ISRCTN29148209 https://doi.org/10.1186/ISRCTN29148209

An investigation into how adding an inhaled steroid to COPD treatment may potentially protect against heart disease.

Submission date 08/11/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 18/12/2023	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 07/04/2025	**Condition category** Respiratory	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
Chronic obstructive pulmonary disease (COPD) is a common lung disease that affects people's breathing. People with COPD also have an increased risk of cardiovascular disease (e.g. heart disease and strokes), especially during an exacerbation (or flare-up) of COPD. Platelets are a type of blood cell that helps the blood to clot. Blood tests have shown that people with COPD have more active platelets than people without COPD. This is particularly noticeable during COPD flare-ups. This is one possible reason why people with COPD have a higher risk of having a heart attacks or strokes than people without COPD.

A recent study appeared to show that a new inhaler used to treat COPD, which contains a steroid called budesonide, provides some protection against cardiovascular disease when compared to a similar inhaler that doesn't contain budesonide. It is important for us to improve our understanding of the link between COPD and cardiovascular disease and why adding an inhaled steroid to treatment appears to provide some protection.

The COPD CardioProtect Study will look at the effect that adding an inhaled steroid (budesonide) has on platelet activity and function in people with COPD.

Who can participate?
Participants aged 40 years or older, with COPD, from the Hull University Teaching Hospitals NHS Trust.

What does the study involve?
Each participant will remain in the trial for 20-weeks. Study participants will receive both the steroid-containing and non-steroid containing inhalers at different times during the study. The order that they receive the different inhalers will be chosen at random. Participants will complete some questionnaires, breathing tests and have blood tests taken before and after receiving the study inhalers. This type of study is called a randomised, controlled, cross over trial.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
The inhaled medicines that participants will take during this study are both licensed for the treatment of COPD and are being used within their license. Inhaled corticosteroids (ICS) are known to reduce the risk of exacerbations in COPD. However, this effect is limited to those with evidence of eosinophilic inflammation. To minimise the risk of exacerbations related to ICS withdrawal in study participants, potential participants using an ICS prior to enrollment will not be eligible for inclusion if the eosinophil count at baseline is 0.3 or above. Use of both steroid and non-steroid containing inhalers are necessary in this study to enable evaluation of the impact of steroid treatment on platelets.

Some study procedures have potential to cause some discomfort to participants, for example, spirometry and blood tests. However, these procedures are routinely performed during the usual care of COPD patients and are known to be safe in this patient population. Procedures will only be undertaken by appropriately trained members of the research team.

Participation in the research will require time commitment. Compensation will be provided to cover travel costs to sites. Participants will be provided with refreshments during study visits. Participants will be made aware of the time required for study visits prior to being asked to provide informed consent.

Where is the study run from?
Hull University Teaching Hospitals NHS Trust (UK)

When is the study starting and how long is it expected to run for?
November 2023 to July 2026

Who is funding the study?
AstraZeneca (UK)

Who is the main contact?
Professor Michael Crooks, Michael.crooks@nhs.net
Hull Health Trials Unit, Copd-cardioprotect@hyms.ac.uk

Contact information

Type(s)
Scientific, Principal Investigator

Contact name
Dr Michael Crooks

Contact details
Castle Hill Hospital
Cottingham
United Kingdom
HU16 5JQ
+44 1482 624067
michael.crooks@nhs.net

Type(s)
Public

Contact name
Dr Hull Health Trials Unit

Contact details
University of Hull
Hull
United Kingdom
HU6 7RX
+44 1482 463444
Copd-cardioprotect@hyms.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1008744

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 1008744

Study information

Scientific Title
An investigation into the effect of inhaled combined BUD/GLY/FORM on platelets in COPD as a potential cardioprotective mechanism: an exploratory, single-centre, investigator-blind, randomised controlled cross-over trial

Acronym
COPD CardioProtect

Study objectives
The primary objective of the trial is to assess the effect of inhaled BUD/GLY/FORM compared with GLY/FORM on platelet reactivity by assessing change in P-selectin expression (primary outcome measure), and Platelet-Monocyte Aggregate (PMA) formation and fibrinogen binding (key secondary outcome measures), when unstimulated and following stimulation with ADP, following each treatment.

We will also investigate the effect of inhaled BUD/GLY/FORM compared with GLY/FORM on other markers of platelet activation and function across the following domains:
1. Platelet leukocyte aggregates
2. Platelet aggregation

3. Platelet secretion
4. Platelet spreading
5. Platelet metabolism

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 15/12/2023, London - Fulham Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8084; fulham.rec@hra.nhs.uk), ref: 23/LO/0958

Study design
Interventional double-blind randomized cross-over controlled trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
Chronic Obstructive Airways Disease [COPD]

Interventions
COPD CardioProtect is an exploratory, single-centre, laboratory-blind, randomised controlled cross-over trial of inhaled trial IMP on platelet reactivity and function in patients with COPD. The trial will compare the trial IMP is Budesonide 160 micrograms, Glycopyrronium bromide 9 micrograms and Formoterol fumarate dihydrate 5 micrograms in the Aerosphere device to be taken 2 inhalations twice daily [BUD/GLY/FORM also known as Trixeo Aerosphere] with the comparator medication of inhaled Glycopyrronium bromide 9 micrograms and Formoterol fumarate dihydrate 5 micrograms in the Aerosphere device to be taken 2 inhalations twice daily [GLY/FORM also known as Bevespi Aerosphere]. All participants will be issued with a SABA reliever [Salamol CFC-Free pMDI: Salbutamol sulfate 100 microgams] alongside their allocated study treatment to be taken 1-2 inhalations as required for relief of symptoms related to bronchospasm in COPD, up to a maximum of 8 inhalations in 24-hours. All participants will receive both trial IMP and comparator medications during the trial. The order of treatments will be randomly allocated using an online tool embedded within the study database in a 1:1 ratio as follows:

A) GLY/FORM (run-in) for 4 weeks; BUD/GLY/FORM (Phase 1) for 4 weeks; GLY/FORM (wash-out) for 4 weeks; GLY/FORM (Phase 2) for 4 weeks
B) GLY/FORM (run-in) for 4 weeks, GLY/FORM (Phase 1) for 4 weeks, GLY/FORM (wash-out) for 4 weeks, BUD/GLY/FORM (Phase 2) for 4 weeks

The trial will recruit 40 participants with COPD from a single centre with each participant remaining in the trial for 16 weeks. There are no follow up visits.

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy

Phase
Phase II

Drug/device/biological/vaccine name(s)
Trixeo Areosphere [formoterol fumarate dihydrate, budesonide, glycopyrronium], Bevespi Aerosphere [glycopyrronium bromide , formoterol fumarate dihydrate]

Primary outcome measure
Current primary outcome measure as of 07/04/2025:
Change in platelet activation measured by P-selectin expression (unstimulated and following stimulation with escalating concentrations of ADP (and collagen-related peptide (CRP)) using FACs analysis following treatment with inhaled BUD/GLY/FORM compared with inhaled GLY /FORM measured at 16 weeks.

Previous primary outcome measure:
Change in platelet activation measured by P-selectin expression (unstimulated and following stimulation with escalating concentrations of ADP and collagen) using FACs analysis following treatment with inhaled BUD/GLY/FORM compared with inhaled GLY/FORM measured at 16 weeks.

Secondary outcome measures
Current secondary outcome measure as of 07/04/2025:
Measured at 16 weeks:
1. Platelet-Monocyte Aggregate formation and platelet fibrinogen binding (unstimulated and following stimulation with escalating concentrations of ADP and collagen-related peptide (CRP)) following treatment with inhaled BUD/GLY/FORM compared with inhaled GLY/FORM.
All other platelet markers/assays (below) will be evaluated before and after treatment with inhaled BUD/GLY/FORM compared with inhaled GLY/FORM.
2. Platelet-leucocyte interactions will be analysed using FACs: Whole blood will be stained with antibodies for CD45 for all white blood cells or CD14 (Monocytes) and CD16 (Neutrophils). CD41 will be used to identify platelets within these different populations to identify platelet-leucocyte aggregates. This will be completed in duplicate.
3. Additional markers of Platelet activity will be assessed using the following assays:
3.1. FACs: Platelet integrin IIb3 activation to escalating doses of different agonists (collagen-related peptide (CRP) and ADP) will be completed, in duplicate.
3.2. Platelet aggregation: Platelet responses to escalating doses of different agonists (collagen and ADP) will be completed.

3.3. Platelet spreading: This technique demonstrates how well platelets adhere and activate on various matrix proteins (fibrinogen and collagen). These proteins are either within the thrombus (fibrinogen) or within the extracellular matrix (collagen).
3.4. Seahorse Analyser (Metabolism): This process identifies how platelets use energy via glycolysis and oxidative phosphorylation in both basal conditions and after stimulation with platelet agonists such as Thrombin and collagen.
4. Additional clinical outcome measures will include:
4.1. Spirometry (FEV-1, FVC, FEV-1/FVC ratio)
4.2. CAT score
4.3. Cardiac biomarkers – high sensitivity troponin T, nt-proBNP

Previous secondary outcome measures:
Measured at 16 weeks:
1. Platelet-Monocyte Aggregate formation and platelet fibrinogen binding (unstimulated and following stimulation with escalating concentrations of ADP and collagen) following treatment with inhaled BUD/GLY/FORM compared with inhaled GLY/FORM.
All other platelet markers/assays (below) will be evaluated before and after treatment with inhaled BUD/GLY/FORM compared with inhaled GLY/FORM.
2. Platelet-leucocyte interactions will be analysed using FACs: Whole blood will be stained with antibodies for CD45 for all white blood cells or CD14 (Monocytes) and CD16 (Neutrophils). CD41 will be used to identify platelets within these different populations to identify platelet-leucocyte aggregates. This will be completed in duplicate.
3. Additional markers of Platelet activity will be assessed using the following assays:
3.1. FACs: Platelet integrin IIb3 activation to escalating doses of different agonists (collagen and ADP) will be completed, in duplicate.
3.2. Platelet aggregation: Platelet responses to escalating doses of different agonists (collagen and ADP) will be completed.
3.3. Platelet spreading: This technique demonstrates how well platelets adhere and activate on various matrix proteins (fibrinogen and collagen). These proteins are either within the thrombus (fibrinogen) or within the extracellular matrix (collagen).
3.4. Seahorse Analyser (Metabolism): This process identifies how platelets use energy via glycolysis and oxidative phosphorylation in both basal conditions and after stimulation with platelet agonists such as Thrombin and collagen.
4. Additional clinical outcome measures will include:
4.1. Spirometry (FEV-1, FVC, FEV-1/FVC ratio)
4.2. CAT score
4.3. Cardiac biomarkers – high sensitivity troponin T, nt-proBNP

Overall study start date
06/11/2023

Completion date
31/07/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 07/04/2025:
1. Males and females aged ≥40 years old
2. Primary respiratory diagnosis of COPD
3. FEV-1 <80% predicted and FEV-1/FVC <0.7 at screening (Spirometry does not need to be

repeated at screening if quality assured spirometry has been completed and is available within the 3 months prior to consent being obtained if contraindicated)
4. Current or former smoker with at least 10 pack year smoking history
5. Able to demonstrate adequate inhaler technique with a pMDI inhaler and willing to take study medications as instructed
6. ≥1 moderate and/or ≥1 severe exacerbation of COPD (AECOPD) within the 12 months prior to recruitment*
7. Willing to undertake study procedures and assessments
8. Provided written informed consent
* A moderate exacerbation is classified as an AECOPD treated with oral antibiotics and/or corticosteroids without ED attendance and/or hospitalisation. A severe AECOPD is one that requires ED attendance and/or hospitalisation

Previous inclusion criteria:
1. Males and females aged ≥40 years old
2. Primary respiratory diagnosis of COPD
3. FEV-1 <80% predicted and FEV-1/FVC <0.7 at screening
4. Current or former smoker with at least 10 pack year smoking history
5. Able to demonstrate adequate inhaler technique with a pMDI inhaler and willing to take study medications as instructed
6. ≥2 moderate and/or ≥1 severe exacerbation of COPD (AECOPD) within the 12 months prior to recruitment*
7. Willing to undertake study procedures and assessments
8. Provided written informed consent
* A moderate exacerbation is classified as an AECOPD treated with oral antibiotics and/or corticosteroids without ED attendance and/or hospitalisation. A severe AECOPD is one that requires ED attendance and/or hospitalisation

Participant type(s)
Patient

Age group
Adult

Lower age limit
40 Years

Sex
Both

Target number of participants
40

Key exclusion criteria
1. Other significant respiratory condition felt to be the primary cause for the patients symptoms and/or exacerbations (e.g. predominant asthma, bronchiectasis or interstitial lung disease)
2. Exacerbation of COPD requiring oral steroids and/or antibiotics within the 4 weeks prior to recruitment
3. Unstable vascular disease (e.g. unstable angina, acute myocardial infarction), cerebrovascular event (transient ischaemic attack or stroke), peripheral vascular disease (symptomatic intermittent claudication, critical limb ischaemia) within 3 months of screening.

4. Venous thromboembolic event (e.g. deep vein thrombosis or pulmonary embolism) within 3 months of screening
5. Treatment with 1 or more medication that will impact outcome measure assessment (e.g. clopidogrel, ticagrelor etc). *low dose Aspirin therapy will be permissible if taken at a stable dose throughout the study
6. Taking an inhaled corticosteroid (ICS) prior to study entry with a blood eosinophil count ≥0.3 x 10^9 per litre during the screening visit
7. (This criterium has been included to avoid risk to patients from ICS withdrawal during run-in and wash-out periods for patients considered to have required ICS by a clinician prior to study entry and with evidence of steroid responsive disease [Eos ≥0.3 x 10^9/L])
8. Known allergy/sensitivity to study medications
9. Current participation in another interventional clinical study within 30-days or, if involving an Investigational Product, 5-half-lives, whichever is longer
10. For women of child bearing potential only - currently pregnant, breast feeding, or planned pregnancy during the study or not using acceptable contraception, as judged by the investigator

Date of first enrolment
09/09/2024

Date of final enrolment
30/06/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Castle Hill Hospital
Castle Road
Cottingham
United Kingdom
HU16 5JX

Sponsor information

Organisation
Hull University Teaching Hospitals NHS Trust

Sponsor details
Daisy Building
Castle Hill Hospital
Cottingham
England

United Kingdom
HU16 5JQ
+44 (0)1482 601903
james.illingworth3@nhs.net

Sponsor type
University/education

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Conference presentation
Publication on website
However, the study results will be presented at meetings and conferences and published in peer-reviewed scientific journals

Intention to publish date
31/07/2027

Individual participant data (IPD) sharing plan
This is a commercially sponsored study and the raw data will not be shared.

IPD sharing plan summary
Not expected to be made available