A Phase IIa Randomised, Double Blind, Placebo Controlled, Parallel Arm, Multi-Centre Study to Evaluate the Efficacy and Safety of Mitiperstat (AZD4831), for 12-24 Weeks, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Published: 26-10-2022
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To evaluate the effect of AZD4831 as compared to placebo on the time to first COPDCompEx event in participants with moderate to severe COPD.

Ethical review	Approved WMO
Status	Completed
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Interventional

Summary

ID

NL-OMON53515

Source
ToetsingOnline

Brief title
CRESCENDO

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
Chronic Obstructive Pulmonary Disease, COPD

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: opdrachtgever/sponsor AstraZeneca

Intervention

Keyword: AZD4831, Chronic Obstructive Pulmonary Disease (COPD), Exacerbations, Myeloperoxidase (MPO) inhibitor

Outcome measures

Primary outcome

Primary objective; To evaluate the effect of AZD4831 as compared to placebo on

the time to first COPDCompEx event in participants with moderate to severe COPD.

Primary Endpoint: time to first COPDCompEx event.

Secondary outcome

Secundary objective: To assess the PK of AZD4831 in participants with moderate

to severe COPD.

Secundary endpoint: plasma AZD4831 concentration-time profiles during the

intervention and follow-up periods, and PK parameters

Secundary objective: To evaluate the effect of AZD4831 as compared to placebo

on the time to first moderate or severe COPD exacerbation.

Secundary endpoint: time to first COPD exacerbation event

Secundary objective: To assess the effects of AZD4831 as compared to placebo on

post-BD FEV1 in participants with moderate to severe COPD

Secundary endpoint: change from baseline in post-BD FEV1 after 12 weeks

Secundary objective: To assess the effect of AZD4831 compared with placebo on respiratory symptoms in participants with moderate to severe COPD.

Secundary endpoint: change from baseline in EXACT, BCSS score, and Cough VAS at Week 12 and Week 24.

Secundary objective: To assess the effect of AZD4831 compared with placebo on disease impact in participants with moderate to severe COPD.

Secundary endpoint: change from baseline in Total CAT measured in clinic at Week 12.

Study description

Background summary

Chronic obstructive pulmonary disease (COPD) is a common, chronic pulmonary disease which is characterised by airflow obstruction that is only partly reversible, and usually progressive and associated with a decline in lung function. COPD is now the third most common cause of death worldwide. It is also associated with high morbidity and comorbidity and is currently the fifth leading cause of DALYs worldwide. COPD is also associated with an enormous economic burden, costing ~$50 billion in direct and indirect healthcare costs in the USA alone.

COPD is caused by a complex interaction between genetics, early life, and ongoing environmental exposure. The major environmental risk factor is inhaling cigarette smoke and/or other pollutants, which trigger a chronic inflammatory response in the lung that is associated with increased lung levels of oxidative stress and proteolytic injury leading to various pathologic changes in the lung that are heterogeneously expressed by patients. Patients with COPD can have varying combinations of destruction of the alveolar walls (or emphysema), small airway remodelling, and/or changes in the large airway (which manifests clinically as a frequent productive cough characteristic of the chronic

bronchitis phenotype) that vary in severity between patients. The course of COPD can be punctuated by acute exacerbations of COPD which are defined as a sustained worsening of the patient*s condition from the stable state, and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD. The initial exacerbation leading to hospitalisation in a COPD patient is considered a seminal event for the patients as it heralds the onset of subsequent exacerbations that increase in frequency, and 50% of patients die within 3.6 years of their initial exacerbation.

In addition, COPD is also frequently associated with other metabolic or cardiovascular comorbidities, which also contribute to impaired quality of life and poorer survival. There is considerable overlap in the patterns of systemic vascular inflammation seen in COPD and that of advancing atherosclerotic disease and heart failure.

For these reasons, patients with COPD represent a huge unmet medical need.

AZD4831 is a potent, selective, irreversible, and dose-dependent inhibitor of myeloperoxidase (MPO). MPO is a heme-containing enzyme that is stored within the granules of neutrophils. Myeloperoxidase catalyses the oxidation of halide ions by hydrogen peroxide leading to the generation of hypohalous acids which are potent oxidants. Under normal conditions, MPO and the hypohalous acids that it generates within neutrophil granules make crucial contributions to killing of phagocytosed bacteria. However, during excessive inflammation, neutrophil granule contents are extruded, and the extracellular hypohalous acids generated by MPO promote lung inflammation and injure the lung. Delivering an MPO inhibitor to guinea pigs that were exposed to cigarette smoke for 6 months reduced lung oxidative stress levels and lung inflammation and also halted the progression of emphysema and small airway fibrosis in the animals indicating that MPO activity contributes significantly to the pathogenesis of COPD-like disease in animals. MPO has also been linked to human COPD as MPO levels in sputum are elevated in COPD patients versus controls and increase further during exacerbations. In addition, extracellular MPO serum levels are indirectly related to rate of decline in FEV1. Finally, preliminary results for AZD4831 in related cardiovascular studies have shown an acceptable benefit/risk profile of this compound and suggest potential benefits in comorbid conditions commonly associated with COPD. Thus, the clinical development program for AZD4831 will evaluate whether treating COPD patients with AZD4831 reduces exacerbations, and improves symptoms, quality of life, lung function and other clinically-relevant outcomes and comorbidities in patients with COPD.

Study objective

To evaluate the effect of AZD4831 as compared to placebo on the time to first COPDCompEx event in participants with moderate to severe COPD.

Study design

This is a Phase IIa, randomised, placebo-controlled, double-blind, parallel-arm, event-driven study with an up to 24-week treatment time designed to evaluate the efficacy and safety of AZD4831 administered QD using a tablet in adult participants with confirmed moderate to severe symptomatic COPD (FEV1/FVC < 0.7, >= 10 pack-years smoking history, and post-BD FEV1 >= 25% predicted) who are at high risk of exacerbations despite being maintained on optimised SoC inhaled therapies - triple inhaled therapy (ICS + LABA + LAMA) or ICS + LABA dual therapy or LABA + LAMA dual therapy for participants who are deemed unsuitable for ICS. The treatment will be over a minimum 12-week and maximum 24-week period.
* Approximately 406 participants will be randomised into the study to evaluate AZD4831 5 mg QD versus placebo.
* Being at high risk of exacerbations is defined as participants fulfilling one or more of the following criteria:
* >= 1 moderate or severe exacerbation in the last 2 years (defined as requiring systemic corticosteroids and/or antibiotics for at least 3 days duration [or 1 injection of depot formulation], or hospitalisation for reason of AECOPD in the 24 months prior to screening; see Section 5.1).
* Frequent productive cough (see Section 5.1).
* Post-BD FEV1 of < 50% predicted.
* Participants will be randomised 1:1 to AZD4831 5 mg QD or placebo QD.

Intervention

Subjects will be randomized in a 1:1 ratio to either 5 mg AZD4831 or matching placebo both administered once daily during treatment period. The treatment will be over a minimum 12-week and maximum 24-week period.

Study burden and risks

The subject is asked to visit the site at least 7 times. Visit 6 (week 18) is a virtual visit. The visit time will last maximal 1-4 hours.

Blood samples will be taken in this study. The total volume of blood that will be collected is approximately 250 ml.
The subject will undergo:
physical examinations at 4 visits.
Clinic Spirometry (post-BD): 5 times
Virtual Spirometry (post-BD): 4 times will be performed at the participants home prior to attendance at the site
MIR Spirobank SMART and UNIFY application to undertake twice daily, unsupervised PEF-only measurements.

The subject will undergo a spontaneous sputum test at least 2 times during the study
The subject will undergo a nasal lining fluid test at least 2 times during the study.
HR-CT Scan of the thorax will be done: 1 time

The subject will be asked to fill out questionnaires at some hospital visits with a maximum of 3 times.
The subject must fill out questionnaires every day (in the morning and evening) in an e-Diary. This takes approximately 15 minutes a day.

The subject will receive the study medication at visit 3. Study medication will be administered once daily during treatment period. The treatment will be over a minimum 12-week and maximum 24-week period. The study medication may cause allergic reactions, such as Maculopapular rash.

Contacts

Public
Astra Zeneca

Prinses Beatrixlaan 582
Den Haag 2595BM
NL
Scientific
Astra Zeneca

Prinses Beatrixlaan 582
Den Haag 2595BM
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Participant must be 40 to 80 years of age inclusive, at the time of signing the ICF.
2. Participants who have a confirmed primary diagnosis of moderate to severe COPD as per GOLD criteria (FEV1/FVC < 0.7, and post-BD FEV1 >= 25% predicted).
3. Participants who are current or ex-smokers with a tobacco history of >= 10 pack-years.
4. Participants must be deemed at high risk of exacerbations as defined by any one of the following:
a) a documented history of >= 1 moderate or severe AECOPD requiring systemic corticosteroids and/or antibiotics for at least 3 days* duration or hospitalization for reason of AECOPD in the 24 months prior to screening,
b) frequent productive cough (over the past 3 months coughed at least several days a week and phlegm (sputum) is brought up at least several days a week), or
c) post-BD FEV1 < 50% predicted.
5. Participants who have a documented stable regimen of triple therapy (ICS + LABA + LAMA) or dual therapy (ICS + LABA or LABA + LAMA) for >= 3 months prior to enrolment.
6. Participants who are clinically stable and free from an exacerbation of COPD for 1 month prior to SV1 (screening) and prior to Day 1.
7. Participants who are at least 70% compliant with each of the following: morning e-Diary, evening e-Diary, and PEF measurements during the 14 days preceding SV3 based on the e-Diary.
8. Body mass index within the range 18 to 40 kg/m2 (inclusive).
9. Male or female of non-childbearing potential.

Exclusion criteria

- Participants with a significant COVID-19 illness within 6 months of enrolment
- As judged by the investigator, any evidence of any active medical or psychiatric condition or other reason (at SV1 [screening] and SV3 [pre-dose]) which in the investigator's opinion makes it undesirable for the participant to participate in the study. This includes but is not limited to:
(a) Diabetes mellitus,
(b) History of left heart failure
(c) Unstable angina, acute coronary syndrome/acute myocardial infarction or coronary intervention with percutaneous coronary intervention/coronary artery bypass graft within 6 months, arrhythmia requiring treatment, or cardiomyopathy.
(d) Clinically significant aortic stenosis.
(e) Systemic hypertension
(f) Pulmonary arterial hypertension,

-Current diagnosis of asthma
-Clinically important pulmonary disease other than COPD
-Known history of allergy or reaction to any component of the study intervention formulation, including hereditary fructose intolerance.
- Any other clinically relevant abnormal findings on physical examination, laboratory testing including hematology, coagulation, serum chemistry, or urinalysis; or recent lung imaging prior to randomization,
-History of a clinically significant infection (viral, bacterial, or fungal; defined as requiring systemic antibiotics, antiviral, or antifungal medication for > 7 days) within 4 weeks prior to SV3 (Day 1) (including unexplained diarrhea) or clinical suspicion of infection at time of dosing.
-History of ANCA positive vasculitis or ANCA positive skin disease.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	28-02-2023
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mitiperstat
Generic name:	NA

Ethics review

Approved WMO Date:	26-10-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	05-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-01-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2022-002441-18-NL
ClinicalTrials.gov	NCT05492877
CCMO	NL82023.056.22