Trial Protocol

Tailoring Inhaled Corticosteroids in patients with Severe Asthma taking Biologics

Short Title /Study Acronym	**TICSAB**
Sponsor	**University of Dundee**
Sponsor ID	2-071-24
Funder	University of Dundee departmental funding
Chief Investigator Principal Investigator	Dr Brian Lipworth Dr Robert Greig
IRAS Number	346249
Version Number and Date	Version 2 30/06/2025

PROTOCOL APPROVAL
Tailoring Inhaled Corticosteroids in patients with Severe Asthma taking Biologics

Signatures
The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the trial/study/study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Brian J Lipworth		16/05/2025
Chief Investigator	Signature	Date
Brian J Lipworth		16/05/2025
Individual Responsible for Statistical Review	Signature	Date

LIST OF ABBREVIATIONS

ACQ6	Asthma Control Questionnaire
AE	Adverse Event
AHR	Airway Hyperresponsiveness
AMP	Adenosine Monophosphate
AOS	Airway oscillometry
APR	Annual Progress Report
AR	Adverse Reaction
AX	Area under the reactance curve
BD	Twice Daily dosing
BDP	Beclometasone diproprionate
BMI	Body Mass Index
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DBP	Diastolic Blood Pressure
DD	Doubling Dose
DES	Data Entry Site
DMC	Data Monitoring Committee
DMS	Data Management System
DSUR	Development Safety Update Report
EDN	Eosinophil Derived Neurotoxin
Eos	Eosinophils
ERS	European Respiratory Society
EU	European Union
EudraCT	European Clinical Trials Database
FBC	Full Blood Count

FEF25-75	Forced expiratory flow at 25-75% of the pulmonary volume
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IgE	Immunoglobulin E
IL-13	Interleukin-13
IL-4	Interleukin-4
IL-5	Interleukin-5
IMP	Investigational Medicinal Product
IOS	Impulse Oscillometry
IRAS	Integrated Research Application System
IV	Intravenous
LABA	Long-acting β2-adrenoceptor agonist
LAMA	Long-acting Muscarinic Antagonist
MedDRA	Medicinal Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
Mini-AQLQ	Mini-Asthma Quality of Life Questionnaire
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIMP	Non-Investigational Medicinal Product
OCS	Oral Corticosteroids
OD	Once Daily dosing
PD_{10} FEV_1	Provocative dose of mannitol causing 10% fall in
PEF	Peak Expiratory Flow
PI	Principal Investigator
PIS	Participant Information Sheet
PP	Per-protocol population
PR	Pulse Rate

RDR	Response Dose Ratio (% decrease in FEV1 at the final dose of mannitol/cumulative dose given (% / mg)
REC	Research Ethics Committee
R5-R20	Difference between resistance at 5Hz and 20Hz
R&D	Research and Development
RSI	Reference Safety Information
SABA	Short-acting β2-adrenoceptor agonist
SAMA	Short-acting Muscarinic Antagonist
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SCRR	Scottish Centre for Respiratory Research
SD	Standard Deviation
SF	Study File
SHARE	Scottish Health Research Register
SOC	Standard of Care
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SPCRN	Scottish Primary Care Research Network
SUSAR	Suspected Unexpected Serious Adverse Reaction
TASC	Tayside Medical Science Centre
TMF	Trial Master File
TMG	Trial Management Group
TSPL	Thymic stromal lymphopoietin
WOCBP	Woman considered of Childbearing Potential
WNOCBP	Woman considered of non-Childbearing Potential
TSC	Trial Steering Committee

SUMMARY/SYNOPSIS

Trial Title	Tailoring Inhaled Corticosteroids in patients with severe asthma taking biologics (TICSAB)	
Trial Design	Single centre, prospective longitudinal, open label study	
Trial Population	Patients with severe GINA defined asthma taking biologics along with high dose of ICS/LABA inhaled therapy	
Sample Size	Sufficient patients to ensure 46 patients complete (23 patients per biologic).	
Planned Trial Period	Approximately 1 year depending on recruitment	
Clinical phase duration	Approximately 1 year depending on recruitment (7 months per participant)	
Follow up phase duration	None	
Primary	Objectives: To characterize the effect of tapering inhaled corticosteroids on mannitol airway hyperresponsiveness in patients with severe asthma taking dupilumab or Tezepelumab	Outcome Measures Change in mannitol PD_{10} from Visit 1 (post-run-in baseline) to Visit 2
Secondary	Objectives • To characterise symptom control as ACQ and asthma quality of life as mini-AQLQ • To assess type 2 inflammation in blood. • To measure lung function as spirometry and airway oscillometry • To characterise the prevalence of mannitol airway hyperresponsiveness in patients with severe asthma taking dupilumab or Tezepelumab • Assess the effects of taking dupilumab or Tezepelumab on airways remodelling using AX	Outcome Measures • Change in mannitol RDR from screening (post-run-in baseline) to visits 1 and 2. • Post mannitol challenge bronchodilator response • Number of puffs of MART • FeNO • Blood eosinophils • Blood total IgE • Spirometry • Airway oscillometry (AOS) • Asthma Control Questionnaire (ACQ6) • Mini-Asthma Quality of Life Questionnaire (AQLQ) • Diary cards for PEF, symptoms (morning values only) and reliever use (number of puffs)

Inclusion Criteria	• Any patient over 18 years of age with severe asthma taking dupilumab or tezepelumab for severe asthma for at least 6 months • FEV_1 ≥50% at baseline
Exclusion Criteria	• Any patients on maintenance oral steroids or required an oral steroid burst in the past 28 days • Any patient who was switched from another biologic in the past 3 months • Any other respiratory condition such as moderate to severe bronchiectasis or COPD • Currently pregnant

1 INTRODUCTION / BACKGROUND & RATIONALE

Biologics and Mannitol Airway Hyperresponsiveness in Severe Asthma

Asthma is a heterogenous respiratory condition characterized by type 2 (T2) inflammation, variable airflow limitation and airway hyperresponsiveness (AHR). Severe asthma is defined as asthma that persists despite optimal adherence to high dose inhaled corticosteroid (ICS) with long-acting beta agonist therapy and management of contributory factors, or that worsens when such therapy is reduced or withdrawn[1]. Despite constituting an estimated 3.7% of the global asthmatic population, severe asthma consumes approximately 50% of such healthcare resources[1], highlighting an urgent need for more clinical studies to further our understanding. In recent years, biologics targeting various T2 inflammatory pathways reduce severe asthma exacerbations, the oral corticosteroid (OCS) burden as well as improving symptom control and lung function (figure 1)[2,3].

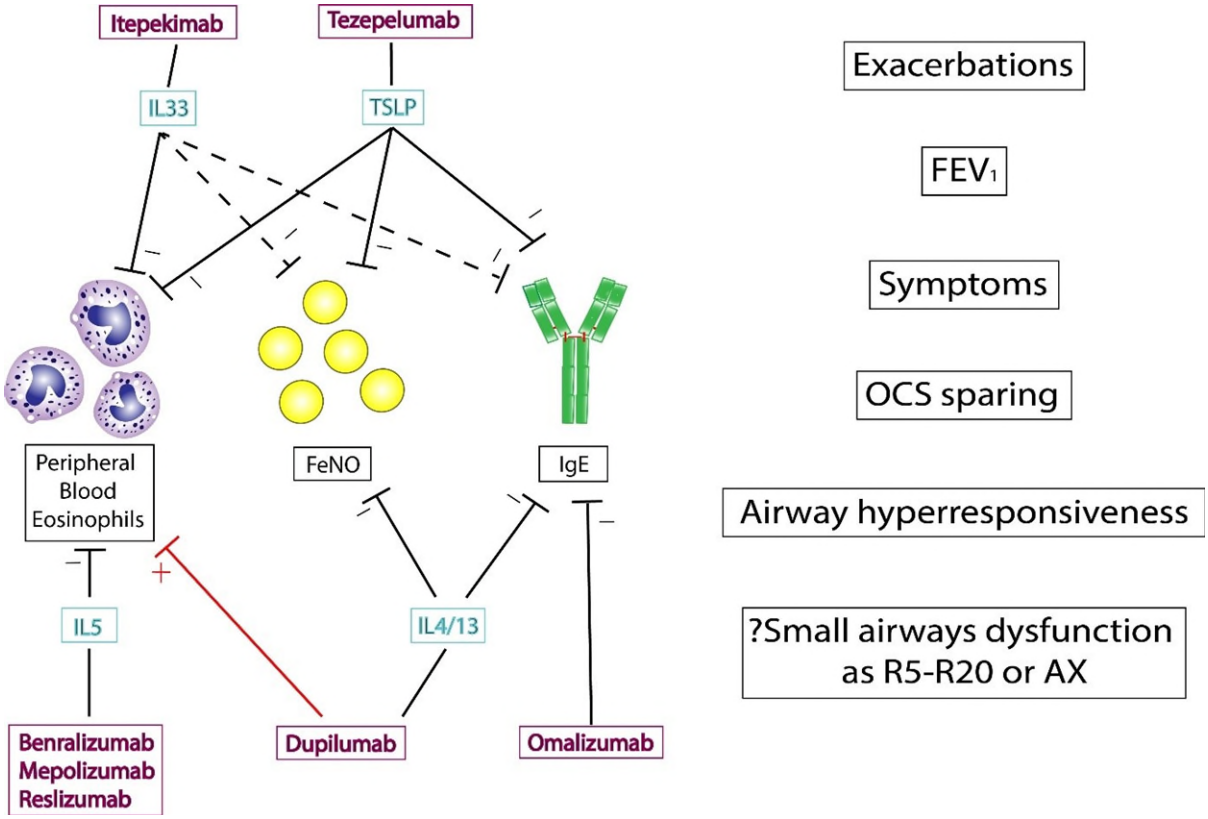


Figure 1 *Effects of biologic and anti-alarmin therapies on upstream epithelial alarmins, downstream cytokines and type 2 biomarkers in the context of key patient clinical outcome measures in severe asthma. Hyper-eosinophilia may be associated with dupilumab. All biologics significantly improve ACQ and prebronchodilator FEV_1 and reduce OCS requiring exacerbations. Interrupted line refers to small but significant suppressive effect of itepekimab on FeNO and total IgE.*

Like other type 1 inflammatory conditions such as ulcerative colitis and rheumatoid arthritis, attempts have been made to define the term clinical remission in severe asthma. An expert consensus statement concluded that the definition of long term clinical remission would need to include cessation of OCS use for exacerbations or disease control; elimination of symptoms;

patient and healthcare professional agreement; and optimisation and stabilisation of lung function[4]. However, this is similar to the definition for short term biologic super-response[5] and therefore additionally, complete remission is defined as clinical remission along with negative AHR,[4] also referred to as AHR remission[6].

However, broadly there is a paucity of data relating to the effect of biologics on AHR and such evidence has stemmed from relatively small studies[7]. AHR, an exaggerated constrictor response of the airways to various stimuli, is a key hallmark of persistent asthma and is closely associated with T2 inflammation, severity of asthma and treatment response to ICS[8]. AHR can be measured 'directly' using agents such as methacholine or histamine, that work directly on bronchial smooth muscle M3 or H1 receptors to cause bronchoconstriction.

In contrast, AHR can also be measured 'indirectly' with drugs such as mannitol that increase the osmolarity of the airway surface liquid to cause airway narrowing via release of eosinophils and mast cells and associated mediators such as histamine and leukotriene D4[9]. In this regard, direct AHR can be viewed as reflecting airway geometry whereas indirect AHR is more closely associated with T2 inflammation[10]. Mannitol sensitivity can be measured at a specific time point by way of the provocative dose of mannitol required to drop forced expiratory volume in 1 second (FEV_1) by 10% (PD_{10}) expressed in milligrams (mg), whereas mannitol reactivity is expressed as response dose ratio (RDR) from the slope calculated by the final drop in FEV_1 divided by the total cumulative dose of mannitol administered expressed as %fall/mg. Both PD_{10} and RDR can be presented as the degree of change in AHR over time usually denoted by doubling differences (DD) where 1DD equates to a two-fold change on a logarithmic scale[11]. A patient would therefore be considered in AHR remission if their FEV_1 dropped by less than 10% after the final cumulative dose of 635mg mannitol was given i.e., mannitol PD_{10} sensitivity threshold ≥635mg.

We have previously shown that three doses of the anti-IL5Rα biologic benralizumab at a dose of 30mg every 4 weeks attenuates AHR as mannitol PD_{10} and RDR in n=21 patients with severe uncontrolled eosinophilic asthma (figure 2)[12]. The mechanism of action for this is likely via depletion of intraepithelial eosinophils that play a key role in AHR[13]. Pointedly, in our study patients who had achieved AHR remission (PD_{10} ≥635mg) had their values censored at the maximum cumulative dose of 635mg for the purposes of analysis. Therefore, the true extent of AHR improvement was underestimated in this study. Despite this the lower 95%CI excluded unity at 12 weeks to denote a clinically relevant effect, since 1DD is considered the biological variability value for mannitol AHR[11].

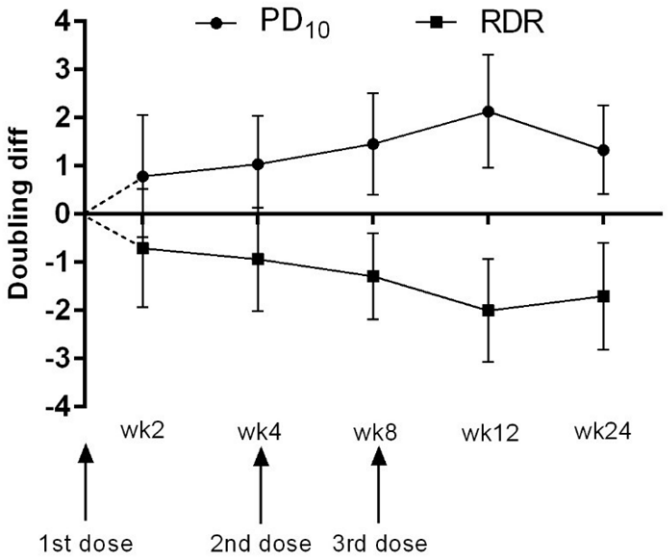


Figure 2 *Mean doubling differences (95%CI) for PD_{10} and RDR at serial timepoints after benralizumab therapy.*

Two previous studies have investigated the impact of anti-TSLP Tezepelumab on mannitol PD_{15}. The first was UPSTREAM (n=40) where three doses of IV 700mg Tezepelumab every 4 weeks demonstrated a numerical but statistically non-significant attenuation in the primary outcome of mannitol PD_{15} after 12 weeks[14]. The second trial was CASCADE (n=48) using subcutaneous 210mg Tezepelumab every 4 weeks which showed a statistically significant attenuation in mannitol PD_{15} after 28 weeks of therapy, albeit this was an exploratory outcome[15]. Another phase IV study is currently under way investigating the anti-IL4Rα biologic dupilumab (EudraCT 2021-005593-25) on the primary outcome of mannitol PD_{10} in patients with severe uncontrolled asthma.

We are aware of only one study that indirectly compares dupilumab (Dupi) and benralizumab (Benra) in severe asthma patients[16]. Here, 12 patients (24 total) from each study (EudraCT 2019-003763-22 and EudraCT 2021-005593-25) were case matched a priori for baseline mannitol PD_{10} to allow for accurate comparison. Although both biologics significantly attenuated mannitol PD_{10} after 12 weeks of therapy, the between treatment attenuation of AHR was significantly greater with dupilumab (figure 3A). Furthermore, dupilumab resulted in a significantly greater number of patients (67%) who achieved AHR remission, defined as a mannitol PD_{10} ≥635mg compared to benralizumab (25%) (figure 3B). Interestingly, the attenuation of AHR was much more heterogenous for benralizumab versus dupilumab, perhaps suggesting AHR remission is more predictable with dupilumab. It has also been shown that dupilumab conferred ICS sparing over a period of 3 months[17].

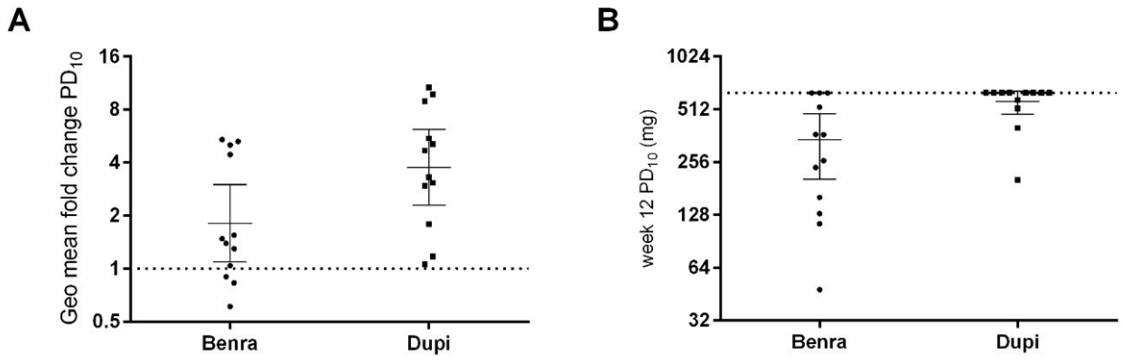


Figure 3 *(A) Individual values along with geometric means (95%CI) for the fold change from baseline in mannitol PD_{10} following 12 weeks of either benralizumab (Benra) or dupilumab (Dupi): Dupi vs Benra $p<0.05$ (B) Number of patients achieving AHR remission for absolute PD_{10} at week 12 (dotted line ≥635mg) depicting geometric means (95%CI).*

As the definition of complete remission requires AHR remission, the proposed study will characterise the prevalence of AHR remission in patients with severe asthma who are currently taking biologics in NHS Tayside. Moreover, it would be interesting to identify any differences in clinical features comparing patients who have or have not achieved AHR remission on such biologic therap.

Biologics and Small Airway Dysfunction in Severe Asthma

Airway oscillometry (AO) is a tidal breathing test that is effort independent and relies on superimposing sound or airwaves to assess airway impedance. Impedance itself comprises two components: resistance to airflow within the airways and reactance which can viewed as lung compliance. Smaller frequencies travel longer distances and therefore resistance at 5Hz (R5) refers to total airway resistance. Conversely, larger frequencies travel shorter distances and large airway resistance can be denoted by resistance at 20Hz. The peripheral airway resistance can be calculated by subtracting R20 from R5 (R5-R20) and is closely related to small airway constriction on lung computational modelling[18]. Peripheral airway reactance can be assessed at a single frequency e.g., at 5Hz (X5) or across a range of frequencies as area under the reactance curve (AX). The impact of biologic therapy on small airway dysfunction (SAD) has been summarised before[19].

In addition to assessing AHR, the study procedures will also include performing AO since SAD is closely associated with poor asthma control[20]. We have previously shown contrasting effects in regard to dupilumab but not benralizumab improving AO-defined small airway dysfunction in patients with severe asthma[21,22], and therefore it would be intriguing to establish baseline AO values in patients taking biologics over the longer term. As the difference in between benralizumab versus dupilumab probably relates in part to the mechanism of action of IL13 signalling and its relationship with bronchoconstriction and mucus plugging, one might expect Tezepelumab to also improve SAD for the same reason.

The reason for combining spirometry with AO pertains to the fact that utilising both lung function modalities increases the probability of detecting patients with more severe asthma at risk of worse outcomes such as symptom control and more frequent exacerbations (figure 4)[23-26].

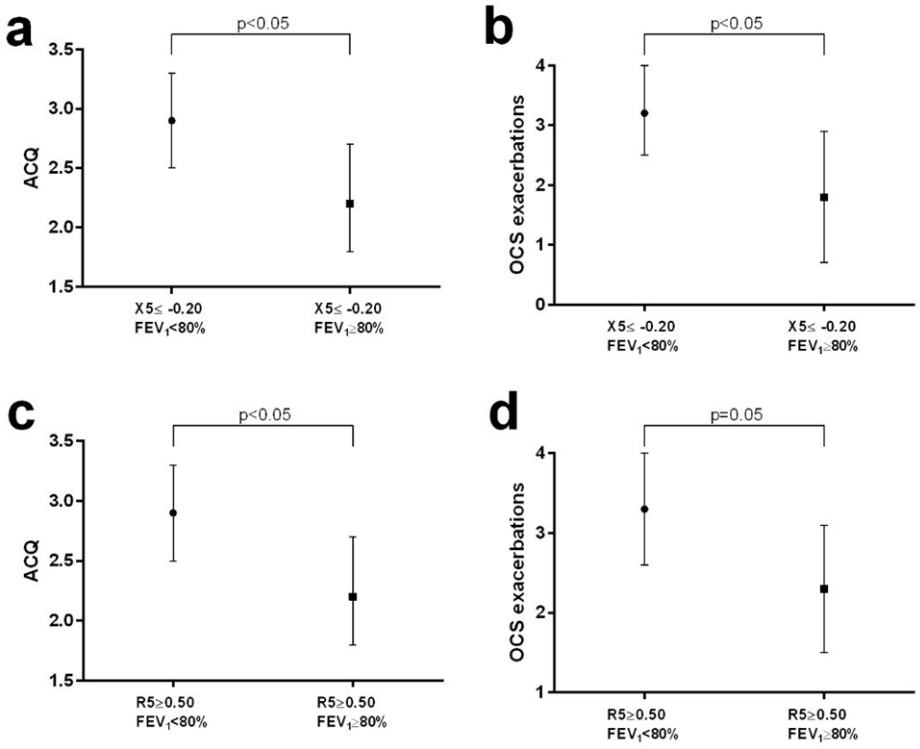


Figure 4 *Comparisons in ACQ and exacerbations in patients with combined impairment of oscillometry and spirometry versus those with impaired oscillometry but preserved spirometry, presented as means and 95%CI.*

Type 2 inflammation in Patients with Severe Asthma Taking Biologics

The upstream epithelial alarmins thymic stromal lymphopoietin (TSLP), IL25 and IL33 result in activation of downstream cytokines IL4, IL5 and IL13 signalling in susceptible asthmatic individuals who are exposed to various environmental allergens[2,3].

Phase 2 and Next Steps

There are adverse systemic effects associated with long term ICS use, including adrenal suppression, reduced bone density, diabetes, hyperlipidemia, skin thinning and cataracts[27]. Once phase 1 data has been generated from the proposed study, I will proceed with phase 2, a prospective longitudinal study looking at the effect of tapering ICS in patients with severe asthma taking different biologics. In present times, NHS Tayside patients who are considered for biologic initiation are only prescribed benralizumab, dupilumab or tezepelumab due to local guidelines.

In this regard, the recent SHAMAL study demonstrated that the majority of patients established on benralizumab were able to taper their ICS dose as the primary outcome, and asthma control was maintained in the majority to almost a year[28]. MART sparing which amounts 1.7 puffs/day (95%CI CI 0.7,2.7) was also seen with dupilumab over a 12 week period in patients using MART therapy with stable ACQ scores[17].

As SHAMAL has reviewed tapering of ICS within the benralizumab cohort, we aim to review those patients taking either dupilumab or tezepelumab. Both dupilumab and Tezepelumab exert an inhibitory effect on IL-13 which regulates bronchial smooth muscle contraction and FeNO. If patients taking either of these biologics were to reduce their ICS dose, one might therefore not expect a worsening of FeNO or lung function. If data were available on ICS tapering for all three biologics, it would also be possible to determine any differences (if any) in the change in mannitol PD_{10} pre- versus post-ICS tapering.

2 TRIAL/STUDY OBJECTIVES & OUTCOMES

This study aims to characterize the effect of taking dupilumab or tezepelumab on mannitol airway hyperresponsiveness (AHR) in patients with severe asthma. It will assess if patients are able to taper inhaled corticosteroids (ICS) while maintaining airway hyper-AHR remission and the longer-term impact on small airways dysfunction. Studies have shown patients have been able to reduce their overall dose of ICS while maintaining symptom control, however, there is no evidence to show if the reductions in ICS dose would result in worsening of AHR, and what clinical implications this may have.

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
To characterise the prevalence of mannitol airway hyperresponsiveness in patients with severe asthma taking dupilumab or Tezepelumab as they taper their inhaled corticosteroid dose	Change in mannitol PD_{10} from Visit 1 (post-run-in baseline) to Visit 2	End of visit 2 (week 26)

Table 2: Secondary Objectives and Outcome Measures

Secondary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**

• To characterise symptom control as ACQ and asthma quality of life as mini-AQLQ • To assess type 2 inflammation in blood. • To measure lung function as spirometry and airway oscillometry • To characterise the prevalence of mannitol airway hyperresponsiveness in patients with severe asthma taking dupilumab or Tezepelumab • Assess the effects of taking dupilumab or Tezepelumab on airways remodelling using AX	• Change in mannitol RDR from screening (post-run-in baseline) to visits 1 and 2 • Post mannitol challenge bronchodilator response • Number of puffs of MART • FeNO • Blood eosinophils • Blood total IgE • Spirometry • Airway oscillometry (AOS) • Asthma Control Questionnaire (ACQ6) • Mini-Asthma Quality of Life Questionnaire (AQLQ) • Diary cards for PEF, symptoms (morning values only) and reliever use (number of puffs)	End of visit 2 (week 26)

4 TRIAL DESIGN

This clinical trial is a phase IV, single arm, open labelled design. This will be a pragmatic trail reviewing the variations between patients that occur on biologic agents and aims to inform on the effects of these on small airways disease and airways remodelling. The project timeline will be approximately 1 year from the date of the first participant consented to study completion.

4.1 INTERVENTION

Participants will already be established on asthma biologic medications (either dupilumab or tezepelumab). All participants will receive the below interventions at visits 1 and 2:

- Airway oscillometry (AOS): This test measures the amount of resistance in the airways. You need to place your mouth around the mouthpiece and breathe normally for approximately 45 seconds. You are able to breathe in and out through the machine normally and the test is repeated 3 times to ensure an accurate result.
- Spirometry: This test measures the amount and speed of air that can be inhaled and exhaled. To do this test, you first breathe in fully and then seal your lips around the mouthpiece of the spirometer. You then blow out as fast and as far as you can until your lungs are empty. During this procedure some patients might feel dizzy. This procedure will be repeated at least three times and will take approximately 5 minutes.

- Fractional exhaled nitric oxide: This test measures the amount of nitric oxide in your exhaled breath and involves breathing into a tube. This gives an indication into the amount of inflammation within the airways.
- Mannitol challenge with salbutamol recovery: This is a lung function test often used to help diagnose asthma and it assesses how "twitchy" your airways are. We will ask you to inhale increasing doses of a challenge agent called mannitol to make your airways twitchy. Serial measurements of your breathing are made until a threshold is reached. Once the threshold is reached, we will give a medication called salbutamol to help your breathing recover from the challenge. We will continue to make measurements of your lung function until you recover fully. During the procedure you might cough or feel wheezy. It is safe and well-tolerated and we will monitor you carefully throughout the procedure to ensure you are comfortable.
- Blood test: This is to measure eosinophils which are a marker of type 2 inflammation
- Questionnaires: A symptom questionnaire (asthma control questionnaire) and quality of life questionnaire (mini-asthma quality of life questionnaire) will be done at each visit.

Screening will involve informed consent, confirmation of inclusion/exclusion critearia, history and examination, medication review, height and weight along side a bronchodilator reversibility test – both AOS and spirometry will be repeated after you are given Salbutamol inhaler to check if there is any significant improvement in your lung function after a short acting bronchodilator. The above listed tests will also be done excluding the mannitol challenge at screening. PI has been involved with the design of the study.

4.2 TRIAL DESCRIPTION

The study will be conducted as follows for each patient:
A screening visit to verify the patient's eligibility for inclusion in the study.

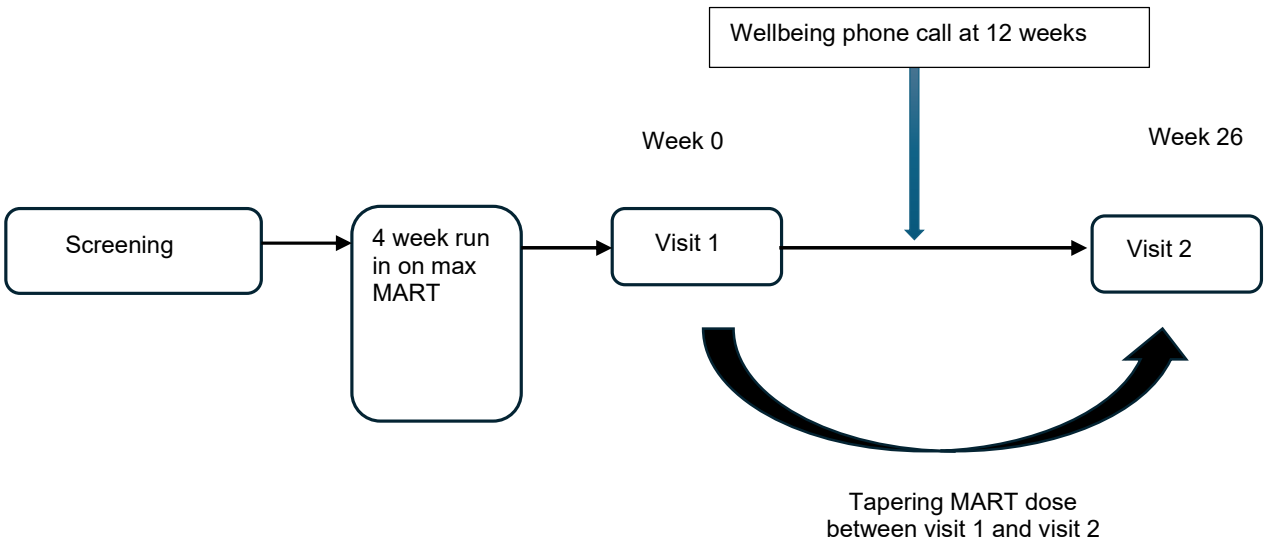
- Before run-in, ICS/LABA maintenance dose will be switched in all patients to beclometasone/formoterol 100/6 ug Fostair NEXThaler dry powder inhaler as 8 puffs per day.
- Fixed dose open (separate ICS/LABA plus LAMA) or closed (ICS/LAMA/LAMA in single inhaler) triple therapy will be converted during the run in Fostair NEXThaler 8 puffs/day.
- The rationale for using 8 puffs/day of Fostair NEXThaler during the run in period is to achieve optimal symptom control and associated mannitol AHR at baseline after the run in, prior to converting to MART therapy 2-8puffs/day over the ensuing 6 months.
- In other words, this will ensure that we achieve a uniform clean baseline after run in for all the patients prior to commencing variable dose MART therapy.
- At the conclusion of the 4-week run-in period (Visit 1), baseline tests will be performed, including a mannitol bronchial challenge test.

- After run-in patients for the ensuing 6 months will take their Fostair NEXThaler as maintenance and reliever therapy (MART) using between 2-8 puffs /day according to symptom control.
- The patient then re-attends 26 weeks later for Visit 2
- At visits 1 and 2 the participant will undertake an asthma control and mini-asthma quality of life questionnaire, spirometry, FeNO, airway oscillometry, blood tests (full blood count) and a mannitol bronchial challenge.
- Throughout the study, participants will maintain a symptom diary, monitor their peak expiratory flow daily and record their daily inhaler use. Pointedly the Nexthaler has a breath actuated dose counter such that it is possible to accurately record dose delivery to the lung. Also, the Nexthaler has an audible click upon breathing in at the correct inspiratory flow rate which helps to reinforce correct dose delivery.
- We will contact patients at 12 weeks to ensure they are maintaining symptom control and ensure they have no unanswered questions.

Data Collection:
Blood collection and sample preparation for blood eosinophil count will be performed according to procedures provided by the local NHS laboratory which will be in charge of transmitting the results to the Investigator for entry in the CRF. Spirometry will be carried out in accordance with guidelines published by the European Respiratory Society (ERS) standards. The AOS measurements will be carried out using the Thorasys TremoFlo C-100 (Thorasys Ltd) according to the instructions of the manufacturer. All AOS measurements will be performed prior to spirometry and mannitol bronchial challenge test. Mannitol will be given via dry powder inhaler (Aridol, Arna Pharma Pty Ltd (Pharmaxis), Sydney, Australia) in dose increments up to a maximum cumulative dose of 635mg as per manufacturer's guidelines until a fall in FEV_1 of 10% from baseline is achieved. The provocative dose to cause this 10% fall in FEV_1 (PD_{10}) can then be calculated. For patients whose FEV_1 does not fall by 10% after 635mg, the maximum achieved fall in FEV_1 will be recorded. Once the PD_{10} mannitol is achieved, the subject will be given rescue nebulised Salbutamol 2.5mg immediately and this can be repeated until the spirometry value has returned to within 5% of the pre-challenge value or according to investigator assessment. This takes approximately 30 to 45 minutes. The asthma control questionnaire and the mini asthma quality of life questionnaire will be used to assess symptom control. These questionnaires will be provided at each visit and participants will complete prior to pulmonary function tests and mannitol challenge.

Purpose and scope: Overall, the aim is to increase our understanding of the long-term effects of biologic medication in asthma on complete remission and to allow patients to reduce their steroid burden without any impact on their quality of life or symptom control.

4.3 TRIAL FLOWCHART



4.4 TRIAL MATRIX

	SCREEN	V1	V2
Confirmation of ID	X		
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Demographics	X		
Medical/Surgical History	X		
Concomitant Medications	X		
Adverse Event Recording	X		
Check Medication Withholding Times	X		
Physical Exam	X		
Height/Weight	X		
Vital Signs	X		

Asthma Control Questionnaire	X	X	X
Mini-Asthma Quality of Life Questionnaire	X	X	X
Spirometry	X	X	X
Airway Oscillometry	X	X	X
FeNO	X	X	X
Bloods: Full Blood Count	X	X	X
Mannitol Bronchial Challenge		X	X

4.5 TRIAL ASSESSMENTS

Demographics
Demographics -age, sex, race, smoking status - will be collected at screening.

Full blood count

Blood collection and sample preparation for FBC and specific IgE will be performed according to procedures provided by the local NHS laboratory which will be in charge of transmitting the results to the Investigator for entry in the CRF.

Specific IgE testing

Specific IgE testing is performed to detect presence of circulating levels of specific IgE antibodies to defined common allergens [Fluorescence enzyme linked immunoassay (Phadia Immunocap 250)]. The test is needed if the participant does not have any previous documented specific IgE test or if the previous test is older than 2 years.

Airway oscillometry

The AOS measurements will be carried out using either the Thorasys TremoFlo C-100 (Thorasys Ltd) or Jaeger Masterscreen (Hochberg, Germany) according to the instructions of the manufacturer. All AOS measurements will be performed both prior and post to spirometry and mannitol bronchial challenge test.

Spirometry

Spirometry will be carried out in triplicate in accordance with guidelines published by the European Respiratory Society (ERS) standards.

Bronchodilator Reversibility Test

Bronchodilator reversibility test using spirometry and AOS with salbutamol 400µg will be carried out at screening visit only.

Mannitol Bronchial Challenge Test

Mannitol will be given via dry powder inhaler (Aridol, Arnaphamrma, Sydney, Australia) in dose increments up to a maximum cumulative dose of 635mg as per manufacturer's guidelines until a fall in FEV_1 of 10% from baseline is achieved. The provocative dose to cause this 10% fall in FEV_1 (PD_{10}) can then be calculated. For patients whose FEV_1 does not fall by 10% after 635mg, the maximum achieved fall in FEV_1 will be recorded.

Once the PD_{10} mannitol is achieved, the subject will be given rescue nebulised Salbutamol 2.5mg immediately and this can be repeated until the spirometry value has returned to within 5% of the pre-challenge value or according to investigator assessment.

Calculating PD10

The provocative cumulative dose of mannitol required to decrease the FEV_1 by 10% of baseline value (PD_{10}) is derived by logarithmic interpolation (log 2 scale) between the highest cumulative dose that causes a decrease of ≥10% and the preceding dose.

The PD_{10} is calculated using the following formula.

$$\text{PD10 FEV1} = \text{anti-log}\left\{\log C1 + \frac{(\log C2 - \log C1)(10 - R1)}{(R2 - R1)}\right\}$$

Where:
C1 = second to last mannitol cumulative dose (cumulative dose preceding C2)
C2 = final cumulative dose of mannitol (cumulative dose that caused a decrease of ≥ 10% from baseline).
R1 = % decrease in FEV_1 after C1
R2 = % decrease in FEV_1 after C2

Response-Dose Ratio (RDR)

Mannitol challenge reactivity will be also calculated as Response-Dose Ratio (RDR), expressed as %/mg. RDR is the maximum % decrease in FEV_1 at the final dose/maximum cumulative dose (%/mg).

FeNO measurement

FeNO measurement will be carried out using NIOX VERO (Aerocrine AB, P.O. Box 1024, SE-171 21 Solna, Sweden) according to manufacturer's instructions.

Diary Card

Throughout the study from screening, patients will be instructed to measure the PEF three times each morning. Participants will also be asked to grade their symptom scores every morning.

At each visit, the diary card dispensed at the previous clinical encounter will be collected by the Investigator or designee who will check it for completeness and correctness. In case mistakes or missing information are found, the patient will be asked during the visit for clarification and when possible to correct and complete the information.

Constant reminders on how to complete the diaries and the importance of them will be made at each visit and phone call to maintain compliance. All diaries returned in the study will be reviewed at each visit to make sure they are completed fully, in ink and in the participants' own handwriting. Any discrepancies or blank entry boxes will be brought to the participant's attention and the reasons noted. All gaps, omissions and /or scored through entries will be queried and the explanations recorded.

ACQ 6 Questionnaire

The ACQ6 questionnaire includes 6 questions to investigate the main symptoms: woken at night by symptoms, waking in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. There is also a question for bronchodilator use.

Mini Asthma Quality of Life Questionnaire (Mini-AQLQ)

The mini-AQLQ has 15 questions in the same domains as the original AQLQ on symptoms, activities, emotions and environment.

4.6 TRIAL SAFETY ASSESSMENTS

- Adverse events (AEs) and adverse drug reactions (ADRs)
- FEV_1 and vital signs
- Diary cards: Morning domiciliary PEF, symptom and use of rescue/ reliever medication and VAS
- ACQ6

Participants will only be selected if they fulfil the predetermined inclusion criteria. A medically qualified doctor, on the Delegation Log and duly trained in the Protocol and potential risks of the IMP will be available on site at Ninewells Hospital throughout the treatment visit of the study if intervention is required due to a side effect occurring following the treatment. During the pre-visit patient phone call, SCRR staff will discuss COVID-19 safety precautions implemented as per the SCRR COVID-19 working practice document.

Physical examination

A qualified medical practitioner registered with the General Medical Council and named on the delegation log will carry this out. It will involve an external examination of cardiovascular, respiratory, gastro-intestinal systems and extremities, as well as the skin and lymph glands. Abnormalities will be recorded in the CRF and acted upon accordingly and volunteers excluded from study if considered clinically significant.

Pregnancy test

A urinary β-hCG will be performed at the time of screening for women considered of childbearing potential (WOCBP – refer to Appendix 1). A pregnancy test will be repeated at each visit in all WOCBP. Contraceptive advice is given fully in the PIS, and to both males and females, at the time of informed consent and reinforced at study visits.

Vital signs (Blood Pressure, Pulse Rate and Oxygen Saturation)

Systolic and diastolic blood pressure (SBP, DBP – mmHg), pulse rate (PR), and oxygen saturation will be measured in supine position after 5-min rest. One single measurement per time point will be done however all Vital signs may be repeated at the discretion of the investigator for the purposes of safety.

Bronchodilator Reversibility Test

Bronchodilator reversibility test using spirometry and AOS with salbutamol 400µg will be carried out at screening visit only. WThis will ensure all partiipants have an FEV1 >50% predicted.

4.6 TISSUE

No tissue will be collected.

4.8 INCIDENTAL FINDINGS

Any incidental findings (IF: previously undiagnosed condition) considered to be clinically significant will be reported to the participant's GP and/or consultant by the CI or Site PI, with the consent of the participant.

4.9 TRIAL/STUDY POPULATION

Any participant over 18 years of age who is established on dupilumab or tezepelumab with stable airways disease.

4.10 NUMBER OF PARTICIPANTS

Primary outcome 1 - A sample size of n=23 patients per biologic agent will provide a power 80% with alpha error of 0.05 (2 sided) to detect a 1 doubling dose (DD) shift (as change between visit 1 vs visit 3) in mannitol pd10 between responders and non responders assuming within subject SD of 1.2. Sufficient patients will be enrolled to achieve these 23 patients per biologic agent with 46 patients in total. Withdrawn subjects may be replaced. The primary endpoint will be analysed for patients who complete all visits per protocol.

4.11 INCLUSION CRITERIA

- Any patient over 18 years of age with severe asthma taking dupilumab or tezepelumab for severe asthma for at least 6 months
- FEV_1 ≥50% at baseline

4.12 EXCLUSION CRITERIA

- Any patients on maintenance oral steroids or required an oral steroid burst in the past 28 days
- Any patient who was switched from another biologic in the past 3 months
- Any other respiratory condition such as moderate to severe bronchiectasis or COPD
- Currently pregnant

Individuals will not be enrolled to the trial/study if they are participating in the clinical phase of another interventional trial/study or have done so within the last 30. Individuals who are participating in the follow-up phase of another interventional trial/study, or who are enrolled in an observational study, will be co-enrolled where the CIs of each study agree that it is appropriate.
Women of child-bearing potential (WOCBP), who do not abstain from sex, must be willing to have pregnancy testing prior to study entry. In addition, women of child bearing potential, who are sexually active, must be willing to use a form of a medically approved birth control method eg; · Combined Oral Contraceptive Pill or Placement of a intrauterine device - 'coil'or Barrier methods of contraception: male condom only or Established use of oral, injected, transdermal or implanted hormonal methods of contraception or Male partner sterilisation.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Potential participants will be recruited from secondary care, as well as a SCRR database of volunteers who have agreed to be contacted with regards to participating in departmental clinical research. Patients will be recruited from the severe asthma clinic and the NHS database of those on asthma biologics by the severe asthma team. These NHS patient will be contacted by one of the members of the team who are within the NHS severe asthma direct care team (Dr

Robert Greig, Dr Rory Chan or Prof Brian Lipworth) either in clinic or via the telephone. They will receive a written PIS inviting them to take part and detailing the trial requirements and the extent of their participation before attending for a screening visit. They will have the PIS for at least 24 hours and be encouraged to discuss the study and their potential involvement with both study staff and others, such as family and friends. The site may also recruit patients via National Health Service (NHS) Research Scotland's Scottish Health Research Register (SHARE) register and/or Scottish Primary Care Research Network (SPCRN) if there is difficulty achieving the required numbers. If needed, we will also utilise print advertisement to facilitate recruitment. Patients will be recruited by Prof Brian Lipworth, Dr Rory Chan or Dr Robert Greig who will also confirm eligibility. We will recruit sufficient patients to obtain 46 (23 per biologic agent) evaluable patients. Withdrawn subjects may be replaced.

5.2 CONSENTING PARTICIPANTS

The informed consent process will be conducted in compliance with the Sponsor's SOP. Consent will only be taken/received by study staff trained in the protocol and RSI who is on the Delegation Log. The CI will be responsible for ensuring informed consent is obtained before any protocol-specific procedures are carried out as the decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved. The verbal explanation to the participant will be performed by the CI or designate and will cover all the elements specified in the PIS (which potential participants will be given a minimum of 24 hours to review) and Informed Consent Form (ICF).

Adequate time shall be given to the patient to ask the CI or designee about any clarification needed and to consider his or her decision to participate in the trial. The participant will be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant will be given sufficient time to consider the information provided and to discuss this information with friends and family. It will be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled. Where a participant requests to speak with a physician from the study team, the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

The participant will be informed, and must agree to, their study records being inspected by appropriate personnel from the University of Dundee, NHS Tayside and the regulatory authorities, but it will be explained that their name will not be disclosed outside the study site.

The CI or delegate and the participant will sign and date the ICF as appropriate to confirm that consent has been obtained. The original will be retained separately from the Trial Master File (TMF) in the SCRR office while the study is active, a copy in the SCRR medical notes, and one copy must be given to the participant.

Where a participant requests to speak with a physician from the study team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

For adults who lose capacity, the participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.

The informed consent process will be conducted in compliance with TASC SOP07: Obtaining Informed Consent from Potential Participants in Clinical Research

5.3 SCREENING FOR ELIGIBILITY

N/A

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

5.5 RANDOMISATION

This is an open label, single intervention study so no randomisation is required

5.6 WITHDRAWAL PROCEDURES

Participants are free to withdraw at any time and are not obliged to give reason(s). The CI, PI or delegate will make a reasonable effort to ascertain the reason(s), both for those who express their right to withdraw and for those lost to follow up, while fully respecting the individual's rights.

Participants may be withdrawn by the CI or PI or delegate if it is considered to be in in their best interest. A full explanation will be provided. Those withdrawn, including those lost to follow-up, will be identified and a descriptive analysis of them provided, including the reasons for their loss, if known, and its relationship to treatment and outcome.

If a participant is withdrawn from the study after receiving the test treatment, the participant study number and corresponding test treatments will not be reassigned to another patient.

If after post run-in visit (Visit 1), the participants experience any deterioration of asthma symptoms or any exacerbation, one course of oral corticosteroids +/- antibiotics, or any number of emergency care visits without hospitalisation, is permitted. The subsequent study visit with mannitol bronchial challenge can be performed at least 2 weeks after the last dose of oral corticosteroids. Participants will be completely withdrawn from the study if they require hospitalisation due to asthma exacerbations.

6 DATA COLLECTION & MANAGEMENT

6.1 DATA COLLECTION

A paper case report form (CRF) will be compiled for each participant. Each CRF will have individual AE Logs and Concomitant Medication Logs. Data from study visits will be entered into the participant's paper CRF at the time of measurement (procedures at each visit are described previously). The CRF will not collect more information than is required to meet the aims of the study and to ensure the eligibility and safety of the patient. Prompts may be added to ensure protocol compliance. The CRF will be version controlled and based on the requirements of the protocol. The CRFs will not contain any patient identifiable information.

Participants will be allocated a code number and will be identified by this, their initials and date of birth. Identifiers used in the screening and treatment logs will be used as the identifiers for the CRFs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Data will be collected at each visit within the SCRR laboratory. Source data will include the CRF, the SCRR laboratory reports, print-outs or electronic files from equipment used and all will be anonymised where required. Data will be collected by a trained investigator or technician performing the study visit and named on the delegation log.

Data collected from CRFs will be entered into trial-specific Excel spreadsheet that are specified in the protocol on PCs following the Sponsor's SOPs using Excel. The Excel spreadsheet will be version controlled. No identifiable information will be retained in the CRF or in the Excel spread sheet used for data management. The spreadsheet will be saved on University of Dundee secure server at the end of each data entry session which is backed up daily. PCs are password protected and kept in the SCRR office which can be locked to prevent unauthorised access and the PCs are accessible only to named study individuals and each individual have a unique log on.

The CRF will be stored securely (in a locked room) within SCRR, and will be accessible only by those directly involved with the trial. The data will be entered onto the Excel spreadsheet by SCRR staff named on the delegation log, on the same day as the participant visit or as soon as possible afterwards. The data will be transcribed to Excel from the paper CRF. Prior to any data transfer to any other programme for analysis and all queries must be clarified with the CI or PI and any changes to the data in the CRF must be made with a single line drawn through, initialled and dated. The original data must be clearly visible.

The data on the Excel spreadsheet will be re-checked against the CRFs to confirm accurate entry. Data queries should be identified by using the Insert Comment Function in Excel and resolved or explained as soon as possible. A final check on the accuracy of the data will be performed by individuals who, where possible, were not involved in the original data entry.

6.2 DATA MANAGEMENT SYSTEM

Data management will be conducted in compliance with TASC SOPs on Data Management, including TASC SOP Data Management Systems in Clinical Research.

The data management system (DMS) will be Excel, as approved by Sponsor.
The DMS will be based on the protocol and CRF for the trial/study and individual requirements of the investigators. The CRF will collect only information that is required to meet the aims of the trial/study and to ensure the eligibility and safety of the participant. The trial/study database will be compliant with TASC SOP Data Management Systems in Clinical Research and TASC SOP: Data Management In CTIMPS Using Excel.
The database is managed in line with all applicable principles of medical confidentiality and data laws. The Data Controller will be the University of Dundee and the Data Custodian will be the CI.

The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the trial/study team.

Database lock will be conducted in compliance with TASC SOP Locking Clinical Study Databases.

7 STATISTICS AND DATA ANALYSIS

7.1 SAMPLE SIZE CALCULATION

Primary outcome 1 - A sample size of n=23 patients per biologic agent will provide a power 80% with alpha error of 0.05 (2 sided) to detect a 1 doubling dose (DD) shift (as change between visit 1 vs visit 2) in mannitol pd10 between responders and non responders assuming within subject SD of 1.2. Sufficient patients will be enrolled to achieve these 23patients per biologic agent with 46 patients in total. Withdrawn subjects may be replaced. The primary endpoint will be analysed for patients who complete all visits per protocol.

7.2 PROPOSED ANALYSES

- Statistical analysis will be performed using SPSS v29.
- Demographics and baseline characteristics will be summarised using descriptive statistics for the population completed per protocol.
- Descriptive statistics for continuous variables will include: n (number of observed values), arithmetic mean, standard deviation, median, interquartile ranges, minimum and maximum.
- Categorical variables will be summarised as frequency count and percentage distribution.

Primary outcome analysis: Analysis of Variance (ANOVA) will be used to determine any significant differences between patients who have achieved AHR remission versus those who have not, with a two tailed alpha error of 0.05. Mannitol PD_{10} values will be log transformed to the base 10 to normalise distribution and therefore geometric means will be presented. Subgroup analysis: Analysis of any significant differences between patients who have achieved AHR remission versus those who have not will be reviewed in subgroups of patients on each biologic (dupilumab or tezepelumab).

Secondary outcome analysis: ANOVA will be utilised to determine significant differences in T2 biomarkers, spirometry, oscillometry, ACQ and mini-AQLQ.

The statistical analysis will be done by the study team and overseen by the chief investigator.

7.3 MISSING DATA

Missing data and the possible outliers will be reviewed, which may involve modifying outliers.

If needed, multiple imputations will be applied to replace missing data.

7.4 TRANSFER OF DATA

The data will be entered onto the Excel spreadsheet by SCRR staff named on the delegation log, on the same day as the participant visit or as soon as possible afterwards and anonymised. The data will be transcribed to Excel from the paper CRF with the data anonymised. Prior to any data transfer to any other programme for analysis and all queries must be clarified with the CI or PI and any changes to the data in the CRF must be made with a single line drawn through, initialled and dated. The original data must be clearly visible. Data will not be transferred off the secure UoD password protected servers.

8 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

8.1 TRIAL MANAGEMENT GROUP

The trial/study will be co-ordinated by a Trial/Study Management Group (T/SMG), consisting of the grant holder Chief Investigator (CI) and principal investigators (PIs).

8.2 TRIAL STEERING COMMITTEE

Not required as this is a single-site non- CTIMP with oversight by the Trial Management Group.

8.3 DATA MONITORING COMMITTEE

Not required as this is a single-site non- CTIMP with oversight by the Trial Management Group.

8.4 INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

9 GOOD CLINICAL PRACTICE

9.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

9.2 CONFIDENTIALITY AND DATA PROTECTION

The CI and trial staff will comply with all applicable medical confidentiality and data protection principles and laws with regard to the collection, storage, processing and disclosure of personal data.

The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All trial records and personal data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate personal data will have limited access measures via user names and passwords.

Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by 0the Sponsor, its designee or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The CI and trial staff will not disclose or use for any purpose other than performance of the trial, any personal data, record, or other unpublished, confidential information disclosed by those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the CI and appropriate delegated trial staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

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

The CI will be responsible for the conduct of the trial. Site delegate(s) will oversee the trial and will be accountable to the CI. Site delegates include medically qualified clinical research fellow(s)/ doctor(s), study/ project managers and clinical trial assistants. A trial-specific Delegation Log will be prepared, detailing the duties of each member of staff working on the trial. The study will not commence until a a favourable REC opinion is obtained. The study will

not start until formal Green Light by the Sponsor. Any changes in study activity, except those necessary to remove an apparent, immediate hazard to the participant, will be reviewed and approved by the CI. All amendments including Substantial Amendment to the protocol must be reviewed and approved by the Sponsor prior to submission to the REC and NHS Tayside R&D Office for their approvals and permissions, and prior to participants being consented into an amended protocol. The REC are not required to approve or be notified of non-substantial amendments. They are notified of non-substantial amendments at the next Substantial Amendment request or within Annual Report.

9.3 INSURANCE AND INDEMNITY

The University of Dundee is sponsoring the study.

Insurance – The University of Dundee holds Clinical Trials indemnity cover which covers the University's legal liability for harm caused to patients/participants. Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity - The Sponsor does not provide study participants with indemnity in relation to participation in the Study but has insurance for legal liability as described above.

10 ADVERSE EVENTS

10.1 DEFINITIONS

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • Or is otherwise considered serious

10.2 RECORDING AND REPORTING AE

All SAEs will be recorded on the AE Log in the CRF and will be assessed for severity by the CI or delegate. SAEs will be recorded from the time a participant consents to join the study until the participant's last study visit.

The Investigator will make a clinical judgment as to whether or not an AE is of sufficient severity to require the participant's removal from the study. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant should, if required, be offered an end of study assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. SAEs will be followed up until 30 days after participant's last visit.

The CI or delegate will ask about the occurrence of SAEs and hospitalisations at every visit during the study. **SAEs which are both unexpected and related to study participation** will be submitted on an HRA NCTIMP Safety Report form to the REC by the CI, within 15 days of becoming aware of the SAE, and copied to the Sponsor Research Governance Office.

Worsening of the condition under study will not be classed as an AE, but will be defined as an outcome. Pre-specified outcome(s) will not be classed as an AE but as an outcome. Elective admissions and hospitalisations for treatment planned prior to randomisation, where appropriate, will not be considered as an AE. However SAEs occurring during such hospitalisations will be recorded.

11 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in CTIMPs and Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

Any safety reports additional to SAE reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor as a potential breach report. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately

12.2 STUDY RECORD RETENTION

Archiving of study documents will be for ten years after the end of study.

12.3 END OF STUDY

The end of study is defined as last patient last visit (LPLV). The Sponsor, CI and/or the SC have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

13.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

13.3 PEER REVIEW

The research methodology has been reviewed by the Sponsor. It is generally the practice of most journals to send the manuscript for peer review prior to publication.

14 REFERENCES

1. Global Initiative for Asthma. Difficult-to-treat and Severe Asthma in Adolescent and Adult Patients. V4.0 August 2023. Date Accessed: January 25, 2024.
2. Chan R, RuiWen Kuo C, Lipworth B. Pragmatic Clinical Perspective on Biologics for Severe Refractory Type 2 Asthma. J Allergy Clin Immunol Pract 2020;8(10):3363-3370. DOI: 10.1016/j.jaip.2020.06.048.
3. Chan R, Stewart K, Misirovs R, Lipworth BJ. Targeting Downstream Type 2 Cytokines or Upstream Epithelial Alarmins for Severe Asthma. J Allergy Clin Immunol Pract 2022;10(6):1497-1505. DOI: 10.1016/j.jaip.2022.01.040.
4. Menzies-Gow A, Bafadhel M, Busse WW, et al. An expert consensus framework for asthma remission as a treatment goal. J Allergy Clin Immunol 2020;145(3):757-765. DOI: 10.1016/j.jaci.2019.12.006.
5. Upham JW, Le Lievre C, Jackson DJ, et al. Defining a Severe Asthma Super-Responder: Findings from a Delphi Process. J Allergy Clin Immunol Pract 2021;9(11):3997-4004. DOI: 10.1016/j.jaip.2021.06.041.
6. Lipworth B, Kuo CR, Stewart K, Chan R. Should Airway Hyper-Responsiveness Be Included in the Definition of Clinical Remission With Biologic Therapy in Severe Asthma. J Allergy Clin Immunol Pract 2024;12(4):904-907. DOI: 10.1016/j.jaip.2023.12.013.

7. Chan R, Lipworth B. Efficacy of biologic therapy on airway hyperresponsiveness in asthma. Ann Allergy Asthma Immunol 2023;131(1):37-41. DOI: 10.1016/j.anai.2023.02.016.
8. O'Byrne PM, Inman MD. Airway hyperresponsiveness. Chest 2003;123(3 Suppl):411S-6S. DOI: 10.1378/chest.123.3_suppl.411s.
9. Brannan JD, Lougheed MD. Airway hyperresponsiveness in asthma: mechanisms, clinical significance, and treatment. Front Physiol 2012;3:460. DOI: 10.3389/fphys.2012.00460.
10. Van Den Berge M, Meijer RJ, Kerstjens HA, et al. PC(20) adenosine 5'-monophosphate is more closely associated with airway inflammation in asthma than PC(20) methacholine. Am J Respir Crit Care Med 2001;163(7):1546-50. DOI: 10.1164/ajrccm.163.7.2010145.
11. Sverrild A, Leadbetter J, Porsbjerg C. The use of the mannitol test as an outcome measure in asthma intervention studies: a review and practical recommendations. Respir Res 2021;22(1):287. DOI: 10.1186/s12931-021-01876-9.
12. Chan R, RuiWen Kuo C, Jabbal S, Lipworth BJ. Eosinophil depletion with benralizumab is associated with attenuated mannitol airway hyperresponsiveness in severe uncontrolled eosinophilic asthma. J Allergy Clin Immunol 2023;151(3):700-705 e10. DOI: 10.1016/j.jaci.2022.10.028.
13. Al-Shaikhly T, Murphy RC, Parker A, et al. Location of eosinophils in the airway wall is critical for specific features of airway hyperresponsiveness and T2 inflammation in asthma. Eur Respir J 2022;60(2). DOI: 10.1183/13993003.01865-2021.
14. Sverrild A, Hansen S, Hvidtfeldt M, et al. The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM). Eur Respir J 2022;59(1). DOI: 10.1183/13993003.01296-2021.
15. Diver S, Khalfaoui L, Emson C, et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med 2021;9(11):1299-1312. DOI: 10.1016/S2213-2600(21)00226-5.
16. R. Chan KES, C.R. Kuo, B.J. Lipworth. Relative Attenuation of Mannitol Challenge by Anti-IL5RA or Anti-IL4RA in Severe Uncontrolled Asthma (abstract). American Journal of Respiratory and Critical Care Medicine 2024;209:A1375.
17. Stewart K, Kuo CR, Chan R, Lipworth B. Evaluating an electronic device to monitor the type 2 high unified airway response to dupilumab. Ann Allergy Asthma Immunol 2024;133(2):211-213. DOI: 10.1016/j.anai.2024.04.015.
18. Foy BH, Soares M, Bordas R, et al. Lung Computational Models and the Role of the Small Airways in Asthma. Am J Respir Crit Care Med 2019;200(8):982-991. DOI: 10.1164/rccm.201812-2322OC.
19. Chan R, Lipworth BJ. Impact of Biologic Therapy on the Small Airways Asthma Phenotype. Lung 2022;200(6):691-696. DOI: 10.1007/s00408-022-00579-2.
20. Manoharan A, Anderson WJ, Lipworth J, Ibrahim I, Lipworth BJ. Small airway dysfunction is associated with poorer asthma control. Eur Respir J 2014;44(5):1353-5. DOI: 10.1183/09031936.00082314.
21. Chan R, Lipworth B. Real-life effects of dupilumab on airway oscillometry in severe uncontrolled asthma. Ann Allergy Asthma Immunol 2023;131(5):664-666. DOI: 10.1016/j.anai.2023.07.021.
22. Chan R, Lipworth BJ. Real-life effects of benralizumab on airway oscillometry in severe eosinophilic asthma. BMJ Open Respir Res 2023;10(1). DOI: 10.1136/bmjresp-2022-001472.
23. Chan R, Lipworth B. Interactions between spirometry and oscillometry in patients with moderate to severe asthma. Eur Respir J 2022;60(4). DOI: 10.1183/13993003.00543-2022.

24. Chan R, Lipworth B. Forced Vital Capacity and Low Frequency Reactance Area Measurements Are Associated with Asthma Control and Exacerbations. Lung 2022;200(3):301-303. DOI: 10.1007/s00408-022-00542-1.
25. Chan R, Lipworth BJ. Determinants of asthma control and exacerbations in moderate to severe asthma. J Allergy Clin Immunol Pract 2022;10(10):2758-2760 e1. DOI: 10.1016/j.jaip.2022.06.042.
26. Chan R, Lipworth BJ. Combining low-frequency oscillometry and spirometry measurements in relation to asthma control and exacerbations in moderate-to-severe asthma. J Allergy Clin Immunol Pract 2022;10(7):1910-1912 e1. DOI: 10.1016/j.jaip.2022.03.023.
27. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med 1999;159(9):941-55. DOI: 10.1001/archinte.159.9.941.
28. Jackson DJ, Heaney LG, Humbert M, et al. Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study. Lancet 2024;403(10423):271-281. DOI: 10.1016/S0140-6736(23)02284-5.