A Phase III, Multicentre, Randomized, Double-blind, Chronic-dosing, Parallel-group, Placebo-controlled Study to Evaluate the Efficacy and Safety of Two Dose Regimens of Tozorakimab in Participants with Symptomatic Chronic Obstructive Pulmonary Disease (COPD) with a History of COPD Exacerbations (Oberon)

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This study has been transitioned to CTIS with ID 2023-503571-19-00 check the CTIS register for the current data. The objective of this phase III study is to evaluate the efficacy and safety of Tozorakimab according to 300 mg every 8 weeks (Q8W) and...

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

Summary

ID

NL-OMON54370

Source
ToetsingOnline

Brief title
OBERON

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
(Chronic Obstructive Pulmonary Disease), chronic bronchitis, COPD

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Chronic Obstructive Pulmonary Disease (COPD), exacerbations, IL-33 inhibition, Tozorakimab

Outcome measures

Primary outcome

To evaluate the effect of 2 dose regimens of Tozorakimab as add on to SoC

compared with SoC plus placebo on the rate of moderate to severe COPD

exacerbations in former smokers.

Secondary outcome

Key Secondary Endpoints:

- To evaluate the effect of 2 dose regimens of Tozorakimab as add on to SoC

compared with SoC plus placebo on the rate of moderate to severe COPD

exacerbation in former and current smokers.

- To evaluate the effect of 2 dose regimens of Tozorakimab as add on to SoC

compared with SoC plus placebo on change in pre-BrochoDilator lung function.

- To evaluate the effect of 2 dose regimens of Tozorakimab as add on to SoC

compared with SoC plus placebo on respiratory symptoms.

- To evaluate the effect of 2 dose regimens of Tozorakimab as add on to SoC

compared with SoC plus placebo on respiratory health status/health-related

quality of life.

Study description

Background summary

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world. The disease is characterized by
persistent respiratory symptoms and respiratory limitation due to airway and/or alveolar abnormalities.
COPD is only partially reversible, usually progressive and associated with an enhanced chronic inflammatory response in the lungs. The expression of interleukin-33 (IL-33) is increased in the lungs of COPD patients, inversely related to lung function and plays a role in inflammatory and epithelial processes within COPD.
Tozorakimab is a monoclonal antibody that binds to IL-33 and thereby robustly and specifically blocks IL-33 and the associated signal cascades. The mechanism of action of Tozorakimab is hypothesized to have a positive impact on airway inflammation, phlegm and cough symptoms and lung function during disease progression in COPD and that it affects the frequency and severity reduce exacerbations.

Study objective

This study has been transitioned to CTIS with ID 2023-503571-19-00 check the CTIS register for the current data.

The objective of this phase III study is to evaluate the efficacy and safety of Tozorakimab according to 300 mg every 8 weeks (Q8W) and 300 mg every 4 weeks (Q4W) dosing regimens administered in adult participants with symptomatic COPD and a history of >= 2 moderate or >= 1 severe exacerbation of COPD in the past 12 months.

The rationale for this change follows recent data from Phase II studies in moderate to severe atopic dermatitis and asthma, in which lower trough PK concentrations (30%-35%) were observed compared with the Phase I healthy volunteer study. With this updated exposure data,
predicted IL-33 lung inhibition reduces from 94% to 92%, but remains above 90% for the 300 mg Q4W regimen; the 2% drop suggests this dose is on the flat portion of the dose response curve. However, the predicted IL-33 inhibition for

the 300 mg Q8W regimen reduces
by approximately 5% to below 80%.

On this basis, together with the acceptable safety profile of tozorakimab across all dosing regimens, randomisation to the 300 mg Q8W arms will be stopped after approval of this amendment.
There will be no impact on participants already randomised to the 300 mg Q8W arm, who will continue to complete the study. Data collected from this arm will only be used for characterisation of the dose-response curve, and not for confirmatory hypothesis testing. The overall sample size and multiple testing procedures are amended accordingly.

Study design

This is a Phase III, multicenter, randomized, double-blind, chronic dose, parallel group, placebo-controlled study to evaluate the efficacy and safety of Tozorakimab 300 mg Q4W administered subcutaneously, in adult participants with symptomatic COPD and history of COPD exacerbations.
The randomization will be stratified by region, maintenance inhalation therapy (dual vs triple), and smoking status (current vs former). The study includes: former and current smokers, but randomization to the cohort of current smokers will be maximized to ensure that at least 75% of participants are former smokers. Approximately 80% of the participants in the study will be on triple (ICS/LABA/LAMA) therapy.

Intervention

Subjects are randomized in a 1:1 ratio to the 300 mg Q4W Tozorakimab group or to a matched placebo recipient group. Subjects get administered s.c. every 4 weeks during the treatment period at a total of 13 administrations between Day 0 and Week 52.

Study burden and risks

The subject is asked to visit the site at least 15 times. During the intervention period, the subject receives 13 administrations of the study intervention. The test subject will undergo a physical examination during hospital visit. The subject will undergo a spirometry test at least 11 times during the study. The subject will undergo twice a CT scan during the study. The subject must complete assignments in an eDiary every day during the intervention and follow-up periods. Women of childbearing potential should provide a urine sample for pregnancy testing during screening, follow-up, and each pre-study drug visit. The study drug may cause gastrointestinal side effects and severe hypersensitivity. The study physician will supervise the administration of the study medication and observe the subject for a minimum of

1 to 2 hours.

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)

Inclusion criteria

1. Participant must be >= 40 years of age and capable of giving signed informed consent.
2. Documented diagnosis of COPD for at least one year prior to enrolment.
3. Post BD FEV1/FVC < 0.70 and post-BD FEV1 >20% of predicted normal value.
4. Documented history of >= 2 moderate or >= 1 severe COPD exacerbations within 12 months prior to enrolment.
5. Documented optimized dual or triple treatment with COPD and at a stable dose for at least 3 months prior to enrolment.
6. Smoking history of >= 10 pack-years.

7. CAT total score >=10, with each of the phlegm (sputum) and cough items >= 2.

Exclusion criteria

1. Clinically important pulmonary disease other than COPD.
2. Radiological findings suggestive of a respiratory disease other than COPD that is significantly contributing to the participant*s respiratory symptoms.
3. Current diagnosis of asthma, prior history of asthma, or asthma-COPD overlap. Childhood history of asthma is allowed and defined as asthma diagnosed and resolved before the age of 18.
4. Any unstable disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric disorder, major physical and/or cognitive impairment that could affect safety, study findings or participants ability to complete the study.
5. COPD exacerbation, within 2 weeks prior to randomization, that was treated with systemic corticosteroids and/or antibiotics, and/or led to hospitalization.
6. Active significant infection within the 4 weeks prior to randomization, pneumonia within 6 weeks prior to randomization, or medical condition that predisposes the participant to infection.
7. Suspicion of, or confirmed, ongoing SARS-CoV-2 infection.
8. Significant COVID-19 illness within the 6 months prior to enrolment.
9. Unstable cardiovascular disorder.
10. Diagnosis of cor pulmonale, pulmonary arterial hypertension and/or right ventricular failure.
11. History of known immunodeficiency disorder, including a positive test for HIV-1 or HIV 2.
12. Medical history or treatment for hepatitis B or hepatitis C, except for cured hepatitis C.
13. Evidence of active liver disease, including jaundice during screening.
14. Malignancy, current or within the past 5 years, except for adequately treated non-invasive basal cell and squamous cell carcinoma of the skin and cervical carcinoma-in-situ treated with apparent success more than one year prior to enrolment. Suspected malignancy or undefined neoplasms.
15. Participants who have evidence of active TB.
16. Participants that have previously received Tozorakimab.
17. Any clinically significant abnormal findings in physical examination, vital signs, ECG, or laboratory testing during the screening period, which in the opinion of the investigator may put the participant at risk because of their participation in the study, or may influence the results of the study, or the participant*s ability to complete the entire duration of the study.
18. Active vaping of any products or using smoked marijuana within the 6 months prior to randomization and during the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-05-2022
Enrollment:	38
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	18-01-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	21-02-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-08-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-09-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-09-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-09-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-10-2023

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-10-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-11-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
EU-CTR	CTIS2023-503571-19-00
EudraCT	EUCTR2021-003797-30-NL
CCMO	NL79306.100.22