Bronch visit +/- 14d	BL +/- 7d	Wk4 +/- 7d	Wk8 +/- 7d	Wk12 +/- 7d	Wk16 +/- 7d	Wk20 +/- 7d	Wk24 +/- 7d	Wk28 +/- 7d	Wk32 +/- 7d	Wk36 +/- 7d	Wk40 +/- 7d	Wk44 +/- 7d	Wk48 +/- 7d
Informed consent	X																	
Algorithm for inclusion/exclusion	X																	
Pregnancy test (female post-pubertal pts)[4]	X				X													
Randomisation					X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics	X																	
Asthma / exacerbation history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Past medical and drug history	X																	
Current medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
cACT/ACT		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mini PAQLQ		X	X	X		X			X									X
CASI		X	X	X		X			X									X
IMP (omalizumab / mepolizumab)[5]					X	X	X	X	X	X	X	X	X	X	X	X	X	
Pulmonary function testing																		
Spirometry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BDR		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Labs																		
Urine sample		X		X		X			X									X
Saliva for cotinine		X																
Full Blood Count		X		X		X			X									X
Eosinophils		X		X		X			X									X
Vitamin D3 level		X																
Total IgE		X																
Specific IgE RASTs		X																
Genotype (blood)		X																
Other study bloods		X				X												
Inflammometry																		
Sputum induction and processing				X		X			X									X
Exhaled nitric oxide (50ml/sec)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other procedures																		
Electronic monitoring device given		X																
Skin prick tests		X																
Bronchoscopy				X														
Broncho-alveolar lavage				X														
Endobronchial biopsy				X														
Endobronchial brushings				X														
Nasal brushings				X														
Nasosorption				X														
oropharyngeal swab				X		X			X									X
nasal swab				X		X			X									X
eNOSE (sub-study only)			X						X									X

Notes

1. Screening and baseline visits can take place on the same day in which case assessments do not need to be repeated
2. Participants with poor control and poor adherence at the end of the monitoring study may undergo one further period of enhanced monitoring; baseline and follow up assessments will be repeated
3. Only those participants with ongoing poor control despite good adherence proceed to bronchoscopy study
4. When menarche occurs after screening or randomisation visits, a pregnancy test will be performed before the drug is administered to a patient.
5. Some participants will receive 2 weekly injections. Study drug will be given, vital signs observed, AEs tracked.

Key for costing categories

Standard treatment	
Treatment/Excess treatment cost	
Support cost	
Research cost	

6.3 Screening

Written informed consent will be obtained before the patient undergoes any research procedures, including screening tests required by the study.

6.4 Randomisation

In order to conceal treatment allocation, minimisation (with a 10% random component) will be performed using an online randomisation system. Stratification variables will be blood eosinophils (<300/≥300 per mcl)[58] and IgE (<30, 30-1500, >1500IU/ml) and STRA or Refractory DA.

6.5 Run-in phase visits

The following assessments will be carried out at the baseline run-in visit: demographics, asthma history, allergy history, skin prick tests for atopy, asthma medication, exacerbation history, ACT/cACT, PAQLQ, CASI, lung function (spirometry), FeNO, saliva for cotinine, urine, blood tests (total IgE, specific IgE, vitamin D, eosinophils, genotype), unless done in the last 12 months.

All patients will be given an electronic monitoring device at the run-in phase baseline visit.

Patients will be followed up 8-12 weeks after baseline and the following will be carried out: adherence assessment; ACT/cACT, PAQLQ, CASI, treatment changes, exacerbation history, spirometry, FeNO.

6.6 Flexible bronchoscopy visit

For children meeting the criteria to proceed to the RCT phase of the study, a bronchoscopy visit will be arranged within a month.

Children identified with STRA and Refractory DA (persistent poor control through either electronic or enhanced adherence monitoring) will undergo a clinically indicated bronchoscopy. As this will be a clinically indicated procedure, if the child's clinician does not think a bronchoscopy is needed, it will not be undertaken. Specifically, children that have had a bronchoscopy in the previous 6-12 months may not undergo a repeat procedure.

Samples to be taken at bronchoscopy (with informed consent from participants and carers) include blood, broncho-alveolar lavage, endobronchial biopsies and endobronchial brushings, nasal brushings, nasal and oropharyngeal swabs, nasosorption. Of these, all except the bronchoalveolar lavage will be additional samples for research.

Assessments of inflammation, specifically eosinophil activation and function, will be made in bronchoalveolar lavage and endobronchial biopsy, in addition, the molecular gene signature and phenotype will be defined by undertaking transcriptomics analysis of nasal and bronchial epithelial cells. Assessments of infection (bacterial culture and viral PCR) will be undertaken in bronchoalveolar lavage as per routine clinical practice in each hospital laboratory, additional broncho-alveolar lavage and brushings and the nasal and oropharyngeal swabs will be used to assess the lower airway microbiome. Blood tests to assess eosinophil count, eosinophil peroxidase, total IgE will be taken at bronchoscopy.

6.7 Baseline visit – RCT phase

The baseline visit for the RCT phase will include: physical examination; CASI, ACT/cACT; PAQLQ, lung function, FeNO, asthma medication, exacerbation history, sputum induction (cell count, eosinophil peroxidase), urine, saliva and research blood tests.

6.8 4-weekly visits

4 weekly visits until intervention complete (52 weeks) will include: administration of omalizumab or mepolizumab, physical examination; ACT/cACT; exacerbation history; PAQLQ; lung function; FeNO; treatment changes.

Children with the highest doses of omalizumab will attend visits 2-weekly to have their omalizumab. Vital signs will also be checked at these 2-weekly visits.

6.9 Research assessment visits (4, 16 weeks)

At the above time points, the visits will include the following additional assessments: CASI, induced sputum for inflammation, research bloods (week 4 only), eosinophil peroxidase, urine, nasal and oropharyngeal swabs, eNose at selected centres.

6.10 End of study visit (52 weeks)

The final study visit will take place 4 weeks after the final dose of omalizumab / mepolizumab is given. The following assessments will be carried out: CASI; ACT/cACT; exacerbation history; PAQLQ; lung function; FeNO; treatment changes; induced sputum for inflammation, eosinophil peroxidase, urine, nasal and oropharyngeal swabs, eNose at selected centres.

6.11 Laboratory assessments

- Blood tests analysed at local hospital laboratories: full blood count, eosinophils (baseline, 4, 16, 52 weeks)
- Saliva collected at the baseline visit will be frozen for quantification of cotinine
- Urine samples taken at baseline, 4, 16, 52 weeks will be frozen at -80 degrees for future analysis of metabolomics
- Blood taken at the bronchoscopy (or baseline visit if no bronchoscopy done) will be sent to the local laboratory for a full blood count, total IgE and specific IgE to cat, dog, house dust mite, grass, tree pollen, peanut, milk, egg, moulds.
- Additional blood (baseline) will be stored in paxgene tubes for genotyping and transcriptomics analysis
- Additional serum (baseline) will be stored for ImmunoCAP testing
- Bronchoalveolar lavage (BAL) will be processed in the local laboratory for bacterial culture and viral PCR and for a cytology count
- Additional BAL will be frozen for microbiome analysis and for transcriptomics gene sequencing (according to SOPs)
- Endobronchial biopsies will be fixed in formal saline and processed to paraffin blocks
- Endobronchial brushings will be stored in RNA later for transcriptomics analysis (SOP) and frozen for microbiome analysis (SOP)
- Nasosorption fluid collected during bronchoscopy will be frozen at -80 degrees for future analysis of inflammatory mediators
- Nasal and oropharyngeal swabs will be frozen at -80 degrees for future analysis of the microbiome

7. TREATMENTS

7.1 Treatment arms

For the RCT phase of the trial, 150 children will be randomised on a 1:1 basis to either omalizumab or mepolizumab (75 per arm). Both products are licensed for use in children with severe asthma.

The IMP will be administered subcutaneously every 4 weeks (or every 2 weeks for children that require a high dose of omalizumab).

7.2 Investigational Medicinal Product Details

The IMPs to be used in the trial are omalizumab and mepolizumab. Mepolizumab will be supplied for the trial free of charge by GSK. Omalizumab is manufactured by Novartis Pharmaceuticals but the trial supply will be from usual pharmacy stock at participating NHS Trusts.

The trial will be carried out under a Clinical Trial Authorisation (CTA). The IMPs are therefore only to be used by the named investigators, for the patients specified in this protocol, and within the trial.

A Summary of Product Characteristics will be used for both IMPs, sites should refer to their Investigator Site File or ICTU for the current version.

Both IMPs are marketed products and are manufactured in accordance with GMP standards.

7.3 Labelling & Packaging

The mepolizumab supply will be labelled as IMP and shipped to sites by a third party packaging/distribution company. Omalizumab will be used from participating hospitals' own stock and IMP labels will be provided to sites to be added to omalizumab prior to dispensing.

7.4 Storage, Dispensing and accountability

Both IMPs should be stored in a refrigerator at 2-8^{0}C. Sites should refer to the Summary of Product Characteristics and study-specific IMP manual for full details of the storage conditions.

IMPs will be prescribed using a study-specific prescription and dispensed by site pharmacy staff for administration during study visits.

Site pharmacies will maintain accountability records which will be reviewed during site monitoring visits throughout the trial. Any unused mepolizumab IMP supply will be checked by the study Monitor and destroyed locally following.

7.5 Study drug administration, Dosage, Duration and Compliance

IMP will be administered every 2-4 weeks (duration 52 weeks) at the trial site as a subcutaneous injection. Administration will be as per standard care for children with severe asthma and all sites will be specialist asthma centres with expertise in using these products. Administration of IMPs will be recorded in the medical records as per routine care and monitored as part of on-site study monitoring procedures.

Dose of omalizumab will range from 75-600mg, determined by the patient's weight and IgE. High doses of omalizumab will require 2-weekly visits and up to 4 injection sites.

The mepolizumab dose will be 40mg (6-11yrs) or 100mg (≥ 12 yrs) every 4 weeks.

7.6 Drug interactions / Precautions / Contraindications

Sites should refer to the Summary of Product characteristics for either IMP for up to date information regarding drug interactions, precautions and contraindications.

Omalizumab:

Since IgE may be involved in the immunological response to some helminth infections, omalizumab may indirectly reduce the efficacy of medicinal products for the treatment of helminthic or other parasitic infections.

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of omalizumab; thus, there is little potential for drug-drug interactions. Medicinal product or vaccine interaction studies have not been performed with omalizumab. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma or chronic spontaneous urticaria (CSU) will interact with omalizumab.

The only contraindication is hypersensitivity to omalizumab or to any of the excipients.

Mepolizumab

No interaction studies have been performed.

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of mepolizumab. Increased levels of pro-inflammatory cytokines (e.g. IL-6), via interaction with their cognate receptors on hepatocytes, have been shown to suppress the formation of CYP450 enzymes and drug transporters, however, elevation of systemic pro-inflammatory markers in severe refractory eosinophilic asthma is minimal and there is no evidence of IL-5 receptor alpha expression on hepatocytes. The potential for interactions with mepolizumab is therefore considered low.

The only contraindication is hypersensitivity to mepolizumab or to any of the excipients.

7.7 Overdose of IMP

Sites should refer to the Summary of Product characteristics for either IMP for up to date information regarding a potential overdose. If an overdose is suspected, the patient should be monitored for any abnormal signs or symptoms. Medical treatment should be sought and instituted appropriately.

7.8 Dose Modifications for Toxicity

There are no recommendations for dose modification of the IMPs, doses will be prescribed in accordance with the applicable Summary of Product Characteristics.

7.9 Pre-medications / Non-IMP details

There are no pre-medications or non-Investigational Medicinal Products (NIMPs) for this trial.

7.10 Permanent Discontinuation of Study Treatment and Withdrawal from Study

(i) Permanent discontinuation of study treatment

Participants may discontinue study treatment for the following reasons:

- At the request of the patient / patient's family
- Adverse Event/ Serious Adverse Event: that has resulted from treatment administration where the Investigator considers that it would not be safe for the patient to continue treatment, e.g. anaphylaxis. A serious adverse event that is not considered clinically related to the drug intervention will not be a criteria for withdrawal. It may be necessary to temporarily stop treatment for some expected Serious Adverse Events, e.g. injection site reaction, but treatment will be recommenced when clinically indicated and safe to do so.
- Eligibility violation e.g. contraindication of IMP, pregnancy or participating in another trial of an investigational medicinal product
- Allergic reaction to IMP
- If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study.
- Sponsor terminated study
- DMEC/TSC terminated study

(ii) Withdrawal from Study

Withdrawal from the study refers to discontinuation of study treatment <u>and</u> study procedures and can occur for the following reasons:

- Participant decision
- Loss to follow-up

(iii) Procedures for withdrawal from Study

If a participant permanently discontinues the trial intervention, they will be invited to continue to attend trial visits if possible to allow for collection of key outcome and safety data.

If a participant withdraws from trial procedures, an assessment must be made as to whether trial data and samples collected to date can be retained and analysed for the trial.

The decision to withdraw from further trial procedures will be documented on the electronic case report form (eCRF) and in the medical notes. If the participant does not agree for data and samples collected to be retained, the samples must be destroyed and data excluded from the analyses.

Participants who have discontinued the trial intervention and/or have withdrawn from the trial will not be replaced, as the sample size allows for potential loss to follow-up.

8. PHARMACOVIGILANCE

8.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial medication, whether or not considered related to the IMP.

(i) Adverse Event recording

For the purposes of the study, AEs will be followed up according to local practice until the event has stabilised or resolved, or the final Follow-up Visit, whichever is the sooner. SAEs will be recorded throughout the study.

All such AEs, whether expected or not, should be recorded in the adverse event section of the case record form within one month of the form being due.

The trial physician will decide what the best course of action is i.e. referral to GP, hospital, clinic or other. AEs will be followed up according to local practice until stabilised, resolved, diagnosed/treated or the last trial follow-up visit, whichever is sooner.

(ii) Severity of Adverse Events

Definitions for assessment of severity:

Mild: Awareness of event but easily tolerated
Moderate: Discomfort enough to cause some interference with usual activity
Severe: Inability to carry out usual activity

(iii) Causality of Adverse Events

Definitions for assessment of causality:

Unrelated: No evidence of any causal relationship
Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Causality assessment will be performed by the Principal Investigators at sites and expectedness assessment will be performed by the Sponsor or person delegated by the Sponsor to access expectedness.

8.2 Abnormal Laboratory Test Results

All clinically important abnormal laboratory test results occurring during the study will be recorded as adverse events. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made.

8.3 Adverse Events of Special Interest (AESI)

The following adverse events of special interest have been defined for this trial, these will be captured on specific forms on the eCRF:

- Anaphylaxis
- Infections
- Injection site reactions

8.4 Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the subject 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.
** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

(ii) AEs/SAEs excluded from safety reporting

Asthma exacerbations will be excluded from safety reporting as they will be reported as study-specific endpoints on the appropriate form within the eCRF.

(iii) Reporting of SAEs

Rapid reporting of all SAEs i.e. within 24 hours occurring during the study must be performed as detailed in the study specific safety reporting instructions. If the investigator becomes aware of safety information that appears to be drug related, involving a subject who

participated in the study, even after an individual subject has completed the study, this should be reported to the Sponsor.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF). Copies of completed/updated SAE reports will be sent to the Sponsor throughout the trial. The SAE form asks for the nature of the event, date of onset, severity, corrective therapies given, outcome, expectedness and causality.

(iv) Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as a SAE that is judged to be related to any dose of study drug administered to the subject.

(v) Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the Reference Safety Information (RSI) section of the Investigator Brochure (IB) or Summary of Product Characteristics (SPC).

(vi) Reporting of SUSARs

SUSARs should be notified to the appropriate regulatory authority, the relevant REC and the Sponsor in accordance with regulatory requirements. SUSARs which are fatal or life-threatening will be reported not later than seven days after alerting the sponsor to the reaction. Any additional relevant information will be sent within eight days of the report.
A SUSAR which is not fatal or life-threatening will be reported within 15 days.

Follow up of patients who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

8.5 Developmental Safety Update Reports / Annual Safety Reports

Developmental Safety Update Reports (DSUR) will be submitted to the Sponsor, the Ethics Committee and Regulatory Authority in accordance with local / national regulatory requirements.

8.6 Pregnancy

For the purpose of this study, f*emales capable of becoming pregnant are defined as: fertile, following menarche and until unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.*

These women should only be included in the trial after a confirmed menstrual period and a negative pregnancy test, and providing they are willing to use effective contraception.

Patients will be advised to inform the research team if menarche occurs after screening or randomisation visits. In that case, the pregnancy test will be performed before the study drug is administered to a patient.

All women of childbearing potential will have a pregnancy test performed at visit 1 (screening visit) and on the day of 1st dose (visit 6), within 7 days before the first dose of study drug is administered.

The inclusion of women of childbearing potential requires use of a highly effective contraceptive measure therefore all female patients of childbearing potential (those who are menstruating) will be counselled on the need for contraception should they be sexually active or, in the opinion of the Investigator, likely to be sexually active. Women of childbearing potential must agree to use one of the following methods of acceptable contraception for the duration of the trial and up to 100 days after the last dose of IMP:

1. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
   a) oral
   b) intravaginal
   c) transdermal
2. Progestogen-only hormonal contraception associated with inhibition of ovulation:
   a) oral
   b) injectable
   c) implantable
3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)
5. Bilateral tubal occlusion
6. Vasectomised partner
7. Sexual abstinence
8. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
9. Male or female condom with or without spermicide
10. Cap, diaphragm or sponge with spermicide
11. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods)

If a patient becomes pregnant whilst taking part in the trial or during a stage where the foetus could have been exposed to an IMP, the Investigator must ensure that the participant and the participant's healthcare professional are aware and that follow-up information is reported on the outcome of the pregnancy. If the participant leaves the area, their new healthcare professional should also be informed. Each pregnancy occurring while the participant is on study treatment must be reported to ICTU within 24 hours of learning of its occurrence. Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment.

8.7 Reporting urgent safety measures

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

9. STATISTICAL ANALYSES

9.1 Sample size and power considerations

9.1.1 Selection of the margin of non-inferiority

In order to determine the probability that mepolizumab is not inferior to omalizumab a threshold (margin of no difference) needs to be selected.

Children coming into the study will have experienced a minimum of four attacks[59]. Omalizumab is expected to reduce the average rate by approximately 50%[60]. A non-inferiority margin of 0.5 exacerbations (i.e. one exacerbation difference over 2 years) is proposed as the primary threshold to calculate the posterior probability for mepolizumab not being inferior to omalizumab (Prob ($\mu_m - \mu_o \leq 0.5$ exacerbations). This margin was elicited from discussion with parents and patients as the maximum change (threshold) they felt would <u>not</u> be a meaningful difference to them i.e. they consider a change of half an exacerbation per year to be acceptably close to zero. In contrast, one exacerbation per year was viewed as a meaningful increase.

In a frequentist framework the choice of the non-inferiority (NI) margin is pivotal as this impacts the power to perform the hypothesis 'test' of non-inferiority at a set significance level (usually 0.05). In a Bayesian approach, where the sample size is fixed and the philosophy is one of evaluating accumulated evidence, we can calculate posterior probabilities for a range of varying thresholds. The choice of threshold should be a value which is not deemed to include an important difference. Often ½ the minimal clinical important difference is used. The important minimum difference for this outcome (asthma exacerbation) may vary somewhat depending on who is consulted on this opinion e.g. regulator, manufacturer, clinician, patient, parent. We set 0.5 exacerbations per year as the primary threshold of interest after discussion with patients and parents but we will also report on the posterior probability of non-inferiority in 0.1 increments from 0 to 1 as secondary information.

9.1.2 Proposed sample size

A frequentist approach to a non-inferiority trial of mepolizumab to omalizumab would result in an unfeasibly large sample size. Rather than not undertake the trial at all, the evidence will be evaluated in a Bayesian analytical framework. The planned sample size has been based on what is possible to recruit nationally in a feasible time scale and budget. In a survey of 11 specialist paediatric severe asthma centres in the UK centres taking part in this trial it was found that there are a combined 170 annual new referrals of PSA. Each centre already has a cohort of eligible PSA patients (≈50 each) so in 3 years an estimated 1,060 children with PSA will be eligible and invited to the run-in study. Assuming a 50% acceptance rate, based on previous experience of trial in this population and PPI group feedback, we anticipate n≈500 will be recruited to the run-in study. Pilot data show approximately 30% of PSA will have STRA and 15% have RDA giving 225 eligible children. Assuming a higher recruitment rate of 66% of these patients (based on their commitment to the run-in study and severity of their condition), we anticipate it will be possible to enrol and randomise a minimum of 150 into the randomised trial. The estimated withdrawal rate is unlikely to be higher than 15% (seen in a 48-week trial where children had to cross-over treatments)[61]. Anticipated worst case is full (52 week) follow up for 130 children.
In Table 3 three scenarios are presented to indicate the strength of evidence this study may provide. This included a prior for β strongly in favour of mepolizumab and a prior strongly in favour of omalizumab. Sample size used is 130 (n=65 per arm), results are based on 1000 simulations. Data were simulated using a Poisson distribution with vague Gaussian prior

distributions for the log rate in change (mean 0, SD 10), and log baseline rate with baseline of 3 and 2.5 exacerbations (mean 1.1 and 0.92 respectively, SD 10). The predicted probabilities for non-inferiority (i.e. mepolizumab is not inferior to omalizumab) are reported in the table.

Table 3. Estimated predicted probabilities and resulting Incidence Rate Ratio based on 1000 simulations, sample size of 130 using centralised but vague prior distributions

	Mepolizumab mean rate	Omalizumab mean rate	Incidence Rate Ratio	**Predicted probability** *
Scenario 1: Efficacy of mepolizumab = omalizumab	2.5	2.5	1.00	0.92 †
	3.0	3.0	1.00	0.86
Scenario 2: Efficacy of mepolizumab > omalizumab	2.0	2.5	0.80	0.99
	2.5	3.0	0.83	0.99
Scenario 3: Efficacy of mepolizumab < omalizumab	3.0	2.5	1.20	0.61
	3.5	3.0	1.17	0.52

† Example interpretation **'This study estimates that the probability mepolizumab is not inferior to omalizumab for reducing the asthma attack rate is 0.92'** alternatively **'This study found that there is a 92% chance that mepolizumab is not inferior to omalizumab in reducing the asthma attack rate'**. Calculations assume a non-inferiority margin of 0.5 exacerbations per year. The study will also report the Incidence Rate Ratio and 95% credible interval so the treatment effect can be evaluated.

9.2 Planned Recruitment rate

The study will take place across 11 specialist paediatric severe asthma centres in the UK. It is estimated that an average of 1-2 patients will be recruited at each centre per month, giving a total of 500 children recruited to the run-in period over 3 years.

9.3 Statistical Analysis

The primary analysis population will be an intention to treat (ITT) analysis population. All randomised patients will be analysed in the arm they are allocated to regardless of treatment received. It is often suggested that the ITT estimate is anti-conservative in the non-inferiority setting[62] but this will not always be the case[63]. In this head-to-head trial of monoclonal antibodies in children there is uncertainty in both arms over the proportion of children who will complete 52 weeks treatment, and the duration of treatment in those that stop. This means we are uncertain at this stage whether the ITT analysis will be anti-conservative or not. Given both treatments are from the same drug class (monoclonal antibodies) and are delivered by the same route, with adverse event profiles that are not expected to differ substantially, we have chosen the ITT population to be the primary analysis population as we anticipate that the treatment proportions and average treatment duration will be similar. We will also undertake an analysis on a per-protocol (PP) population and this will be achieve in two ways:

1) By removing the participants who did not adhere ('comply') with planned trial treatment schedule. Compliance will be defined for two thresholds: ≥50% treatment duration (6 months); ≥75% (9 months) in the Mepolizumab arm only and then for both arms.
2) By comparing exacerbation rate between treatment arms for all participants but only for the time when they are taking the treatment ('on treatment' + 4 weeks after stopping treatment). This treats those stopping treatment as a missing data problem and this analysis will valid under a missing at random assumption.

The estimates from the 'PP' populations and ITT population will be assessed and presented in tandem for all NI margins included in the analysis. We have set 0.5 exacerbations as the primary threshold but we will also report on the posterior probability of non-inferiority in 0.1 NI increments from 0 to 1 as secondary information.

European Medicines Agency (EMA) guidance suggests that inference on both ITT and PP will allow robust conclusions[64]. If there are discrepancies of concern between the ITT and PP results for the primary 0.5 NI margin this will then be investigated further. As we have remove randomised participants from the PP analysis we will no longer have the protection of randomisation for balancing confounders between arms. We will therefore undertake a sensitivity analysis with based on the proportion of study drug received between 50%-100% for the 0.5 NI margin. Alongside this we will undertake a complier-adjusted causal effect (CACE) on the proportion of children who had at least one exacerbation using the principal strata approach[65]. This analysis aims to compare participants in the other arm who would have also taken the treatment had they been randomised to receive it[66]. This will be undertaken for 'compliers' of Mepolizumab, and then for 'compliers' of Omalizumab. If there are differences in results between PP and ITT analysis the conclusions will be appropriately caveated for the primary ITT population.

The safety population for the analysis of adverse events will be all participants who received at least one dose of study medication, and this analysis will be repeated for all participants but only during the time they are on study drug (+ 4 weeks after stopping).

Baseline characteristics will be summarised by treatment arm and overall using suitable measures of central tendencies and measure of spread. For continuous data (means and medians), variability (SD) and interquartile range (IQR), and frequencies and proportions for categorical data. No hypothesis tests will be performed to test for differences in baseline characteristics by arm. Trial results will be reported according to Consolidated Standards of Reporting Trials (CONSORT) and the CONSORT extension for non-inferiority and equivalence randomised trials[67,68].

A log-linear Poisson regression model will be used to model the primary outcome with treatment arm and randomisation stratification variables (blood eosinophils (<300/≥300 per mcl)[58] and IgE (<30, 30-1500, >1500IU/ml), type (RDA/STRA)) included as covariates. Recruitment site will be included as a random effect unless there are fewer than expected sites or another reason to model site as a fixed effect[69]. Follow-up time will be included as an offset term to model the rate of exacerbations. Follow-up time will be calculated from the time of randomisation to the participants last study visit regardless of treatment status. A Negative Binomial regression or Zero-Inflated Poisson model will replace the Poisson model if there is evidence for over dispersion. A Bayesian approach to the analysis will be used to allow us to combine clinical knowledge based on existing evidence for this population (prior) with the observed data collected in this study (likelihood) to estimate a posterior probability distribution for the treatment effect (Exp(β) =Incidence Rate Ratio(IRR); β= change in log

rate). This posterior distribution will be used to derive the probability that mepolizumab is not inferior to omalizumab (e.g. if baseline rate 3 per year with NI margin of 0.5 a relative NI rate is 3.5 and IRR = Exp(β) = 1.166 and Prob(β < 0.1541)). We will also report the IRR and 95% Credible Interval. For the primary analysis a Gaussian prior distribution for β and α (log baseline rate) will be used. The parameter for the prior distributions will be elicited from clinical experts. The approach to obtaining this information is described further below in the section ***'Eliciting information to define the prior distribution'***. This process with be further detailed in a prior elicitation plan (PEP) written in addition to the full statistical analysis plan (SAP). In addition to the primary endpoint analysis on the ITT and PP populations there will be three sensitivity analyses performed examining the impact of alternative prior distributions. These will be 1) non-informative priors for α and β (Uniform and Gaussian); 2) Gaussian prior distribution for β where mepolizumab is inferior (shift of 1 exacerbation); 3) Gaussian prior for β where omalizumab inferior (shift of 1 exacerbation). Diagnostic plots will be used to examine Markov chain Monte Carlo (MCMC) convergence; effective sample sizes and correlation times will be calculated. Posterior probabilities of non-inferiority will be reported.

Every effort will be taken to minimise missing data. All participants will be followed up and the primary outcome data will be collected unless the participant requests to withdraw from data collection. Missing data will be examined and quantified, this will include the time of withdrawal and tabulation for reasons for withdrawal by arm. Patterns of missingness and relationship between variables and outcome will be explored. The primary analysis will include all participants up until the point they withdraw or their last follow up visit expected at 52 weeks (regardless of treatment status). Sensitivity analysis will be conducted to explore the impact of missing primary outcome data (patients who have <52 week follow-up due to withdrawal) using a mean score approach[70].

We will explore whether baseline serum IgE, baseline blood/BAL/sputum eosinophils are associated with treatment benefit (measured using both CASI and then asthma exacerbations count). We will first examine each arm separately by fitting a suitable generalised linear model (Linear, Poisson, Negative Binomial, Zero-Inflated Poisson regression) examining the bivariate associations for a number of selected baseline variables including serum IgE, blood eosinophils, and RDA/STRA before fitting a multivariable model. Correlations between variables and collinearity will be assessed to help inform variable selection. We will then examine both arms in the same model and include an interaction term between IgE and treatment arm, and then a second model with eosinophils and treatment arm (repeated for blood/BAL/sputum measures), adjusted for selected variables and centre effect. The modelling approaches will examine IgE and eosinophils as a continuous covariate in the model with the possibility of allowing for a non-linear effect of the baseline values through use of fractional polynomial approach, and also as categorical variables (<30, 30-1500, >1500IU/ml) and (<300/≥300 per mcl). We also hypothesise that response may vary between STRA and Refractory DA and this will be examined using the same approach and, if feasible, including an interaction between diagnosis and treatment into the same model.

If mepolizumab has a high predicted probability (>80%) of non-inferiority compared to omalizumab we will examine whether mepolizumab is working through reducing blood eosinophils and/or sputum eosinophils compared to omalizumab. This will examine if changes (improvement) on two outcomes (CASI and exacerbation rate) is mediated by

changes in eosinophils. The proposed mediators are measured at 4,16, and 32 and will be adjusted for baseline value in the model[71,72].

For continuous secondary outcomes (CASI, PAQLQ, FEV_1, FeNO, ACT, visual analogue scale patient burden) that have been repeatedly measured we will fit a mixed effect linear regression model with random subject effects, minimisation stratification variables, centre and time. Non-inferiority will not be the focus of these analyses but we aim to estimate the mean difference between treatment arms with 95% Confidence Intervals (CI). A time by arm interaction will be included to obtain estimates for mean differences at 24 and 52 weeks. Model assumptions will be examined using residual analysis including examination of graphical displays such as normal quantile plots.

Information on adverse events (AEs) will be collected from several sources: spontaneous reports from participants and carers; clinical examination and observation; clinical and laboratory tests. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). AEs will be summarised at the Preferred Term level and System Organ Class level. The cumulative hazard function will be used to examine rates of withdrawals by arm due to any AE. Specific AEs of interest are infection, injection site reaction and anaphylaxis. These specific AEs will be examined between arm by comparing the cumulative hazard function and mean cumulative function (with plot) that can account for recurrent events[73].All AEs will be tabulated by arm and severity for the number of participants with at least one adverse event, and the number of adverse events occurring amongst all participants. We will also calculate ORs/IRRs and their 95% CIs for binary and count AE outcomes at SOC level using logistic regression and Zero-Inflated Poisson model or negative Binomial model, adjusting where possible for minimisation stratification variables, and centre either as a random effect or fixed effect (following the decision made for the primary analysis). The results from these models will be presented graphically along with the raw counts using visual approaches[74,75]. Clinical and laboratory measurements will be analysed as continuous outcomes calculating a mean difference and 95% CIs over the study follow-up period using a linear mixed effect model. These outcomes will also be categorised as abnormal/normal and analysed as described above for AE reports

'Eliciting information to define the prior distribution'

We will develop a prior elicitation plan (PEP) to elicit information to define the prior distributions for the primary analysis. The PEP will be influenced by the good practice frameworks suggested by Hampson et al[76], and the approach of Dallow et al[77] who describe the SHELF framework[78]. In brief we will hold a 1 day meeting inviting the clinical experts at each participating recruiting site. In this meeting we will elicit prior opinion on the 52-week exacerbation rate in this population treated with omalizumab, prior opinion of the relative benefits for mepolizumab, and a measure of uncertainty around both these estimates. The day will be facilitated by the trial statisticians who will provide an introduction to Bayesian Analysis and demonstrate the resulting distributions of the chosen parameters as they are discussed. Opinion will be initially elicited on an individual basis and will be collected via questionnaire. The questions will be carefully phrased to aid understanding. Each expert will then have the chance to present their choice and reason to the group. They will then have to update their selection and the afternoon will be dedicated to consensus discussions.

A statistical analysis plan (SAP) will be written detailing all analysis included for the trial with model specifications, checks and statistical code.

10. REGULATORY, ETHICAL AND LEGAL ISSUES

10.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 7th revision of the 1964 Declaration of Helsinki.

10.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

10.3 Research Ethics Committee (REC) Approval

10.3.1 Initial Approval

Prior to the shipment of IMP and the enrolment of subjects, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Patient Information Sheet and Consent Form, any other written information that will be provided to the subjects, any advertisements that will be used and details of any subject compensation.

10.4 Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

The trial team, in collaboration with the Sponsor will assess whether a proposed amendment is substantial or non-substantial. For each proposed amendment, a revised version of the protocol will be prepared using tracked changes, a new version number assigned and the revised document will be reviewed and approved by Protocol Development Group and Sponsor prior to submission to the REC and Health Research Authority (HRA). The amended protocol will be sent to participating sites for local approval to be granted and the approved version will be shared with all staff involved in the trial.

10.4.1 Annual Progress Reports

Annual Progress Reports will be submitted to the Research Ethics Committee (REC) and the Sponsor in accordance with local and national requirements. The Annual Progress Report will also detail all SAEs recorded.

10.4.2 End of Trial Notification

The REC will be informed about the end of the trial, within 90 days as per current UK requirements.

10.5 Regulatory Authority Approval

The study will be performed in compliance with UK regulatory requirements. Clinical Trial Authorisation from the MHRA must be obtained prior to the start of the study. In addition, the MHRA must approve amendments prior to their implementation (as instructed by the

Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.

This study has sought Clinical Trials Authorisation from the UK Competent Authority; MHRA. Reference: EudraCT 2019-004085-17.

10.6 HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

10.7 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator, and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor on a monthly basis.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial subjects; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the MHRA and REC within 7 days of becoming aware of the serious breach.

10.8 Insurance and Indemnity and Sponsor

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Imperial College London will act as the main Sponsor for this trial. Delegated responsibilities will be assigned to the NHS trusts taking part in the trial.

10.9 Trial Registration

The study will be registered on a trial database (ISRCTN) in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

10.10 Informed Consent

Parents of potential patients will be offered a patient information sheet at a clinic visit. Additional permissions will not be required to approach potential patients as site staff will be part of their usual care teams. The patient information sheet will describe the study including any risks and potential benefits of enrolling. Written informed consent will be obtained from a parent of the patient prior to commencing any research procedures. Information sheets, with content appropriately adapted for age, will also be provided to the children approached about the study and assent will be sought where appropriate. Participant information sheets will be prepared in partnership with Asthma UK and the patient advisory group.

Parents will be given an adequate amount of time to consider their child's participation in the trial. If the parent agrees for their child to participate in the trial they will be asked to sign the Informed Consent Form which will then be countersigned by the responsible clinician / researcher. The patient will retain one copy of the signed Consent Form. Another copy will be placed in the patient's medical records whilst the original will be retained in the research record for the patient at sites. Written informed consent must be obtained prior to any trial specific tests which would not have been performed during routine management of the patient.

The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

10.11 Contact with General Practitioner

It is the investigator's responsibility to inform the subject's General Practitioner (where applicable) by letter that the subject is taking part in the study provided the patient agrees to this, and information to this effect is included in the Patient Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

10.12 Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained. On the eCRF or other documents submitted to the Sponsors, subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to subjects' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

10.13 Data Protection and Patient Confidentiality

The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

10.14 End of Trial

For safety reporting and regulatory purposes, End of Trial will be when all study visits are complete, all data are captured on the database and the study database is declared clean and hard-locked.

10.15 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another

party or move them to another location, written agreement must be obtained from the Sponsor.

11. DATA MANAGEMENT

11.1 Source Data

Source documents include original documents related to the trial, to medical treatment and to the history of the participant, and adequate source documentation must be maintained to allow reliable verification and validation of the trial data. What constitutes the source data for this trial will be outlined in the trial Monitoring Plan.

11.2 Language

eCRFs will be in English. Generic names for concomitant medications should be recorded in the eCRF wherever possible. All written material to be used by subjects must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

11.3 Database

Trial data will be collected on an electronic case report form (eCRF). The principal means of data collection from participant visits will be Electronic Data Capture (EDC) via the internet using the InForm database. Data is entered into the EDC system by trained site personnel. All data recorded in the eCRF will be signed off by the Investigator or his/her appropriate designee. All changes made following initial submission of data will have an electronic audit trail with a date. Specific instructions and further details will be outlined in the study specific eCRF manual.

11.4 Data Collection

Details of procedures for eCRF/CRF completion will be provided in a study manual.

11.5 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

STUDY MANAGEMENT STRUCTURE

11.6 Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, the Chief Investigator and Trial Manager. Two patient representatives will also be included on the TSC. The role of the TSC is to provide overall supervision of trial conduct and progress. The TSC will meet approximately 6-monthly throughout the duration of the trial. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.7 Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, community representative, trial statistician and trial manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate Terms of Reference. Two parent representatives will also be invited to join the TMG.

11.8 Data Monitoring and Ethics Committee

A fully independent Data Monitoring and Ethics Committee (DMEC) will be set up to monitor progress, participant safety and any ethical issues involved in this trial. They will review trial progress, recruitment rates and safety data. A separate DMEC Charter will be drawn up defining their responsibilities, frequency of meetings and reporting to the TSC. Meetings will be approximately 6-monthly.

The statistician will analyse interim data for DMC meetings and act as data manager, in raising and resolving data queries with participating sites, via the Trial Manager. Closed DMC reports will include recruitment, randomisation balance and stratification effectiveness, baseline characteristics, withdrawals, compliance, concomitant medications, efficacy, mediators, and adverse events. Open DMC and TSC reports will be provided without outcome or arm information.

11.9 Patient advisory group (PAG)

A Patient Advisory Group (PAG) consisting of approximately four parent-child pairs will be convened. The role of this group will be to review the trial design and schedule of assessments, and to advise on recruitment, retention, engagement and dissemination strategies for the trial. The Ethics application and participant materials will be prepared in collaboration with the PAG.

11.10 Early discontinuation of the study

There are no statistical criteria defined for termination of the TREAT trial. The DMC Charter will define procedures for early termination of the study due to safety, should this be required.

11.11 Risk assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of ‘low’, ‘medium’ or ‘high’ to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Study Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

11.12 Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan, developed in accordance with the risk assessment.

11.13 Quality control and quality assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

11.14 Peer review

The trial has undergone independent peer review via the NIHR-EME funding programme. The trial has also been reviewed by senior members of ICTU and researchers at Imperial College London.

11.15 Patient and public involvement

Involvement in development of proposal

Parents and children were actively involved in developing this study. A workshop was held with children with problematic severe asthma and their parents (4 children/parent pairs); an overview of the proposal was shared with the families and their feedback on key questions was sought. All participants confirmed that they would agree to participate in the trial, agreed that the research question and primary outcome measure are appropriate and that they have no concerns about the proposed trial visit schedule.

In addition to the workshop to discuss this study, Asthma UK facilitated a workshop including patient representatives to determine the important research questions that need to be answered for patients with difficult asthma. The patient representatives said a trial that addresses the management of difficult asthma in children is an essential unmet need. The trial design was developed in discussion with the Asthma UK Centre for Applied Research patient group.

Involvement throughout research

The aims of active involvement of service users in this project are:

- Ensure the research is relevant to children with severe asthma and addresses key unmet needs of this population.
- Ensure the methods and outcome measures proposed for the study are acceptable and sensitive to the situations of potential research participants
- Support efficient and cost-effective recruitment and retention of research participants
- Support ongoing and wider public engagement with and participation in research via the communication of activities and findings of this study, and the establishment of a wider PPI paediatric severe asthma network.

11.16 Publication and dissemination policy

Results will be presented at national and international scientific meetings to both paediatric and adult respiratory, allergy and general physicians. All results will be published in high impact, general medical journals using open access policies. We anticipate several publications to arise, including details of the prevalence to true severe asthma and refractory difficult asthma in children. We will communicate the results to the general public, specifically those with asthma via our PPI groups and our co-applicant at Asthma UK, ensuring results, once confirmed are distributed via their web-site and Twitter feeds. We will also use appropriate media channels via Imperial College Public Relations team to disseminate results. All participating sites will be informed of the results and encouraged to disseminate findings via their own institutional social media platforms and patient and public engagement groups.

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP/device and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore, all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

Any request by site investigators or other collaborators to access the study dataset must be formally reviewed by the TSC.

The results may be published or presented by the investigator(s), but the Funder will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC and MHRA within a year of the end of study. The results will also be submitted to the EudraCT results database in accordance with regulatory requirements.

12. REFERENCES

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SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Treating severe paediatric asthma; a randomised controlled trial of mepolizumab and omalizumab

Protocol Number: 19IC5548

Signed: S. Saglani

Professor Sejal Saglani

Date: 12 March 2020

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Treating severe paediatric asthma; a randomised controlled trial of mepolizumab and omalizumab

Protocol Number: 19IC5548

Signed: _____

Name of Sponsor's Representative Keith Boland
Title Clinical Trials Manager
Sponsor name Imperial college London

Date: 13/3/2020

SIGNATURE PAGE 3 (SENIOR STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Treating severe paediatric asthma; a randomised controlled trial of mepolizumab and omalizumab

Protocol Number: 19IC5548

Signed: _____

Dr Victoria Cornelius, Imperial Clinical Trials Unit

Date: 12/03/2020

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: **Treating severe paediatric asthma; a randomised controlled trial of mepolizumab and omalizumab**

Protocol Number: 19IC5548

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____