A multi-center, randomized, double-blind, parallel-group, placebo controlled study of mepolizumab 100 mg SC as add-on treatment in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels (Study 208657)

Published: 09-10-2019
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Primary objective:To evaluate the efficacy of mepolizumab 100 mg subcutaneous (SC) compared to placebo, given every 4 weeks in liquid formulation by safety syringe (SS) to COPD participants at high risk ofexacerbations despite the use of optimized…

Ethical review	Approved WMO
Status	Completed
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON54648

Source
ToetsingOnline

Brief title
MATINEE

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Chronic inflammation in the airways and the lungs, COPD

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: GlaxoSmithKline

Intervention

Keyword: Chronic Obstructive Pulmonary Disease, COPD, Lung, Mepolizumab

Outcome measures

Primary outcome

Primary objective:

To evaluate the efficacy of mepolizumab 100 mg subcutaneous (SC) compared to placebo, given every 4 weeks in liquid formulation by safety syringe (SS) to COPD participants at high risk of exacerbations despite the use of optimized COPD maintenance therapy.

Secondary outcome

Secondary objective:

To evaluate mepolizumab 100 mg SC compared to placebo given every 4 weeks in liquid formulation by SS on additional efficacy assessments, health related quality of life (HRQoL), health care utilization, and symptoms

Study description

Background summary

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response, in the airways and the lung, to noxious particles or gases. While the disease course is marked by progressive

deterioration in airflow it is punctuated by acute exacerbations of COPD (AECOPD) which contribute to the overall disease severity and which increase in frequency as the disease worsens. In addition to the increased risk of morbidity and mortality associated with COPD exacerbations, these events place a significant economic burden on healthcare systems which is predicted to increase with the increasing global disease prevalence.

Mepolizumab has been studied in patients with COPD with limited or no treatment options. The initial Phase IIIA COPD mepolizumab program consisted of two 52-week multicenter, randomized, double blind, placebo-controlled studies, MEA117106 and MEA117113. These studies compared treatment with mepolizumab to placebo when added to maximum inhaled standard of care. Evidence from MEA117113 and MEA117106 demonstrated a consistent and clinically relevant impact of treatment with mepolizumab 100 mg SC compared with placebo on exacerbation reduction in participants with COPD who frequently exacerbate despite treatment with ICS-based inhaled triple maintenance therapy (ICS plus LABA plus LAMA). This study is designed to confirm the benefits of mepolizumab treatment on the primary outcome of moderate/severe exacerbations as well as to more robustly inform on outcomes which are less frequent such as exacerbations requiring emergency department (ED)/hospitalization as well as additional important health related quality of life data.

Study objective

Primary objective:
To evaluate the efficacy of mepolizumab 100 mg subcutaneous (SC) compared to placebo, given every 4 weeks in liquid formulation by safety syringe (SS) to COPD participants at high risk of
exacerbations despite the use of optimized COPD maintenance therapy.

Secondary objective:
To evaluate mepolizumab 100 mg SC compared to placebo given every 4 weeks in liquid formulation by SS on additional efficacy assessments, health related quality of life (HRQoL), health care utilization, and symptoms

Study design

This is a multi-center, randomized, placebo-controlled, parallel group, double-blind, trial evaluating mepolizumab 100 mg SC compared with placebo given every 4 weeks as a liquid formulation in a pre-filled safety syringe injection for max 104 weeks.

Intervention

Subjects will receive a subcuteanous injection with mepolizumab or placebo once

every 4 weeks for a total period of max 104 weeks.

Study burden and risks

The study medication may cause side effects.
Mepolizumab has been studied in patients with severe asthma and COPD. Known side effects of mepolizumab based on studies in patients with severe asthma are listed below. There were no additional side effects reported from studies in patients with COPD.
• The following side effects were very likely (in every 10 people these side effects can occur in 1 or more people):
o Headache
• The following side effects were likely (in every 100 people this side effect can occur in 1 or more people, but in less than 1 in 10 people):
o Injection-site reaction (pain, skin redness, swelling, itching, and burning sensation of the skin near where the injection was given)
o Back pain
o Pharyngitis (sore throat)
o Lower respiratory tract infection (congestion, cough)
o Nasal congestion (stuffy nose)
o Upper abdominal pain (stomach pain or discomfort in the upper area of the stomach)
o Eczema (itchy red patches on the skin)
o Urinary tract infection (blood in urination, painful and frequent urination, fever, pain in lower back)
o Fever (high temperature)
• The following side effects were rare (in every 10,000 people this side effect can occur in 1 or more person, but in fewer than 1 in 1,000 people):
o Hypersensitivity (allergic reaction) including anaphylaxis (an allergic reaction that can be life threatening)
• Allergic reactions may require immediate medical attention or advice. Call the study doctor right away if you think you are having an allergic reaction.
o Hypersensitivity reactions including anaphylaxis (an allergic reaction that can be life threatening) or allergic-like reaction have been reported with mepolizumab. These events often occur within hours of receiving mepolizumab, but in some instances can have a delayed onset up to days later. Symptoms of these reactions more frequently reported include dizziness, feeling tired, itchy skin, hives, redness in skin, flushing, sick to stomach, muscle pain, joint pain and headache. Symptoms reported less frequently, some of which have been severe, include chest discomfort, chest tightness, cough, difficulty breathing, low blood pressure, and swelling in the face and other areas of the body.
• New previously unknown side effects may also occur.
Some patients have developed anti-mepolizumab antibodies. So far, no effects due to these antibodies have been observed in clinical studies.
If you have pre-existing parasitic infection you will not be able to participate in this study. If you become infected with parasite during the

study and treatment for this infection is not effective, you may have to interrupt study treatment until the infection resolves.

Despite recent advances in treatment of patients with COPD, there is a unmet need for an effective treatment with a long duration of response. The sponsor feels that the side effects and the burden associated with participation are in proportion considering the positive effects that participation in the study might have on the patient*s disease progression.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1.Participant must be at least 40 years of age at Screening Visit 1.
2. A peripheral blood eosinophil count of >=300 cells/µL from the hematology

sample collected at Screening Visit 0.
AND
A documented historical blood eosinophil count of >=150/µL in the 12 months prior to Screening Visit 0 that meets the following: It must have been measured between 12 months and 1 month prior to Visit 0, and it must not have been measured within 14 days of a COPD exacerbation.
Participants with no documented historical blood eosinophil count of >=150 cells/µL must meet this threshold at the Screening Visit 1 assessment in order to return for Randomization Visit 2.
3.Participants with a clinically documented history of COPD for at least 1 year in accordance with the definition by the American Thoracic Society/European Respiratory Society.
4.Participants must present with the following:
• A measured pre- and post-salbutamol FEV1/FVC ratio of <0.70 at Screening Visit 1 to confirm the diagnosis of COPD.
• A measured post-salbutamol FEV1>20% and <=80% of predicted normal values calculated using NHANES III reference equations at Screening Visit 1.
5. Participants must have a well-documented history (e.g., medical record verification) in the 12 months prior to Screening Visit 1 of:
• Two or more moderate COPD exacerbations that were treated with systemic corticosteroids (intramuscular (IM), intravenous, or oral) with or without antibiotics.
OR
• At least one severe COPD exacerbation requiring hospitalization
Note: At least one exacerbation must have occurred while the participant was taking inhaled triple therapy, ICS plus LABA plus LAMA unless documented intolerance or safety risk with either of the two long-acting bronchodilators. If intolerance is documented, ICS plus LABA or ICS plus LAMA would be allowable after discussion with the Medical Monitor.
Note: COPD exacerbations related to COVID-19 infection must not be counted as COPD exacerbations for inclusion in the study.
6. Participants must have a well-documented requirement for optimized standard of care background therapy that includes ICS plus 2 additional COPD medications (i.e., ICS-based triple therapy) for the 12 months prior to Screening Visit 1 and meets the following criteria:
• Immediately prior to Screening Visit 1, minimum of 3 months of use of an a) inhaled corticosteroid at a dose >=500 mcg/day fluticasone propionate dose equivalent plus b) LABA and c) LAMA unless documentation of safety or intolerance issues related to LABA or LAMA.
• For participants who are not continually maintained on ICS plus LABA plus LAMA for the entire 12 months prior to Visit 1 use of the following is allowed (but not in the 3 months immediately prior to Visit 1):
a.inhaled corticosteroid at a dose >=500 mcg/day fluticasone propionate dose equivalent plus
b.inhaled LABA or inhaled LAMA and
c.Phosphodiesterase-4-inhibitors, methylxanthines, or scheduled daily use of short acting beta2-agonist (SABA) and/or short acting muscarinic

antagonist (SAMA).
Note: Where intolerance or safety risk is documented for either LAMA or LABA, ICS-based inhaled dual maintenance therapy, either ICS plus LABA or ICS plus LAMA, is allowed in the 12 months prior to Visit 1 and during the clinical trial but must be discussed with the Medical Monitor.
Note: Participants must be willing to receive optimized maintenance COPD therapy for the duration of the study.
7. Current or former cigarette smokers with a history of cigarette smoking of >=10 pack-years at Screening (Visit 1) [number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Screening Visit 1.
Note: Pipe and/or cigar use cannot be used to calculate pack-year history.
8. Contraceptive use for women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
Female Participants:
A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
o Is not a woman of childbearing potential (WOCBP)
o Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 5, during the intervention period and for at least 16 weeks after the last dose of study intervention. The principal investigator (PI) should evaluate the effectiveness of the contraceptive method in relation to the first dose of study intervention.
• A WOCBP must have a negative highly sensitive pregnancy urine test within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are located in Appendix 3
• The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk of inclusion of a woman with an early undetected pregnancy
9. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Exclusion criteria

1. Participants with a past history or concurrent diagnosis of asthma are excluded regardless of whether they have active or inactive disease.
2. The Investigator must judge that COPD is the primarydiagnosis accounting for the clinical manifestations of the lung disease. Participantswith α1-

antitrypsin deficiency as the underlying cause of COPD are excluded. Also,excluded are participants with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung diseases
or other active pulmonary diseases.
3. Participants with pneumonia, COPD exacerbation, or lower respiratory tract infection within the 4 weeks prior to Screening Visit 1.
4. Participants with lung volume reduction surgery within the 12 months prior to Screening Visit 1.
5. Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening Visit 1. Participants who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.
6. Participants receiving treatment with oxygen more than 2 L/min at rest over 24 hrs. For participants receiving oxygen treatment, participants should demonstrate an oxyhemoglobin saturation greater than or equal to 89% while breathing supplemental oxygen.
7. Participants with a QT interval, from the ECG conducted at Screening Visit 1, corrected with Fridericia's formula (QTcF) >450 msec (or QTcF >480 msec in participants with bundle branch block).
QTcF is the QT interval corrected for heart rate according to Fridericia*s formula that is selected for this study. It is either machine-read or manually over-read. when not automatically machine read. This specific formula must be used to determine eligibility and discontinuation for an individual participant. Participants are excluded if an abnormal ECG finding from the 12-lead ECG conducted at Screening Visit 1 is considered to be clinically significant and would impact the participant's participation during the study, based on the evaluation of the Investigator.
Note: Where a single ECG demonstrates a prolonged QTcF interval, obtain two more ECGs readings at a minimum of 2 min apart over a brief recording period (e.g., 5-10 min), The average of the triplicate QTcF measurements should be used to determine eligibility.
8. Participants with any of the following would be excluded:
• Myocardial infarction or unstable angina in the 6 months prior to Screening Visit 1
• Unstable or life threatening cardiac arrhythmia requiring intervention in the 3 months prior to Screening Visit 1
• New York Heart Association (NYHA) Class IV Heart failure
9. Participants with (historical or) current evidence of clinically significant, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the
opinion of the Investigator, would put the safety of the participant at risk through participation, or which could affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
10. Participants with other conditions that could lead to elevated eosinophils such as Hypereosinophilic syndromes including Eosinophilic Granulomatosis with

Polyangiitis (EGPA, also known as Churg-Strauss Syndrome), or Eosinophilic Esophagitis.
11. Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening Visit 1.
12. A current malignancy or previous history of cancer in remission for less than 12 months prior to Screening Visit 1 (Participants that had localized carcinoma of the skin or cervix which was resected for cure will not be excluded).
Note: for South Korea: Korean participants with a diagnosis of malignancy within 5 years of Visit 1 are excluded.
13. A known immunodeficiency (e.g. human immunodeficiency virus - HIV), other than that xplained by the use of corticosteroids taken for COPD.
14. Cirrhosis or current unstable liver disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, or persistent jaundice. Stable noncirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) is acceptable if the participant otherwise meets entry criteria
15. Participants who have received interventional product in previous mepolizumab studies are excluded.
16. Subjects who have received any monoclonal antibody within 5 half lives of Screening Visit 1
17. Participants who have received an investigational drug within 30 days of Visit 1, or within 5 drug half-lives of the investigational drug, whichever is longer (this also includes investigational formulations of a marketed product).
18. Participants who have received short term use of oral corticosteroids within 30 days of Visit 1
19. Participants with a known allergy or sensitivity to any of the study interventions, or components thereof, or drug or other allergy
20. Participants at risk of non-compliance, or unable to comply with the study procedures.
21. Participants with a history of psychiatric disease, intellectual deficiency, poor motivation or other, conditions that will limit the validity of informed consent to participate in the study. , e.g uncontrolled psychiatric disease or intellectual deficiency.
22. A known or suspected history of alcohol or drug abuse within 2 years prior to Screening Visit 1.
23. Is an Investigator, sub-Investigator, study coordinator, employee of a participating Investigator or study site, or immediate family member of the aforementioned that is involved in this study.
24. COVID-19: a- Participants that have a current active COVID-19 infection, either laboratory confirmed or according to the investigator's medical judgement.
Note: Participants who have confirmed or suspected COVID-19 infection may be re-screened 4 weeks or more after the resolution of the COVID-19 infection and only after approval from the Medical Monitor.
b- Participants known to be in contact with active COVID-19 positive

individuals within the past 14 days.
Note: Participants may be re-screened 14 days or more following the contact, during which the participant should remain symptoms free, and only after approval from the Medical Monitor.

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:	Completed
Start date (anticipated):	27-01-2020
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mepolizumab
Generic name:	Mepolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	09-10-2019

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-11-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	18-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-02-2024
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	EUCTR2018-001540-56-NL
CCMO	NL70400.056.19