

Investigation of steroid responsiveness in patients with chronic obstructive pulmonary disease

Submission date	Recruitment status	<input checked="" type="checkbox"/> Prospectively registered
10/11/2016	No longer recruiting	<input type="checkbox"/> Protocol
Registration date	Overall study status	<input type="checkbox"/> Statistical analysis plan
15/11/2016	Completed	<input checked="" type="checkbox"/> Results
Last Edited	Condition category	<input type="checkbox"/> Individual participant data
30/01/2026	Respiratory	

Plain English summary of protocol

Background and study aims

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease and currently a leading cause of chronic morbidity (long-term illness) and mortality (death). Inhaled corticosteroids (ICS) belong to the first line treatment for COPD patients; however, there are patients who do not get a significant clinical benefit from ICS. Additionally, ICS overuse results in considerable side effects and economic burden. The aim of this study is to investigate parameters that may help to identify COPD patients that respond better from patients that respond worse to treatment with ICS.

Who can participate?

COPD patients aged 40 and over

What does the study involve?

Participants undergo bronchoscopy, where an instrument called a bronchoscope is threaded through the nose and down the throat to examine the airways and take biopsies (tissue samples). Participants are then divided into two groups based on the area of airway smooth muscle cells (ASMCs). Group A includes patients with ASMC area over 20% and group B includes patients with ASMC area of 20% and lower. All patients are treated for 6 weeks with all three drugs: LAMA (aclidinium), LABA (formoterol) and ICS (budesonide). Patients from each group are then randomly allocated to receive either treatment with LAMA, LABA and ICS (groups A1 and B1) or treatment with LAMA, LABA and placebo (dummy drug) (groups A2 and B2) for 12 months. Participants are followed up at 3, 6, 9 and 12 months, undergo lung function and walking distance tests, and give blood samples and oropharyngeal (throat) swabs.

What are the possible benefits and risks of participating?

Participants receive all tests and treatments for free for the duration of the study (12 months). The risks of the study procedures are considered to be mild. The medication is licensed for use in COPD. Bronchoscopy is a routine test in patients with COPD and the risks of the procedure are minimal. Additional blood samples are taken at the start of the study, scheduled visits and COPD episodes. Oropharyngeal swabs are an established method to take samples and can cause mild

discomfort. All other procedures, including lung function and walking distance tests, are standard tests in COPD treatment. The side effects of inhaled steroids are usually mild, such as oral candidiasis (fungal infection in the mouth) and hoarseness. Patients are instructed at each visit how to avoid side effects (e.g. washing the mouth). The study team examine patients for any side effects.

Where is the study run from?

University Hospital Basel (Switzerland)

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

September 2016 to February 2020

Who is funding the study?

1. University Hospital Basel (Switzerland)
2. AstraZeneca (UK)

Who is the main contact?

Prof. Daiana Stolz

Daiana.Stolz@usb.ch

Contact information

Type(s)

Scientific

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Additional identifiers

Protocol serial number

N/A

Study information

Scientific Title

Histological, cellular and molecular investigation of steroid responsiveness in chronic obstructive pulmonary disease - the HISTORIC study

Acronym

HISTORIC

Study objectives

Chronic obstructive pulmonary disease (COPD) patients with increased airway smooth muscle cell (ASMC) area respond better to inhaled corticosteroids (ICS) and this type of histological analysis can predict steroid responsiveness in COPD patients.

Ethics approval required

Old ethics approval format

Ethics approval(s)

EKNZ (Ethikkommission Nordwest and Zentralschweiz), 12/12/2016, ref: 2016-01880

Study design

Investigator-initiated and -driven double-blind randomized placebo-controlled trial

Primary study design

Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Chronic obstructive pulmonary disease

Interventions

188 patients with COPD, GOLD groups B-D, are recruited within 18 months. Based on the histological analysis of endobronchial biopsies taken by flexible bronchoscopy, patients are divided into two groups. Group A includes patients with ASMC area >20% and group B includes patients with ASMC area ≤20%. All patients follow a run-in period of 6 weeks on open-label triple therapy with LAMA (aclidinium 400 mcg, bid), LABA (formoterol 12 mcg, bid) and ICS (budesonide 400 mcg, bid). Subsequently, patients from each group are randomized (1:1) to receive either:

1. Triple treatment with LAMA, LABA and ICS (groups A1 and B1) or
2. Combined bronchodilator therapy with LAMA and LABA and placebo for ICS (groups A2 and

B2)

Randomization will be stratified by group (A vs B), follow a block size of 4. The duration of treatment will be 12 months, with follow-up at 3, 6, 9 and 12 months after randomization.

Intervention Type

Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)

Budesonide, aclidinium, formoterol

Primary outcome(s)

To compare the differences in the mean decrease of post-bronchodilator FEV1 in milliliters measured using a spirometer at 12 months, between patients with low ($\leq 20\%$) and high ($> 20\%$) ASMC area and according to whether they received ICS or not

Key secondary outcome(s)

Immediately after the run-in phase, at 3, 6, 9 and 12 months after randomization to compare changes in:

1. Modified Medical Research Council (MMRC) dyspnea scale
2. COPD assessment test (CAT)
3. Health-related quality of life, measured using SF-36, SGRQ
4. Pre and post bronchodilator body plethysmography/DLCO
5. Expiratory FeNO
6. Single and multiple-breath N2 wash-out
7. Forced impulse oscillometry
8. 6-minute walking distance (6MWD)
9. Movement patterns, measured using accelerometry
10. Therapy-related side effects (oral candidiasis, tachycardia, tremor, hoarseness, pneumonia)
11. Exacerbations rate
12. Serum biomarkers

between patients with low ($\leq 20\%$) and high ($> 20\%$) ASMC area and according to whether they received ICS or not

Completion date

30/04/2021

Eligibility

Key inclusion criteria

1. Age ≥ 40 years
2. COPD, as defined by the GOLD Guidelines and categorization in groups B-D
3. No acute exacerbation of COPD or any respiratory infection requiring medical attention or leading to a change in medication within the last 4 weeks
4. Unchanged respiratory medication regimen within the last 8 weeks
5. At least one exacerbation in the previous year
6. Current or ex-smokers with smoking history of ≥ 10 pack-years
7. Willingness to participate in a longitudinal, cohort study
8. Capability to provide written informed consent

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

190

Key exclusion criteria

1. Rapid fatal disease (with life expectancy less than 3 months)
2. Pulmonary condition other than COPD as the main respiratory disease
3. Current diagnosis of bronchial asthma
4. Severe immune-suppression including HIV, organ transplantation, ongoing chemotherapy for cancer
5. Pregnancy or breastfeeding
6. Chronic use of oral steroids (> 10 mg per day) for COPD
7. Intolerance or contraindication to aclidinium, formoterol or budesonide

Date of first enrolment

01/03/2017

Date of final enrolment

31/03/2020

Locations

Countries of recruitment

Switzerland

Study participating centre

University Hospital Basel

Petersgraben 4

Basel

Switzerland

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Sponsor information

Organisation

University Hospital Basel

ROR

<https://ror.org/04k51q396>

Funder(s)

Funder type

Hospital/treatment centre

Funder Name

University Hospital Basel

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

All relevant information regarding the datasets (including all analyses described in the primary and secondary outcome measures) are/will be available upon request from Prof. Daiana Stolz (Daiana.Stolz@usb.ch). Informed consent was obtained from all patients included in the study.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<u>Results article</u>		20/07 /2023	25/07 /2023	Yes	No
<u>Results article</u>		19/04 /2024	22/04 /2024	Yes	No
<u>Other publications</u>		29/05 /2024	30/05 /2024	Yes	No
<u>Other publications</u>	SUMF1 Common Variant rs793391 Is Associated with Response to Inhaled Corticosteroids in Patients with COPD	21/10 /2025	30/01 /2026	Yes	No