A Phase II, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy, Safety and Tolerability of MEDI3506 in Participants with Moderate to Severe Chronic Obstructive Pulmonary Disease and Chronic Bronchitis

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To evaluate the effect of MEDI3506 as compared with placebo on pulmonary function in subjects with moderate to severe COPD and chronic bronchitis.

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

Summary

ID

NL-OMON55071

Source
ToetsingOnline

Brief title
FRONTIER 4

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
(Chronic Obstructive Pulmonary Disease) and 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 Bronchitis, Chronic Obstructive Pulmonary Disease (COPD), IL-33 inhibition, MEDI3506 mAb

Outcome measures

Primary outcome

To assess the effects of MEDI3506 compared with placebo on pulmonary function in participants with COPD and chronic bronchitis, the change from baseline to Week 12 in pre-BD FEV1 measured in clinic will be used as primary endpoint.

Secondary outcome

The study uses secondary outcomes to gather evidence to support the mode of action of MEDI3506, concentrating on lung physiology, mucus, cough, and ePROs related to symptoms and disease impact. Therefore the study includes secondary outcomes to assess the PK of MEDI3506 in participants with COPD and chronic bronchitis; to asses the immunogenicity of MEDI3506 compared with placebo in participants with COPD and chronic bronchitis; to assess the effect of MEDI3506 on COPDCompEx event in participants with COPD and chronic bronchitis; to assess the effect of MEDI3506 compared with placebo on respiratory symptoms in participants with COPD and chronic bronchitis; to assess the effect of MEDI3506 compared with placebo on disease impact in participants with COPD and chronic bronchitis; to assess the effect of MEDI3506 compared with placebo on airway resistance and reactance in participants with COPD and chronic bronchitis; and to evaluate the effect of MEDI3506 compared with placebo on objective cough

measures in participants with COPD and chronic bronchitis.

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 airflow limitation that is due to airway and/or alveolar abnormalities. COPD is not fully reversible, usually progressive and associated with an enhanced chronic inflammatory response in the lung. Patients with active chronic bronchitis symptoms bear a greater burden of disease than those without and are characterized by more rapid loss of lung function, increased mortality and increased risk of exacerbation. Interleukin-33 (IL-33) expression is upregulated in the lungs of patients with COPD, is inversely correlated with lung function, and has a role in inflammatory and epithelial processes in COPD. MEDI3506 is a monoclonal antibody that binds to IL-33 and potently and specifically blocks all forms of IL-33 to prevent their signaling. Its mode of action is hypothesized to impact airway inflammation, mucus and cough symptoms and lung function endpoints in COPD, and through modification of these factors, reduce frequency and severity of exacerbations. The purpose of the present study is to test the hypothesis that MEDI3506 will improve lung function in participants with COPD and chronic bronchitis.

Study objective

To evaluate the effect of MEDI3506 as compared with placebo on pulmonary function in subjects with moderate to severe COPD and chronic bronchitis.

Study design

This is a Phase II, randomized, double-blind, placebo-controlled, proof-of-concept study to assess the efficacy, safety, and tolerability of MEDI3506 600 mg administered by SC injection Q4W in participants with moderate or severe COPD receiving Standard of Care as maintenance therapy, which is dual therapy (ICS + LABA, or LABA + LAMA) or triple therapy (ICS + LABA + LAMA). Participants also have a history of *1 moderate or severe acute exacerbation in the previous 24 months while on stable background treatment, and moderate to severe chronic bronchitis, with active sputum and cough symptoms. The study will randomize approximately 322 participants 1:1 to MEDI3506 600 mg SC Q4W or placebo for 7 doses. The randomization will be stratified by baseline blood eosinophils (< 300 cells/*L vs * 300 cells/*L) and background medication (includes ICS vs does not include ICS). Approximately 60% of participants will be included in the baseline eosinophils < 300 cells/*L strata. At least 70% of

participants will be included in the strata who are receiving ICS.

Intervention

Subjects will be randomized in a 1:1 ratio to either 600 mg of MEDI3506 or matching placebo both administered Q4W SC. During treatment period, IP will be administered from day 0 until week 28.

Study burden and risks

The subject is asked to visit the site at least 16 times. During the intervention period, the subject will receive 7 administrations of study intervention. The subject will undergo physical examinations at every site visit. The subject will undergo a spirometry test at least 12 times during the study. Additionally, nasal mucosal samples (2 times), nasal epithelial lining fluid (8 times) and spontaneous sputum samples (6 times) will be collected during site visits. The subject (only in the sub-study) will undergo a CT-scan once during the study. The subject must perform spirometry measurements at home on each day throughout intervention and follow-up periods. The subject must complete eDiary assessments on each day throughout the intervention and follow-up periods. Woman of child bearing potential have to provide a urine sample to test for pregnancy at screening, once during follow-up and each time before administration of study medication. The study medication may cause gastrointestinal adverse reactions and serious hypersensitivity. A study physician will supervise the administration of the study drug and will observe the subject at the study center for a minimum of 1 to 2 hours after each injection.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Participant must be 40 to 75 years of age inclusive, at the time of signing the ICF.
2. Participants who are current or ex-smokers with a tobacco history of * 10 pack-years.
3. Participants who are up-to-date on pneumococcus and influenza vaccines as per local
treatment guidelines.
4. Participants who have a documented history of COPD for at least 1 year.
5. Participants who have a post-BD FEV1/FVC < 0.70 and a post-BD FEV1 > 30% and < 80% predicted normal value at screening.
6. Participants who have a physician confirmed participant history of chronic bronchitis as
defined as presence of cough and sputum on most days for * 3 mos/yr in at least the 2 year period immediately prior to SV1 (screening).
7. Participants who have an average BCSS score of * 2 in cough and * 2 in sputum domains
assessed over the 14 days preceding SV3.
8. Participants who have a documented stable regimen of dual therapy (ICS + LABA or LABA + LAMA) or triple therapy (ICS + LABA + LAMA) for * 3 months prior to enrolment; there should have been no change in treatment after the previous exacerbation prior to entering into the study.
9. Participants who have a documented history of * 1 moderate or severe AECOPD requiring systemic corticosteroids and/or antibiotics for at least 3 days duration (or 1 injection of depot formulation), or hospitalization for reason of AECOPD in the previous 24 months prior to screening. A verbal history from the participant of AECOPD is not sufficient.
10. Participants who are clinically stable and free from an exacerbation of COPD for 1 month prior to SV1 (screening) and prior to Day 1.

Exclusion criteria

1. Participants with a positive diagnostic nucleic acid test for SARS-CoV-2 at SV1 or SV2.
2. Participants with a significant COVID-19 illness within 6 months of enrolment
3. As judged by the investigator, any evidence of any active medical or psychiatric condition or other reason (at screening [SV1 and SV2] and SV3 [pre-dose]). See exclusion criteria number 3 in the protocol.
4. Asthma as a current or past diagnosis.
5. Clinically important pulmonary disease other than COPD (
6. Increased pre-BD FEV1 at randomization visit (SV3) compared to Screening SV1 of * 400 mL or * 25% of SV1 FEV1.
7. A family history of heart failure defined as either of the following: * 2 first degree relatives with clinically significant heart failure, or * 1 first degree relative with heart failure known to be heritable (eg, hypertrophic cardiomyopathy), unless inheritance is excluded by genetic testing.
8. A LVEF < 45% measured by echocardiogram during screening, between the time of signing informed consent and prior to randomization.
9. History of a clinically significant infection (viral, bacterial, or fungal) within 4 weeks prior to Day 1 (SV3) (including unexplained diarrhea) or clinical suspicion of infection at time of dosing.
10. Prior history of/planned: lung pneumonectomy for any reason, or lung volume reduction procedures (including bronchoscopic volume reduction) for COPD. Note: Surgical biopsy, or segmentectomy, or wedge resection, or lobectomy for other diseases would not
be excluded.
11. Long term oxygen therapy.
12. Use of any non-invasive positive pressure ventilation device.
13. Participants with a recent history of, or who have a positive test for TB, Hep B, Hep C or HIV.
14. Receiving any of the prohibited concomitant medications as specified in the CSP.

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:	Recruitment stopped
Start date (anticipated):	26-08-2021
Enrollment:	31
Type:	Actual

Ethics review

Approved WMO Date:	22-10-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-12-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-01-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-02-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-03-2021

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-09-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-09-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-11-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-11-2021
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
EudraCT	EUCTR2020-000571-20-NL
CCMO	NL74611.100.20