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Measuring response to inhaled asthma therapy using pulmonary imaging

Submission date	**Recruitment status**	[_] Prospectively registered
15/03/2024	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
15/03/2024	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
18/03/2024	Respiratory	

Plain English summary of protocol

Background and study aims
The purpose of this study is to evaluate the effectiveness of treatment with triple therapy (an inhaler that contains three types of asthma medications) on participants with poorly controlled asthma. The triple therapy medication contains fluticasone furoate, an inhaled corticosteroid (ICS) which reduces inflammation in the lungs; umeclidinium (UMEC), a long-acting muscarinic antagonist (LAMA), a medication which helps open up the airways; and vilanterol (VI), a long-acting beta2-adrenergic agonist (LABA) which also helps open up airways, delivered in a single daily inhalation via an Ellipta inhaler. The Investigators will evaluate lung structure and function using magnetic resonance imaging (MRI). Participants will inhale xenon gas before an MRI image of their lungs is taken. Using a special technique xenon is visible in MRI images, so this lets us see how air spreads in the lungs. In healthy lungs, the gas fills the lungs evenly, but in unhealthy lungs, the gas may fill the lungs unevenly and they will appear patchy. The patchy areas are called ventilation defects. A CT of the chest will be done to assess the structure of the lungs. The Investigators will also be using lung function testing and questionnaires to compare them to MRI ventilation defect measurements.

Who can participate?
Males and females aged 18-75 years with a clinical diagnosis of eosinophilic asthma

What does the study involve?
Vital signs will be recorded at the beginning of the visit. Lung tests and an MRI scan will be performed before and after inhaling four puffs (100 mcg each) of a bronchodilator and quietly resting for 15 minutes. Questionnaires will be completed after post-bronchodilator assessments are completed. For Visit 3, participants who choose to attend an in-person visit are to withhold their medication as described and the process for Visits 1, 2 and 4 will be followed. Participants who choose a phone call Visit 3 will be asked a series of questions regarding their breathing, asthma control and general health and they will complete questionnaires. For all participants, Visit 5 will entail a phone call check-in for adverse events. CT will be acquired at Visit 2, whilst MRI will be acquired on Visits 2, 4 and for those who prefer an in-person visit, on Visit 3.

What are the possible benefits and risks of participating?
Participants with poorly controlled disease may benefit from the treatment, including reduced

asthma exacerbations, reduced use of oral corticosteroids (OCS) and improved lung function. The safety of the triple therapy has been previously demonstrated and the most common side effects were nasopharyngitis (a cold), headache and back pain.

Where is the study run from?
Robarts Research Institute, Western University (Canada)

When is the study starting and how long is it expected to run for?
August 2022 to August 2023

Who is funding the study?
GlaxoSmithKline

Who is the main contact?
Grace Parraga, PhD, gparraga@uwo.ca

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04651777

Protocol serial number
Unique Protocol ID: ROB0046

Study information

Scientific Title
Evaluation of triple therapy using magnetic resonance imaging in asthma (ETHA)

Acronym
ETHA

Study objectives
The objective was to quantify small-airways dysfunction using 129Xe MRI ventilation-defect-percent (VDP) before and after 6-weeks ICS/LABA with long-acting muscarinic antagonist (LAMA) and evaluate potential responses with respect to type 2 inflammation.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 06/07/2022, Western University Health Science Research Ethics Board (Office of Human Research Ethics Room 5150, Support Services Building, Western University, 1151 Richmond Street North, London, N8G 1G9, Canada; +1 (0)519 661 3036; ethics@uwo.ca), ref: 118122

Primary study design
Interventional

Study design
Single-center open-label single-arm pilot study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Step 4 or 5 asthma according to Global Initiative for Asthma (GINA)

Interventions
Participants stop previous ICS/LABA medication on the day prior to the first of three visits, before treatment initiation (week 0; Visit 1, V1). At V1, blood is drawn for complete blood count and chest CT, FeNO, ACQ-6, Asthma Quality-of-Life Questionnaire (AQLQ) and St George's Respiratory Questionnaire (SGRQ) are completed. Spirometry, plethysmography, airwave-oscillometry and 129Xe MRI are performed before (pre-bronchodilator; pre-BD) and 15 minutes after (post-bronchodilator; post-BD) inhalation of 4 × 100µg Novo-Salbutamol Hydrofluoroalkane (Teva Novopharm Ltd., Toronto, ON, Canada) using an AeroChamber (Trudell Medical International, London, ON, Canada). After being trained on the use of a proprietary multi-dose dry powder inhaler (ELLIPTA), participants will inhale the first dose of FF/UMEC/VI (200/62.5/25 µg) at the study centre, under observation, with instructions to continue once every morning until Visit 2 (V2, 6 weeks ± 5 days after V1) or Visit 3 (V3, 12 weeks ± 5 days after V2). All measurements acquired at V1 are repeated on V2 and V3, except for blood work and CT. Study doses are provided on V1 and again on V2 for those participants who decided to continue to V3.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Fluticasone-furoate/umeclidinium/vilanterol 200/62.5/25 µg (FF/UMEC/VI) (Trelegy)

Primary outcome(s)
Ventilation defect percent (VDP) measured using 129Xe MRI at V2

Key secondary outcome(s)
1. Change in FeNO levels measured using the FeNO device between baseline and visit 2
2. Change in forced expiration volume in one second measured using spirometry between baseline and visit 2
3. Change in forced vital capacity measured using spirometry between baseline and visit 2
4. Change in residual volume measured using plethysmography between baseline and visit 2
5. Change in total lung capacity measured using plethysmography between baseline and visit 2
6. Change in oscillometry measurements of small-airway resistance (R5-19) measured using the forced oscillation technique between baseline and visit 2
7. Change in lung clearance index (LCI) measured using multiple breath nitrogen washout between baseline and visit 2
8. Change in asthma control measured using the ACQ-6 questionnaire between baseline and visit 2

Completion date
25/08/2023

Eligibility

Key inclusion criteria
1. Participant understands study procedures and is willing to participate in the study as indicated by the participant's signature
2. Provision of written, informed consent prior to any study-specific procedures
3. Males and females with a clinical diagnosis of eosinophilic asthma (based on FENO ≥40ppb, blood eosinophilia ≥200 cells/µl at screening) aged 18 to 70 years, inclusively, at the time of Visit 1 (enrolment), under the care of a respirologist
4. FEV1 ≥35 and ≤80% predicted
5. Participant is a current non-smoker and non-vaper, having not smoked tobacco or cannabis, pipe or cigar or vaped any product for at least 12 months prior to the study with a tobacco smoking history of no more than 1 pack-year (i.e. 1 pack per day for 1 year).
6. Women of childbearing potential (after menarche) must use a highly effective form of birth control (confirmed by the investigator or designee)
A highly effective form of birth control includes true sexual abstinence, a vasectomized sexual partner, Implanon®, female sterilization by tubal occlusion, any effective intrauterine device (IUD)/levonorgestrel intrauterine system (IUS), Depo-ProveraTM injections, oral contraceptive and Erva PatchTM or NuvaringTM
7. Women of childbearing potential (after menarche) must agree to use a highly effective form of birth control, as defined above, from enrolment, throughout the study duration, and 8 weeks after the last dose of the study drug, with negative pregnancy test result at Visit 1
8. Male participants who are sexually active must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of the study drug until 8 weeks after the last dose
9. Participant has documented treatment with a stable dose of low to medium dose inhaled corticosteroids (defined as >250 and ≤500 mcg fluticasone proprionate/day or equivalent or, >400 to ≤800 mcg Budesonide/day for at least 6 months prior to enrolment
long-acting β2-agonist (LABA) for at least 6 months prior to enrolment
10. Participant has blood eosinophils ≥ 200 cells/µl or FENO ≥25ppb at Visit 1 for all participants except for those with previous biologic therapy without washout who will be required to

washout prior to screening.
11. Participant has ACQ-6 ≥ 1.5 at visit 1
12. Participant has a history of poorly controlled asthma (i.e. ≥2 exacerbations in the past 24 months)

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
31

Key exclusion criteria
1. Participant is, in the opinion of the investigator, mentally or legally incapacitated, preventing informed consent from being obtained, or cannot read or understand written material
2. Participant has clinically important pulmonary disease other than asthma (e.g. active lung infection, chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha-1 antitrypsin deficiency and primary ciliary dyskinesia) or been diagnosed with pulmonary or systemic disease other than asthma that is associated with elevated peripheral eosinophil counts (e.g. allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome), except for those atopic conditions that can be associated with asthma (e.g. allergic rhinitis, sinusitis with or without polyposis, eczema, and eosinophilic esophagitis)
3. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the Qualified Investigator and/or could affect the safety of the participant throughout the study, influence the findings of the study or their interpretations, or impede the participant's ability to complete the entire duration of the study, as assessed by the Qualified Investigator.
4. Known history of allergy or reaction to the study drug formulation
5. Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date of informed consent
6. Clinically significant asthma exacerbation, defined as a change from baseline deemed clinically relevant in the opinion of the Qualified investigator, including those requiring the use of OCS, or an increase in maintenance dosage of OCS within 30 days prior to the date of informed consent. Participants with an exacerbation after providing informed consent but prior to treatment start will be excluded from the study

7. Receipt of immunoglobulin or blood products within 30 days prior to the date of informed consent
8. Receipt of live attenuated vaccines 30 days prior to the date of enrolment
9. Previously randomized in any FF/UMEC/VI 200/62.5/25ug study
10. Planned surgical procedure during the conduct of the study
11. Concurrent enrolment in another clinical trial
12. Participant has history of alcohol or drug abuse within 12 months prior to the date of informed consent
13. Participant is a female who is ≤8 weeks post-partum or breast feeding an infant
14. Participant is pregnant, or intends to become pregnant during the time course of the study
15. Participant is unable to perform MRI breath-hold maneuver
16. Participant is unable to perform spirometry maneuver
17. Participant is hospitalized or has had a major surgical procedure, major trauma requiring medical attention, or significant illness requiring medical attention within 4 weeks of Visit 1
18. Participant has a blood pressure of >150 mmHg systolic or >95 mmHg diastolic on more than 2 measurements done >5 minutes apart at Visit 1
19. In the opinion of the investigator, participant suffers from any physical, psychological or other condition(s) that might prevent performance of the MRI, such as severe claustrophobia
20. Participant has implanted mechanically, electrically or magnetically activated device or any metal in their body, which cannot be removed, including but not limited to pacemakers, neurostimulators, biostimulators, implanted insulin pumps, aneurysm clips, bioprosthesis, artificial limb, metallic fragment or foreign body, shunt, surgical staples (including clips or metallic sutures and/or ear implants) - at the discretion of the MRI Technologist.

Date of first enrolment
08/08/2022

Date of final enrolment
19/07/2023

Locations

Countries of recruitment
Canada

Study participating centre
Western University (Canada)
Robarts Research Institute
1151 Richmond Street North
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Sponsor information

Organisation

Western University (Canada)

Funder(s)

Funder type
Industry

Funder Name
GlaxoSmithKline

Alternative Name(s)
GlaxoSmithKline plc., GSK plc., GlaxoSmithKline plc, GSK

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analyzed during the current study will be available upon request from Dr Grace Parraga (gparraga@uwo.ca). Data is anonymized; written informed consent was provided by all participants; data will be available starting today for 5 years; all research data are available except for age and sex.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			18/03/2024	No	No
Protocol file	version 11	08/07/2022	15/03/2024	No	No