

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

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<b>Registration date</b> 18/12/2023	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 16/12/2025	<b>Condition category</b> Respiratory	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> 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 December 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

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Public

**Contact name**

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+44 1482 463444

Copd-cardioprotect@hyms.ac.uk

## **Additional identifiers**

**Clinical Trials Information System (CTIS)**

Nil known

**Integrated Research Application System (IRAS)**

1008744

**ClinicalTrials.gov (NCT)**

Nil known

**Protocol serial number**

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**

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### **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

### **Study type(s)**

Efficacy

### **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 micrograms] 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.

### **Intervention Type**

Drug

## **Phase**

Phase II

### **Drug/device/biological/vaccine name(s)**

Triexo Areosphere [formoterol fumarate dihydrate, budesonide, glycopyrronium], Bevespi Aerosphere [glycopyrronium bromide, formoterol fumarate dihydrate]

### **Primary outcome(s)**

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.

### **Key secondary outcome(s)**

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

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## **Completion date**

31/12/2026

## **Eligibility**

### **Key inclusion criteria**

Current inclusion criteria as of 07/04/2025:

1. Males and females aged  $\geq 40$  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.  $\geq 1$  moderate and/or  $\geq 1$  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

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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.  $\geq 2$  moderate and/or  $\geq 1$  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

### **Healthy volunteers allowed**

No

### **Age group**

Mixed

### **Lower age limit**

40 years

### **Upper age limit**

120 years

### **Sex**

All

### **Total final enrolment**

0

### **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  $\geq 0.3 \times 10^9$  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 [ $\text{Eos} \geq 0.3 \times 10^9/\text{L}$ ])
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**

31/01/2026

## **Locations**

**Countries of recruitment**

United Kingdom

England

**Study participating centre**

**Castle Hill Hospital**

Castle Road

Cottingham

England

HU16 5JX

## **Sponsor information**

**Organisation**

Hull University Teaching Hospitals NHS Trust

## **Funder(s)**

**Funder type**

Industry

**Funder Name**

AstraZeneca

**Alternative Name(s)**

AstraZeneca PLC, Pearl Therapeutics, AZ

**Funding Body Type**



Government organisation

**Funding Body Subtype**

For-profit companies (industry)

**Location**

United Kingdom

## **Results and Publications**

**Individual participant data (IPD) sharing plan**

**IPD sharing plan summary**

Not expected to be made available