Summary of Participant Information Sheet- Tailoring Inhaled Corticosteroids in patients with Severe Asthma taking Biologics (TICSAB)

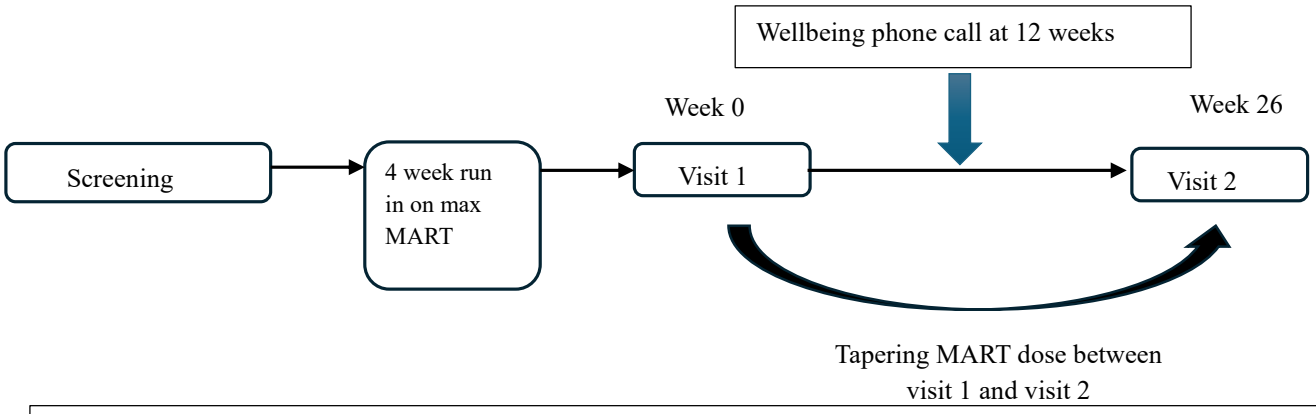
Study Researcher: Dr Robert Greig

Who: Patients with a diagnosis of severe asthma, whose asthma is stable and who are already taking an asthma biologics - either dupilumab or Tezepelumab.

Why: Inhaled corticosteroids are used to help treat severe asthma. We know that long term use of inhaled corticosteroids can cause adverse effects and we proposed to study if biologic medications can allow asthmatics to reduce their overall corticosteroid dose and so ultimately reduce the risk of steroid related side effects in the long term.

What:

The study will take place over a 7 month period per participant with 3 visits total.



Flow chart outlining study with screening visit, 4 week run in on maximal inhaled MART therapy and then visits at week 0 and week 26. A wellbeing phone call will be done at 12 weeks and the MART will be tapered between weeks 0 and 26.

Screening: To assess if participants are eligible to take part in the study. This will include: history and examination, medication check, height and weight, asthma questionnaires, blood tests, breathing tests.

Visits 1 and 2 will include: Blood pressure, asthma questionnaires, blood tests, breathing tests and mannitol test.

Between visits, we will provide you with a diary to record your symptoms and number of puffs used per day of your inhaler. We will phone to ensure you remain well and are happy with progress within the study between the visits at 12 weeks.

Full explanation of the study can be found in the patient information form:

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Participant Information Sheet

Tailoring Inhaled Corticosteroids in patients with Severe Asthma taking Biologics

(TICSAB)

We would like to invite patients with severe asthma who are on biologics (dupilumab or tezepelumab) to take part in a study looking at reducing their dose of inhaled corticosteroids (steroid inhaler). Before you decide if you wish to take part, we would like you to understand why we are doing the study and what it would involve.

The study is being carried out as part of a research project at the Scottish Centre for Respiratory Research, University of Dundee School of Medicine and is funded by the department's own funds. The results of the study will also be used as part of a dedicated clinical research fellow's MD (Doctor of Medicine) degree at the University of Dundee.

The information below describes what we are doing and why. Please read it carefully. If you have any questions, we will be happy to answer them, and please discuss the study with anyone else that you wish. You do not have to decide straight away whether or not you would like to become involved and can take as much time as you need to think about it.

Patients are being recruited from the severe asthma clinic and the NHS database of those on asthma biologics by the severe asthma team. We (those within the severe asthma team) will contact you either in clinic or via the telephone initially to discuss the study and if you would be interested.

Background to the study

The presence of airway twitchiness, also known as airway hyper-responsiveness, is one of the key features of persistent asthma, reflecting increased sensitivity of the airway to a variety of external stimuli. Studies have found that asthmatic patients with airway twitchiness have significantly higher levels of particular white blood cells called eosinophils, and higher levels of a molecule found in exhaled breath called fractional exhaled nitric oxide (FeNO).

Together, eosinophils and FeNO can indicate a specific form of airway inflammation also known as type 2 inflammation. Biologics act on reducing this type 2 inflammation and improving control of airway twitchiness. Inhaled corticosteroids (ICS) are also used for this purpose.

We know there are adverse effects associated with long term inhaled corticosteroid use, including adrenal suppression, reduced bone density, diabetes, hyperlipidemia, skin thinning and cataracts. In this study, we aim to assess if the two biologic medications improve airway twitchiness in severe asthma with type 2 inflammation to the point that the dose of inhaled corticosteroid can be reduced and so reducing overall steroid exposure to patients with severe asthma.

Eligible patients will be those with a diagnosis of severe asthma whose asthma is stable and are already taking dupilumab or Tezepelumab (and so already exhibit a significant degree of airway twitchiness and a raised blood eosinophil level and/or FeNO level). This means you will not have required any courses of oral steroid tables in the past month prior to the study.

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

Do I have to take part?

No. It is up to you to choose, taking part in this study is entirely up to you. You can choose to take part or choose not to take part. If you choose to take part you can stop the study at any time. You do not have to give a reason for not taking part or for stopping. If you do not want to take part or want to stop the trial/study the medical care you get and your relationship with the medical or nursing staff looking after you will not be affected.

What happens if you agree to take part?

Screening Visit / Run-in Period

You will first be invited to come for a screening visit. One of our team will go through this information sheet with you and answer any questions you have. It is completely up to you whether you decide to join the study. Either the investigator(s), co-investigator(s) or a trained member of staff will have a discussion with you about the study so that you understand the visit schedules, dosing requirement and potential side effects. You are welcomed to ask questions about the research. After all your questions have been answered, should you agree to take part, we will then ask you to sign a consent form. You will be asked to read the statements on the Informed Consent Form, initial the boxes against each of these statements, and write your name in full, sign and date. Even after doing this, you are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive in any way. Your GP will be informed if you enrol to the study.

During the screening visit we will:

- Ask you some health-related questions, including asking you to complete some questionnaires about your asthma
- Record demographics – age, sex, race, smoking status.
- Check what medication you are taking
- Perform a urinary pregnancy test in woman considered to have childbearing potential

- Perform a simple blood test for full blood count and allergy testing (latter performed if no previous allergy blood test or skin prick test from past 2 years available)
- Do various breathing tests:
    - 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.
    - 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.

If you are suitable to enter the study after screening, your regular combined inhaled corticosteroid and long-acting bronchodilator inhaler will be changed to **FOSTAIR NEXTHALER** which contains an inhaled corticosteroid and a long-acting bronchodilator (beclometasone 100 micrograms and formoterol 6 micrograms) equivalent to the inhaled dose you are taking at screening visit. This inhaler is activated by breathing in and will click when you have received the dose and the dose counter will drop by 1. The inhaler should be taken twice daily as a maintenance treatment and whenever you need it for asthma symptoms as a reliever up to a maximum of 8 puffs daily including the maintenance doses. This regimen is known as single inhaler for maintenance and reliever therapy (MART). The rest of your asthma medications will be continued. You will then enter the 4-week run-in period during which you will take the maximum inhaled dose of 4 puffs twice a day. If there are no problems during this period and your asthma is stable, you will proceed to the treatment period of the study. If you feel your asthma is worsening at any time, you can contact us, and we can give you appropriate medical advice or see you in person if necessary.

Before leaving the department at the end of the Screening Visit you will be given:

• A peak flow meter and a diary card.

You will keep taking your normal medicines for any other conditions.

Study Visits

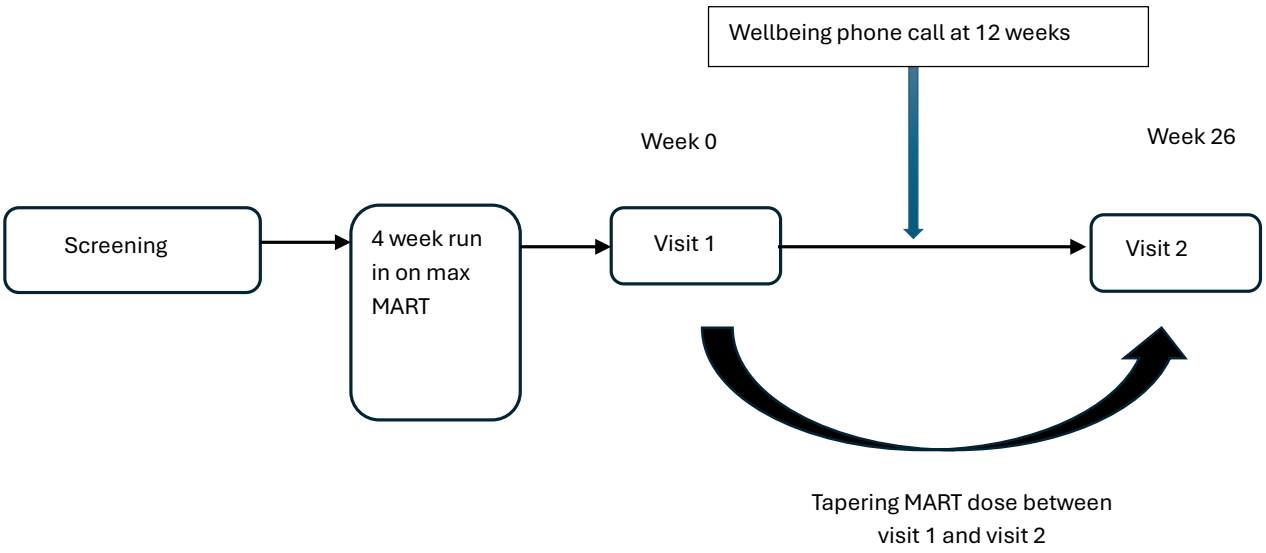
If you decide to join the study and pass the screening visit. You will be started on Fostair NEXThaler inhaler (which you may already be on and if not, is very similar to your current steroid inhaler) for 4 weeks. This will be followed by two study visits which include questionnaires, blood tests, and lung function tests. During this time, you will reduce you use of the ICS inhaler and record your symptoms.

In addition to the lung function tests described in the screening visit, there will also be one additional test called a **mannitol challenge with salbutamol recovery** at Visits 1 and 2. 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 – risks are further discussed on page 7. The mannitol challenge is considered an aerosol generating procedure as it may make you cough. Therefore, as part of standard procedure staff will be mandated to wear personal protective equipment for this part of the visit. This includes a pair of gloves and a face mask.

We will need to know what medications you are taking before your study visits, as some require to be withheld for a period of time before the appointments to ensure we are able to get accurate readings from your lung function tests. These are detailed in the table below and we will check these with you at each visit and ensure you know the instructions for the next visit.

We will inform you of the results at the end of the study and you can request a printed copy from the investigating team.

Study Overview



Flow chart outlining study with screening visit, 4 week run in on maximal inhaled MART therapy and then visits at week 0 and week 26. A wellbeing phone call will be done at 12 weeks and the MART will be tapered between weeks 0 and 26.

Medication	**How long to withhold before your visit**
Long-acting beta-agonist (LABA) inhalers	12 hours (twice daily dosing)

(e.g. Serevent, Oxis, Atimos)	24 hours (once daily dosing)
Inhaled corticosteroids/long-acting beta-agonist combination inhalers (e.g. Seretide, Symbicort, Fostair, Relvar)	12 hours (twice daily dosing e.g. Seretide, Symbicort, Fostair) 24 hours (once daily dosing e.g. Relvar)
Long-acting muscarinic antagonists (LAMA) inhalers (e.g. Spiriva, Eklira, Incruse)	24 hours
Short-acting muscarinic antagonists (SAMA) including Ipratropium bromide (e.g. Atrovent)	6 hours
Inhaled cromones (e.g. Tilade, Intal)	6 hours
Short-acting beta-agonist (SABA) inhalers including Salbutamol (e.g. Ventolin)	6 hours
Montelukast (e.g. Singulair)	48 hours
Theophylline (e.g. Uniphyllin, Slo-Phyllin, Nuelin)	48 hours
Antihistamines	48 hours 5 days (only if allergy blood testing required)

If at any point prior to a study visit, you wish to restart your withheld medications and reschedule the visit, or to withdraw, you are fully within your rights to do so. Please contact us (details below) if this is the case. If at any point you feel that withholding your medications is making you feel unwell, please contact us as soon as possible; you may cancel or reschedule the visit. If you wish to restart your medications, they should be restarted at their usual doses.

Throughout the study, you will be asked to manually record peak flow readings, any symptoms you have and how often you require the ICS/formoterol reliever inhaler and record these in the supplied asthma diary cards. We will explain to you how to fill out the diaries at the screening visit.

After the screening visit, you will undergo a 4 week run in period before the first study visit. During this time, you will take the maximum dose of MART inhaled therapy – 4puffs twice a day. You will then attend visit one and have baseline tests done and then start to reduce your inhaled medication dose as able based on how you feel and your symptoms. You will return one more time at 6 months after visit one for repeat testing to assess your symptoms and airway twitchiness. In total, from screening, the study will take approximately 7 months per participant.

The table below gives a summary of the study visits. **Study Visit Number**	**Estimated duration of study visit**	**What will take place**
Visit 1	2.5 hours	• Blood pressure • Blood sample • Asthma questionnaires • Spirometry, airway oscillometry and mannitol challenge test
Visit 2	2.5 hours	• Asthma questionnaires • Blood pressure • Blood sample • Spirometry, airway oscillometry and mannitol challenge test

Your symptoms may not improve through being in the trial, but the results will help us understand more about how we treat asthma in the future. No study drug will be continued following the end of study.

Contraceptive Advice

Those who are currently pregnant are unable to partake in this trial. While mannitol challenge can be performed in those who are pregnant, this is limited safety data available and there is a risk of reduced oxygen supply to the foetus. As this is for clinical research, the risk to a pregnancy was felt to be unjustified. There is no risk to the foetus in those whose partner is pregnant.

If you are a woman who could get pregnant and you are sexually active you must be willing to have a pregnancy test before starting the trial/study due to the above potential risk to a foetus. You will also be asked to have a pregnancy test at study visits. You must be willing to use a birth control method which is medically approved.

Medically approved birth control:

Combined Oral Contraceptive Pill

Intrauterine device – 'coil'

Male condom

Injected, patch or implant contraceptive

Male partner vasectomy - sterilisation

What are the possible benefits of taking part?

There is no guarantee of any specific benefit. The aim of the study is to establish if the inhaled steroid dose in severe asthmatics can be reduced while ensure the airways do not become more twitchy. If the study does show this, then this would benefit the severe asthma community to suggest they can reduce their corticosteroid dose and thus reduce the risk of corticosteroid related side effects. This would be a benefit to greater society as not all patients will develop these steroid related adverse effects.

What are the possible disadvantages and risks of taking part?

You will already be established on your biologic medications (dupilumab or Tezepelumab). Your inhaler may be changed to facilitate the MART therapy but will contain very similar medications to your previous inhalers.

Blood taking: There are a few small risks associated with with taking blood sample including bruising, soreness and bleeding. There is also a very low risk of infection which is managed by using a sterile technique. Prior to getting blood taken, it is advised you ensure you are hydrated.

Mannitol challenge: This is generally safe under medical supervision, there are some risks associated with the test. These include wheezing and breathlessness – this is expected and will be treated with a salbutamol nebuliser once it occurs; coughing; chest tightness and dizziness – can occur due to hyperventilation (fast breathing).

If you have an asthma exacerbation during the study, you will be allowed one course of oral steroids, usually prescribed as Prednisolone. It is therefore very important that any new health problem or possible side effect is quickly reported to the investigator, regardless of whether or not you think is related to the study. If you should in any way become concerned, you should contact the unit using the contact details under "Contact numbers. If you are unwell and need urgent attention or assistance, you must not delay in seeking further advice or treatment as usual through the NHS services i.e. from your General Practitioner, the ambulance service, NHS24, or the Accident and Emergency Department.

We will need to tell your General Practitioner that you have agreed to take part in this study. We can also give them information that we think may be helpful to your future care (such as lung function test results). Once the study is finished, all the results (or 'data') will be analysed by staff at the Scottish Centre for Respiratory Research. Data is stored on computers that can only be looked at with a password. This is to make sure that only members of our team can look at the information.

Your personal records remain confidential and any information from this study will only be referred to by code. Computerised data collected in this study will be stored securely on password protected computer files for 10 years. Written data collected from this study is stored securely for 10 years before being destroyed. This is a requirement for all studies sponsored by the University of Dundee and NHS Tayside involving medicines in the event that records need to be referred to at a later date.

Incidental Findings

Since this research involves lung function test, blood tests, and an examination by a doctor, it is quite possible that it may show up findings other than those under investigation. These are what we call 'incidental findings', the significance of which is often unclear or, indeed, something that the researchers themselves are not qualified to interpret or act upon. If that is the case, expert advice will be sought. If these findings are significant, we will inform you and either write to or phone your GP about the findings. We will also inform you and your GP of any abnormality found from the tests in which might require further follow up or investigation.

What are my rights?

We hope to get useful information from this study that will improve the care of patients with asthma in the future. Taking part in this study is entirely voluntary and you can decide not to take part or to withdraw from the study at any time without having to give a reason. This would not affect your future medical care in any way. If you have any further questions after reading this information sheet then we will be happy to try to answer them.

This study has been reviewed by ********** Research Ethics Service REC – awaiting review****, which has responsibility for scrutinising proposals for medical research on humans, in accordance with the requirements of the Clinical Trials Regulations. In this case, the reviewing Committee has raised no objections from the point of view of research ethics.

It is a requirement for any study that records made by the study team about you should be made available, if required, for scrutiny to ensure that the study is being conducted correctly. This would involve a clinical trial monitors employed or appointed by NHS Tayside or the University of Dundee or other appropriate staff from NHS Tayside, the University of Dundee and Regulatory Authorities. The data collected during the study will be stored on University of Dundee computers.

What if something goes wrong?

If you are concerned about your participation in the study you have the right to discuss your concern with a researcher involved in the study or a doctor involved in your care. If you have a complaint about your participation first of all please talk to the researcher.

If you are not satisfied, you can make a formal complaint to a senior member of the research team or to the Complaints Officer for NHS Tayside.

Patient Experience Team
NHS Tayside
Ninewells Hospital
Dundee DD1 9SY
Freephone: 0800 027 5507
Email: TAY.feedback@nhs.scot

If you think you have come to harm due to taking part in the study there are no automatic arrangements to get financial compensation.

Insurance:
The University of Dundee is Sponsoring the study. The University of Dundee holds Clinical Trials indemnity cover which covers the University's legal liability for harm caused to patients/participants.

Contact Numbers

If during the study you become unwell and need urgent attention or assistance, you must not delay seeking further advice or treatment as usual through the NHS services i.e. from your General Practitioner, the ambulance service, NHS24, or the Accident and Emergency Department.

Thank you for reading this information sheet and considering taking part in this study. If you would like more information or want to ask questions about the study, please contact:

Scottish Centre for Respiratory Research, Ninewells Hospital

Telephone: 01382 383902

Email: scrr@dundee.ac.uk

One of our team will go through the information sheet with you and answer any questions you have.

Professor Brian Lipworth is the Chief Investigator and is the senior person who will take overall responsibility for the study. He is Professor of Allergy and Pulmonology with the University of Dundee and Honorary Consultant Physician with NHS Tayside.

If you wish to seek independent and impartial advice from a Consultant Respiratory Physician about this study, please contact Dr William Anderson, Consultant Respiratory Physician, Ninewells Hospital. Telephone: 01382 660111. Email: William.Anderson2@nhs.scot

Who is organising and funding this research?

This study is being sponsored by the University of Dundee. It is being funded by the Scottish Centre of Respiratory Medicine. The study is being organised by Prof Brian Lipworth, University of Dundee.

Data Protection Privacy Notice

How will personal information be used?

We will need to use information from you and from your medical records for this research project. This information will include your:

- Initials
- NHS number
- Name
- contact details**.**

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. The University of Dundee is the sponsor of this research. University of Dundee is responsible for looking after your information. We will not share your information related to this research project out with the department. Confidential information about me collected for this study may be used in ethically approved medical research in future within the department.

We will keep all information about you safe and secure by:

- Paper documentation will be kept in a locked room.
- Results will be transcribed to a excel spreadsheet secured on the University of Dundee server that can only be accessed using log in details. These results will be anonymised.

Your data will not be shared outside the UK.

How will we use information about you after the study ends?

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study. We will keep your study data for a maximum of 10 years. The study data will then be fully anonymised and securely archived or destroyed.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. You have the right to ask us to access, remove, change or delete data we hold about you for the purposes of the study. You can also object to our processing of your data. We might not always be able to do this if it means we cannot use your data to do the research. If so, we will tell you why we cannot do this

Where can you find out more about how your information is used?

You can find out more about how we use your information:

- By checking www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to scrr@dundee.ac.uk or by contacting the University of Dundee's Data Protection Officer at DataProtection@dundee.ac.uk

Thank you for taking time to read this information and for considering taking part in this trial.

Trial Outline

	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