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Can commonly used treatment with inhaled corticosteroids protect COPD patients from heart and blood vessel disease?

Submission date 26/09/2024	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 04/10/2024	**Overall study status** Ongoing	
Last Edited 06/03/2025	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims
Chronic obstructive pulmonary disease (COPD) is a common lung disease, mainly caused by smoking. Heart disease is a leading cause of death in COPD patients, but the connection between the two conditions isn't fully clear. Standard treatment for COPD includes inhalers with two bronchodilators, called long-acting muscarinic receptor antagonists (LAMAs) and long-acting β2 agonists (LABAs). For severe COPD or frequent flare-ups, a combination of bronchodilators and inhaled corticosteroids (ICS) is recommended (ICS/LAMA/LABA triple therapy), as it reduces flare-ups and improves survival rates.
The cells lining blood vessels, called endothelial cells, are key for heart and blood vessel health. When these cells age, blood vessels don't work well, leading to heart disease. Studies show that blood cells from COPD patients, which should turn into endothelial cells and repair damage, are dysfunctional and age prematurely. Interestingly, patients treated with both bronchodilators and ICS had healthier endothelial cells than those treated with bronchodilators alone.
This study aims to understand why blood vessels age prematurely in COPD and how ICS treatment may protect patients from heart disease.

Who can participate?
COPD patients aged 18 years and over who have not previously used ICS.

What does the study involve?
Participants will attend the research facility for 2–3 visits. During the first visit (the "screening visit"), we will ask about medical history, do a lung function test, and have participants fill out a questionnaire on their COPD symptoms. Participants will also provide consent to join the study. This visit will include:
1. Lung function test (spirometry)
2. A simple exercise test
3. Questionnaires about breathing symptoms
4. Blood pressure, height, and weight measurements
5. A non-invasive test to assess blood vessel health
6. A blood sample collection

If participants wish, the screening and study visits can be combined into one, lasting less than 4 hours. However, if participants are not suitable after screening, they will not proceed to the main study.
After the first visit, participants will collect their medication from the Royal Brompton Hospital pharmacy. They will then return for a second visit 12 weeks later, where the same tests will be repeated.
Participants will be split into two groups: one group will receive bronchodilators (LABA/LAMA) only, and the other will receive ICS/LAMA/LABA triple therapy for 12 weeks. The study will measure blood vessel function and stiffness and ageing of endothelial cells before and after treatment to determine whether ICS can prevent premature blood vessel ageing and reduce heart disease in COPD patients.

What are the possible benefits and risks of participating?
The procedures in this study are not expected to cause harm. The only risk from the blood test is slight discomfort or bruising, as 80ml of blood (about 4-5 tablespoons) will be taken. Some people (less than 5%) may feel faint, but the amount of blood taken is small and won't have long-lasting effects. The clinical procedures are non-invasive, though the blood pressure cuff used to measure blood vessel health may cause brief discomfort. If it’s not tolerated, the cuff will be deflated.
The inhalers used in the study are commonly prescribed to COPD patients and are usually well tolerated. Participants will be informed of any possible side effects and given instructions on where to seek help if needed.

Where Is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
August 2024 to May 2026

Who is funding the study?
AstraZeneca (UK)

Who is the main contact?
Dr Koralia Paschalaki k.paschalaki@imperial.ac.uk

Contact information

Type(s)
Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1010334

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
173960, IRAS 1010334

Study information

Scientific Title
Understanding the role of inhaled corticosteroids on vascular ageing and cardiovascular comorbidities in COPD

Study objectives
Do inhaled corticosteroids (ICS) reduce endothelial ageing, protecting COPD patients from vascular ageing and cardiovascular events?

1. To correlate molecular with clinical information of endothelial dysfunction
2. To identify molecular abnormalities that promote vascular ageing and novel therapeutic opportunities to restore endothelial dysfunction
3. To study the effect of various drugs against accelerated ageing of endothelial cells isolated from patients' blood samples in the laboratory
4. To confirm the protective effect of ICS/triple combination on endothelial senescence ex vivo using ECFC (2D and 3D culture models)

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 03/10/2024, Wales Research Ethics Committee 3 (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff , CF11 9AB, United Kingdom; -; Wales. REC3@wales.nhs.uk), ref: 24/WA/0260

Study design
Single-blind randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Efficacy

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Chronic obstructive pulmonary disease (COPD)

Interventions
Intervention arm:
Patients randomised to the intervention arm will receive Trixeo Aerosphere (formoterol fumarate/glycopyrronium/budesonide - 5 micrograms/7.2 micrograms/160 micrograms pressurised inhalation, suspension). They will be instructed to take two inhalations twice daily (two in the AM and two in the PM). The treatment duration is 12 weeks.

Control arm:
Patients randomised to the intervention arm will receive Bevespi Aerosphere (formoterol fumarate/glycopyrronium 5 micrograms / 7.2 micrograms pressurised inhalation, suspension). They will be instructed to take two inhalations twice daily (two in the AM and two in the PM). The treatment duration is 12 weeks.

Follow-up activities:
Both groups will receive a telephone call from the trial team at 4 and 8 weeks of the treatment period to reinforce compliance and collect information about adverse events. Once the 12-week treatment period has been completed, patients will attend the clinical research facility to repeat the outcome measures performed at baseline.

Randomisation:
Randomisation will be conducted using sealed envelope, patients will be randomised on a 1:1 ratio stratified by age and gender. The randomisation will occur at the end of visit 1, the trial pharmacist will be unblinded and dispense the medication according to group allocation.

Intervention Type
Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Trixeo (formoterol fumarate dihydrate - approved, glycopyrronium bromide, budesonide), Bevespi (formoterol fumarate dihydrate - approved, glycopyrronium bromide)

Primary outcome measure
Degree of senescence in endothelial progenitors isolated from blood (endothelial colony forming cells: ECFC), measured by markers of senescence and DNA damage response, isolated from COPD patients at baseline and 12 weeks post-treatment

Secondary outcome measures
Measured at baseline and 12 weeks post-treatment:
1. Endothelial function assessed using the EndoPAT device
2. Quality of life assessed using the COPD assessment test
3. Mean arterial pressure calculated from systolic and diastolic blood pressure (BP) readings
4. Prediction algorithms for CVD (Framingham risk score risk prediction model and QRISK3- risk prediction model)
5. Blood eosinophils measured via the patients' blood sample
6. Blood cardiovascular markers (high-sensitivity C-reactive protein, brain-natriuretic-peptide, troponin, fibrinogen, activation of the RAS system [renin to aldosterone ratio]) measured via the patients' blood sample
7. Proteomic analysis of ECFC, serum/plasma for studying the senescence-associated secretome, isolated from the patients' blood sample
8. miR-126-3p and other miRNA dysregulation in ECFC, isolated from the patients' blood sample
9. Markers of senescence and DDR in treated ECFC ex-vivo in 2D culture models, isolated from the patients' blood sample
10. Permeability and markers of senescence in treated microvessels (3D culture models) using ECFC, isolated from the patients' blood sample
11. Spirometry: forced expiratory spirometry maneuvers for the derivation of FEV1 and FVC will be assessed using a spirometer that meets or exceeds the minimum performance recommendations of the ATS. Outcomes will be FEV1, FVC, FEV1/FVC
12. Body mass index (BMI), calculated as weight in kilos divided by height in meters squared. Height measured at the start of the study will be used for both measures. Electronic scales will be used to measure weight.
13. Breathlessness assessed using the extended version of the Medical Research Council Dyspnoea Scale (eMRC)
14. Quality of life measured using St George's Respiratory Questionnaire (SGRQ)
15. Exacerbation history: number of exacerbations in the last year, number of times admitted to hospital with exacerbation the last year and number of times admitted to hospital with exacerbations overall will be recorded.
16. Aerobic capacity and endurance assessed using the 6-Minute Walk Test (6MWT)

Overall study start date
16/08/2024

Completion date
31/05/2026

Eligibility

Key inclusion criteria
1. Clinical diagnosis of COPD
2. Not on regular treatment with inhaled corticosteroids (ICS)
3. Over 18 years of age
4. Symptomatic disease (COPD Assessment Test [CAT] score of ≥10)

5. FEV1 measured by spirometry <80% predicted
6. Able to demonstrate adequate inhaler technique
7. Willing to take study medications as instructed

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
60

Key exclusion criteria
1. Subjects unable to give informed consent form
2. Pregnancy or breastfeeding
3. Patients on regular treatment with inhaled corticosteroids (ICS)
4. Very severe disease FEV1<30%
5. Patients with more than two moderate exacerbations, or one severe (requiring hospitalization) within the last year
6. Patients with significant cardiac comorbidities, arrhythmias and/or on antiplatelet treatment
7. Patients with acute worsening of COPD in the 6 weeks prior to screening resulting in treatment with oral corticosteroids or antibiotics
8. Patients with asthma, other significant comorbidities including cancer, neurological, hepatic, endocrine, renal (creatinine clearance <30 ml/min) disorders, narrow-angle glaucoma or prostatic hypertrophy
9. Patients who are taking part in interventional clinical trials
10. Patients with known hypersensitivity to budesonide, glycopyrronium or formoterol
11. For women of childbearing potential only – currently pregnant, breastfeeding, or planned pregnancy during the study or not using acceptable contraception, as judged by the investigator
12. Patients with allergy to latex
13. As a result of the medical interview, physical examination or screening investigations, the Physician Responsible considers the volunteer unfit for the study

Date of first enrolment
26/02/2025

Date of final enrolment
30/10/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Royal Brompton Hospital
Respiratory Research Facility, Level 1
Fulham Road Wing
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Sponsor information

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Sponsor type
University/education

Website
http://www.imperial.ac.uk/

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Industry

Funder Name

AstraZeneca UK

Alternative Name(s)
AstraZeneca UK Limited, AZ

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Submission to regulatory authorities

Intention to publish date
31/05/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from the primary investigator (Koralia Paschalaki k.pachalaki@imperial.ac.uk). The data that will be shared will be anonymised trial outcome data, for further scientific analysis or systematic reviews/meta-analyses. The primary investigator will assess any requests for data sharing, only data that patients have consented to be shared (upon entry into the trial) will be made available. Data sharing will be conducted electronically via password-protected datasets.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet			04/10/2024	No	Yes
Protocol file	version 1.1	01/10/2024	04/10/2024	No	No