ISRCTN70810039 https://doi.org/10.1186/ISRCTN70810039

The effect of dupilumab on airway twitchiness in severe asthma

Submission date	Recruitment status	[_] Prospectively registered
21/03/2022	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
25/04/2022	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
26/03/2025	Respiratory	

Plain English summary of protocol

Background and study aims
The presence of airway twitchiness, also known as airway hyper-responsiveness, is one of the hallmark 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. Dupilumab also known as Dupixent is a monoclonal antibody. This is a type of protein that recognises and attaches to specific target proteins, called interleukin-4 and interleukin-13.
In this study, we aim to assess if dupilumab, after 12 weeks of treatment, improves airway twitchiness in severe asthma with type 2 inflammation. We believe that dupilumab may result in a rapid and sustained improvement of airway twitchiness in this group of asthma patients.

Who can participate?
Eligible patients will be those with a diagnosis of severe asthma who are already taking a medium to high dose of inhaled corticosteroids (ICS), +/- a long-acting beta-agonist (LABA), who exhibit a significant degree of airway twitchiness and a raised blood eosinophil level and/or FeNO level.

What does the study involve?
Patients with severe asthma will be invited for an initial screening and consent visit, and then a 4-week run-in period on a standardised inhaler. There will be a total of 5 study visits and 3 injection-only visits. During the study visits, patients will be asked to complete questionnaires, have blood samples taken and have lung function tests and mannitol challenge. All patients included in the study will be given dupilumab injections under the skin every 2 weeks for a total of 6 doses over 12 weeks (there is no placebo group).
Each patient will be involved for around 28 weeks (7 months).

What are the possible benefits and risks of participating?
Dupilumab is used together with other medicines (including medium to high doses of ‘steroid inhalers’ plus other asthma medicines) to treat asthma when the disease is not well controlled

by those other medicines alone. Dupilumab may reduce the number of asthma attacks patients are experiencing and decrease their asthma symptoms. Severe allergic reactions such as anaphylaxis to Dupilumab are rare, but we monitor the patient for at least one hour after the injection and also give out an information sheet about potential reactions. The most frequent reactions are injection site redness, throat pain, joint pain or eye inflammation. Taking part in this study is entirely voluntary and the patient can decide not to take part or to withdraw from the study at any time without having to give a reason.

Where is the study run from?
Ninewells Hospital, Dundee (UK)

When is the study starting and how long is it expected to run for?
October 2021 to November 2024

Who is funding the study?
The study is sponsored by the University of Dundee and NHS Tayside (UK), and is supported financially by Sanofi-Genzyme (USA).

Who is the main contact?
Professor Brian Lipworth, scrr@dundee.ac.uk

Contact information

Type(s)
Principal investigator

Contact name
Prof Brian Lipworth

ORCID ID
https://orcid.org/0000-0002-8140-2014

Contact details
Scottish Centre for Respiratory Research
Ninewells Hospital
Dundee
United Kingdom
DD1 9SY
+44 1382 383902
scrr@dundee.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2021-005593-25

Integrated Research Application System (IRAS)
305542

ClinicalTrials.gov (NCT)

Nil known

Protocol serial number
IRAS 305542, CPMS 52391

Study information

Scientific Title
A pragmatic proof of concept study to evaluate the effect of dupilumab on mannitol challenge in severe asthma with type 2 inflammation

Acronym
DISA

Study objectives
To assess the effect of dupilumab on airway hyperresponsiveness (AHR), after 12 weeks of treatment, measured by mannitol challenge as the provocative dose causing a 10% fall in forced expiratory volume in 1 second (FEV1) (PD10 Mannitol), from post-run-in baseline in severe asthma with type 2 inflammation.

The hypothesis proposed is that comparing the post run-in baseline, there will be an improvement in airway hyper-responsiveness following 12 weeks of dupilumab treatment while on the ICS/formoterol maintenance and reliever therapy for asthma.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/02/2022, West of Scotland REC 1 (West of Scotland Research Ethics Service, Ward 1, Dykebar Hospital, Grahamston Road, Paisley PA2 7DE, UK; +44 141-314-0212; WosRec1@ggc.scot.nhs.uk), ref: 21/WS/0151

Study design
Interventional single-centre single arm exploratory open-label study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Adult patients with severe asthma with type 2 inflammation

Interventions
Patients will attend a screening visit to assess if inclusion/exclusion criteria are met and informed consent taken if the patient wants to participate. Their inhaled corticosteroid/long-acting beta agonist (ICS/LABA) inhaler will be switched to standardised ICS/formoterol combined inhaler as maintenance and reliever therapy (MART) at the equivalent dose to their current treatment, to be used during run-in and throughout the study. Any third line controller

therapy will be continued. Throughout the study, patients will be asked to manually record peak flow readings, any symptoms they have and how often they require the ICS/formoterol reliever inhaler and to record these in supplied asthma diary cards. Patients will also be given the option of recording their nasal symptoms and peak nasal inspiratory flow (PNIF) readings. There will be a 4 week run in period followed by visit 1. In total there will be five study visits which includes questionnaires, blood tests, and lung function tests (including mannitol challenge) and three injection-only visits. The first dupilumab injection is administered at visit 1 following monitoring and measurements as per the study schedule. The patient then re-attends 2 weeks later for visit 2, to assess how quickly dupilumab attenuates AHR and improves lung function. Dupilumab will be given at 2-weekly intervals for a total of 6 doses. Study visits occur throughout this time followed by a washout visit 14 weeks after the final treatment dose.

This clinical trial is a phase III, single arm exploratory study, with a single centre, open labelled design, so no randomisation or blinding is required.

Intervention: Dupixent (Dupilumab) 600 mg by subcutaneous injection at first dose followed by 300 mg subcutaneous injection every 2 weeks for a total of 6 doses.

Run-in Standardisation: All participants will be standardised on an ICS/formoterol combined inhaler as maintenance and reliever therapy (MART) to be used during run-in and throughout, and the patient will be given a training session on the correct inhaler technique.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Dupixent (dupilumab)

Primary outcome(s)
Airway hyperresponsiveness measured by mannitol challenge as the provocative dose causing a 10% fall in FEV1 (PD10 Mannitol) at Visits 1-5

Key secondary outcome(s))
1. Mannitol response dose ratio (RDR) will be assessed by mannitol challenge at Visits 1-5.
2. Number of puffs of maintenance and reliever therapy (MART) required as recorded on patient diary cards will be assessed at Visits 1-5 and at 3 injection-only visits.
3. Type 2 biomarkers: Fractional exhaled nitric oxide (FeNO) will be measured with a pulmonary function test and blood eosinophils will be measured with a blood test at screening and Visits 1-5. Blood eosinophil derived neurotoxin (EDN) will be measured with a blood test at Visits 1-5.
4. Spirometry and airway oscillometry pulmonary function tests will be performed at screening and at Visits 1-5.
5. Asthma control questionnaire (ACQ6) and mini-asthma quality of life questionnaire (mini-AQLQ) scores will be assessed with questionnaire completion at screening and Visits 1-5.
6. Domiciliary peak expiratory flow (PEF), asthma symptoms, and reliever use will be recorded either electronically or on daily patient diary cards and will be collected at Visits 1-5 and at 3 injection-only visits.

Exploratory Outcome measures:
7. Nasal symptoms and peak nasal inspiratory flow (PNIF) as recorded on patient diary cards will be collected at Visit 1, Visit 4 and Visit 5.
8. Nasal nitric oxide test will be performed at Visit 1, Visit 4 and Visit 5.
9. Sino-nasal outcome test (SNOT-22) patient questionnaires will be completed at Visit 1, Visit 4 and Visit 5.

Completion date
30/11/2024

Eligibility

Key inclusion criteria
1. Male or female patients, aged 18 to 75 years with severe GINA defined asthma
2. Taking a medium to high dose of ICS/LABA OR high dose ICS with another second line controller (BDP equivalent dose of ≥800µg) of step 4/5 GINA therapy.
3. Established diagnosis of persistent asthma for at least 6 months according to GINA guidelines.
4. Diagnosis should have been properly documented at the screening visit, based on medical documentation and medical history.
5. Uncontrolled asthma as per ACQ6 ≥1.5
6. Forced Expiratory Volume in 1 second (FEV1) ≥50% predicted at screening.
7. Mannitol PD10 ≤635mg at Visit 1
8. Severe asthma with type 2 inflammation as evidenced by:
8.1. Eos ≥300 cells/µl at screening visit or within 6 months prior to screening OR
8.2. Eos ≥150 cells/µl with FeNO ≥25 ppb at screening visit or within 6 months prior to screening OR
8.3. FeNO ≥50 ppb at screening visit or within 6 months prior to screening
8.4. Eosinophil count and FeNO are not inclusion criteria in those patients already taking maintenance oral corticosteroids prior to trial recruitment
9. Ability to give informed consent.
10. Agreement for their GP to be made aware of study participation and to receive feedback as relevant to the participant's wellbeing.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex

All

Total final enrolment
24

Key exclusion criteria
1. Patient who has taken any biologic treatment for asthma within 3 months before V1.
2. Any other respiratory diseases such as COPD and moderate to severe bronchiectasis which in the opinion of the investigator are considered to be clinically significant and may have an impact on the study outcomes. Patients with Asthma COPD Overlap (ACO) may be included providing they meet all the other criteria.
3. Active cancer or a history of cancer with less than 5 years disease free survival time (whether or not there is evidence of local recurrence or metastases).
4. Any known systemic (e.g., blood, liver, kidney, etc.) clinically significant medical condition, known significant laboratory abnormalities or communicable disease that may endanger the health or safety of the patient.
5. Asthma exacerbation or respiratory tract infection requiring systemic steroids and/or antibiotics within 1 month prior to screening visit or 3 months if hospital admission was required.
6. Any disorder that is not stable in the opinion of the Investigator.
7. Patients who are participating in the clinical phase of another interventional trial or have done so within the last 30 days or within 5 half-lives of the previous administered product (whichever is longer) before screening. Individuals who are participating in the follow-up
phase of another interventional trial, or who are enrolled in an observational study, will be co-enrolled where the Coordinating Investigator of each study agree that it is appropriate.
8. Female patients who are pregnant or lactating.
9. Patients unable or unwilling to consent.
10. Patients taking non-permitted medications.
11. Patients with a history of hypersensitivity to any of the study medications components or a history of other allergy that in the opinion of the investigator contraindicates the patient's participation.

Date of first enrolment
04/04/2022

Date of final enrolment
30/10/2023

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
Tayside Medical Science Centre
Ninewells Hospital

Dundee
United Kingdom
DD1 9SY

Sponsor information

Organisation
University of Dundee

ROR
https://ror.org/03h2bxq36

Funder(s)

Funder type
Industry

Funder Name
Sanofi Genzyme

Alternative Name(s)
Genzyme Corporation, Genzyme Corp.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The Investigators and designee will have the access to the final trial dataset.
On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared. Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.
The datasets generated and/or analysed during the current study will be published as a supplement to the subsequent results publication.

IPD sharing plan summary

Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		26/11/2024	26/03/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes