A Multicenter, Randomized, Double-blind, Chronic-dosing, Parallel-group, Placebo-controlled Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab 100 mg in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) with a History of Frequent COPD Exacerbations and Elevated Peripheral Blood Eosinophils (RESOLUTE)

Published: 02-04-2020
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This study has been transitioned to CTIS with ID 2022-503050-39-00 check the CTIS register for the current data. To evaluate the effect of benralizumab 100 mg on COPD exacerbations in patients with moderate to very severe COPD.

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

Summary

ID

NL-OMON52490

Source
ToetsingOnline

Brief title
RESOLUTE

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: Benralizumab, Eosinophils, Frequent exacerbations, Moderate to severe COPD

Outcome measures

Primary outcome

Primary objective: To evaluate the effect of benralizumab 100 mg on COPD

exacerbations in patients with moderate to very severe COPD.

Primary endpoint: Annualized rate of moderate or severe COPD exacerbations,

where a COPD exacerbation is defined by symptomatic worsening of COPD requiring:

• Use of systemic corticosteroids for at least 3 days; a single depot

injectable dose of corticosteroids will be considered equivalent to a 3-day

course of systemic corticosteroids; and/or

• Use of antibiotics; and/or

• An inpatient hospitalization or death due to COPD

Secondary outcome

Secondary objectives:

- To evaluate the effect of benralizumab 100 mg on severe COPD exacerbations

(leading to hospitalization or death). Variable: Annualized rate of severe COPD exacerbations a, where a severe COPD exacerbation is defined by symptomatic worsening of COPD requiring an inpatient hospitalization or results in death due to COPD.

- To evaluate the effect of benralizumab 100 mg on COPD exacerbations involving emergency room visits and hospitalizations. Variable: Annualized rate of COPD exacerbations that are associated with an emergency room/emergency department visit or a hospitalization due to COPD.

- To evaluate the effect of benralizumab 100 mg on other parameters associated with COPD exacerbations. Variable: Time to first COPD exacerbation.

- To evaluate the effect of benralizumab 100 mg on health status/health-related quality of life. Variables: - Change from baseline in SGRQ total a and domain scores. - Change from baseline in CAT total score.

- To evaluate the effect of benralizumab 100 mg on respiratory symptoms. Variable: Change from baseline in E-RS:COPD total and domain scores.

- To evaluate the effect of benralizumab 100 mg on pulmonary function. Variable: Change from baseline in pre-dose/pre-bronchodilator FEV1 at the study site.

- To evaluate the effect of benralizumab 100 mg on all cause and respiratory-related mortality. Variable: Mortality rate.

- To evaluate the effect of benralizumab 100 mg on health care resource utilization due to COPD. Variable: Annual rate of hospitalizations due to COPD; Length of hospital stay; ICU days; annual rate of hospitalizations and emergency department visits combined due to COPD; annual rate of unscheduled

outpatient visits including unscheduled visits to study sites due to COPD; and

annual rate of unscheduled healthcare encounters due to COPD.

- To evaluate the pharmacokinetics and immunogenicity of benralizumab in this

patient population. Variables: - Serum benralizumab concentration. -

Anti-benralizumab antibodies

Study description

Background summary

Chronic obstructive pulmonary disease (COPD) is a progressive disease and a significant cause of morbidity and mortality worldwide. In contrast to other chronic diseases, COPD is increasing in prevalence and is projected to be the third leading cause of death and disability worldwide by 2020.

Acute exacerbations of COPD (AECOPD) are responsible for a large portion of the economic burden of COPD. In addition to a substantial economic burden, AECOPDs are also responsible for much of the morbidity and mortality from COPD. Patients with frequent AECOPD show associated increased airway inflammation and accelerated decline in lung function compared with patients with infrequent exacerbations.

Increasing evidence has accumulated in recent years to support the role of eosinophilic inflammation in COPD. Airway and sputum eosinophilia have been associated with exacerbations of COPD. Blood eosinophil levels are associated with COPD exacerbations and likely predict corticosteroid therapy. These data suggest blood and airway eosinophils may be used to help identify COPD patients most likely to respond to corticosteroid therapy but also imply that therapies specifically targeting eosinophils in COPD patients with elevated blood or airway eosinophils may have beneficial effects.

Benralizumab is a humanized, afucosylated, monoclonal antibody that binds specifically to the human interleukin-5 (IL-5) receptor alpha subunit (IL-5Rα) on the target cell and directly depletes eosinophils through antibody-dependent cell-mediated cytotoxicity. The mechanism of action of benralizumab makes it a potential treatment option for the high unmet need in chronic obstructive pulmonary disease (COPD) patients with eosinophilic inflammation and at risk for exacerbations.

Benralizumab is being developed as an add-on maintenance treatment and for prevention of exacerbations in patients with COPD. The benralizumab COPD clinical program consists of a Phase 2a study (identified as MI-CP196), followed by two Phase 3 studies (identified as GALATHEA [D3251C00003] and TERRANOVA [D3251C00004]) that evaluated benralizumab in patients with moderate to very severe COPD with a history of exacerbations despite standard maintenance therapy with inhaled corticosteroid/long-acting β2 agonist (ICS/LABA), long acting muscarinic antagonist (LAMA)/LABA (double) or ICS/LABA/LAMA (triple) across a range of baseline blood eosinophils.

Study objective

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To evaluate the effect of benralizumab 100 mg on COPD exacerbations in patients with moderate to very severe COPD.

Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3 study to evaluate the efficacy and safety of a benralizumab 100 mg dose administered by subcutaneous (SC) injection every 4 weeks for the first 3 doses and then every 8 weeks thereafter (hereafter referred to as Q8W) in patients with moderate to very severe COPD with a history of frequent COPD exacerbations and elevated peripheral blood eosinophils (>=300/µL). Eligible patients must have a history of >=2 moderate and/or severe COPD exacerbations in the previous year despite receiving triple (ICS/LABA/LAMA) background therapy. Eligible patients must also have an elevated blood eosinophil count of >=300/µL at screening supported by at least 1 historical result of >=150/µL within the previous year. Potentially eligible patients will enter the run-in period of 5 weeks (subject to extension, refer to Section 4.1.1). Patients who meet eligibility criteria will be randomized in a 1:1 ratio to receive either benralizumab 100 mg or placebo Q8W. The treatment period will be of variable duration and will continue until the last patient has the opportunity to complete a minimum of 56 weeks, at which point all patients will complete the study; see Section 4.1.2. The primary endpoint will be analyzed at Week 56. At randomization, patients will be stratified by country and number of exacerbations in the previous year (2 or >=3). Randomization to the stratum of 2 exacerbations in the previous year will be capped to ensure >=70% of patients with >=3 exacerbations in the previous year in the study population.

A total of 868 patients are expected to be randomized in the study at a 1:1 ratio to either benralizumab 100 mg SC or matching placebo treatment groups.

Intervention

Subjects will be randomized in a 1:1 ratio to either 100 mg Benralizumab or placebo administered subcutaneous every four weeks for the first 3 doses and then every 8 weeks thereafter.

Study burden and risks

Potential risks of benralizumab are as follows:
•Serious infections have been reported for benralizumab. A relationship between eosinophil depletion and serious infection has not been established.
•Malignancies have been reported at a low incidence in the completed and ongoing studies of benralizumab. Eosinophils have been found in association with solid tumors, especially tumors of epithelial origin (breast and colon), and may play an active role in tumor defense by modulating host defenses, or may be a bystander effect. However, the cause and consequences (i.e. pro-tumorigenic versus anti-tumorigenic) of eosinophil recruitment and accumulation into tumors are unclear.
•Serious hypersensitivity reactions (including anaphylaxis) are an identified risk of biologic therapy, including benralizumab. Anaphylaxis may be life-threatening. Risk minimization includes a minimum of a 1 hour observation period at the clinical site following IP administration for the appearance of any acute drug reactions.
•Development of anti-drug antibodies (ADA) to benralizumab has been documented. Theoretical risks of developing ADA may include decreased drug efficacy and hypersensitivity reactions (e.g. anaphylaxis or immune complex disease). There was no apparent impact of ADA on overall benralizumab safety or efficacy in the previous Phase 3 studies in COPD patients.
•Eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections, and the presence of infiltrating eosinophils has been circumstantially associated with a positive prognosis in certain solid tumors. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites or negatively impact the natural history of certain malignant tumors. Risk minimization measures include exclusion of patients with untreated parasitic infection and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

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. Provision of informed consent
2. Age 40 to 85 years
3. Male and/or female.
4. Current or former smoker with a tobacco history of >=10 packyears.
5. History of moderate to very severe COPD with a postbronchodilator FEV1/FVC<0.70 and FEV1 <=65% of predicted normal value.
6. Documented history of 2 or more COPD exacerbations that required treatment with systemic corticosteroids and/or hospitalization within 52 weeks prior to enrollment.
(a) Exacerbations treated with antibiotics alone are excluded unless accompanied by treatment with systemic corticosteroids and/or hospitalization.
(b) Hospitalization is defined as an inpatient admission >=24 hours
(c) Previous exacerbations should be confirmed to have occurred while the patient was on stable double or triple (ICS/LABA/LAMA) background therapy for COPD and not as a result of a gap or step down in the treatment.
(d) At least one qualifying COPD exacerbation should occur while on stable uninterrupted triple therapy prior to enrolment.
7 Documented use of triple (ICS/LABA/LAMA3) background therapy for COPD for >=3 months immediately prior to enrollment.

(a) Treatment with at least double inhaled therapy containing ICS (e.g. ICS/LABA or ICS/LAMA) for the remaining of 52 weeks prior to enrolment. Use of LABA/LAMA is allowed if ICS cannot be tolerated.
(b) Total cumulative duration of not using inhaled double or being on triple background therapy must not exceed 2 months.
(c) Stable therapy/doses for the last 3 months prior to randomization.
8. Blood eosinophil count >=300/µL at screening and documented historical eosinophil count of >=150/µL within 52 weeks of enrollment (or repeated testing during run-in).
9. CAT total score >=15 at Visit 1.
10. Negative pregnancy test for females of childbearing potential (WOCBP) at Visit 1.
11. Women of childbearing potential (WOCBP) must agree to use a highly effective method of birth control from randomization throughout the study and 12 weeks after last dose of IP. Women not of childbearing potential are defined as women who are either permanently sterilized or postmenopausal (confirmed by FSH test for women <50 years).

Exclusion criteria

1. Clinically important pulmonary disease other than COPD
2. Current diagnosis of asthma, prior history of asthma or asthma- COPD overlap according to GINA/GOLD. Childhood history of asthma is allowed and defined as asthma diagnosed and resolved before theage of 18.
3. Radiological findings of a respiratory disease other than COPD contributing to respiratory symptoms. Solitary pulmonary nodules without appropriate follow up or results of acute infection.
4. Another pulmonary or systemic disease associated with elevated peripheral eosinophil counts.
5. Any unstable disorder that could affect patient safety, study findings or the patient's ability to complete the study.
6. Any clinically significant abnormal findings in physical examination, vital signs, ECG, laboratory tests could affect patient safety, study findings or the patient's ability to complete the study.
7. Cor pulmonale and/or right ventricular failure.
8. Long-term treatment with oxygen >4.0 L/min and/or oxyhemoglobin saturation <89% while breathing supplemental oxygen.
9. Use of any non-invasive positive pressure ventilation device m(NIPPV). Note: use of CPAP for Sleep Apnea Syndrome is allowed.
10. Known immunodeficiency disorder, including positive HIV-1/2 testing.
11. Active liver disease. Chronic stable hepatitis B and C (including positive HBsAg or hepatitis C antibody testing), or other stable chronic liver disease are acceptable.
12. ALT or AST >=3 times the upper limit of normal, confirmed by repeated testing during the run-in period.

13. Helminth parasitic infection within 24 weeks prior to enrollment, not treated or failed to respond to standard of care therapy.
14. Alcohol or drug abuse within the past year, which may compromise the study data.
15. 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 1 year prior to Visit 1. Suspected malignancy or undefined neoplasms.
16. Evidence of active tuberculosis, as judged by investigator. Patients with a recent (within 2 years) first-time or newly positive PPD or Quantiferon test need to complete an appropriate course of treatment before enrollment. Evaluation will be according to the local standard of care.
17. Participation, or planned participation, in intensive COPD rehabilitation program (maintenance phase of a rehabilitation is allowed).
18. History of surgical or endoscopic lung volume reduction within the 6 months prior to enrollment. History of partial or total lung resection (single lobe or segmentectomy is acceptable).
19. Scheduled major surgical procedure during the study. Minor elective procedures are allowed.
20. History of anaphylaxis to any biologic therapy or vaccine.
21. Receipt of blood products or immunoglobulins within 30 days prior to randomization.
22. Receipt of marketed or investigational biologic product within 4months or 5 half-lives prior to randomization, whichever is longer. Exception: Patients on stable therapy for 3 months before randomization who intend to stay on treatment throughout the study with marketed biologic products that are not likely to interfere with the safety assessment and/or efficacy of benralizumab, for example, for the treatment of osteoporosis, migraine, pain, diabetes, obesity, ocular, cardiovascular, or metabolic diseases, can participate in the study.1
23. Receipt of live attenuated vaccines 30 days prior to randomization.
24. Chronic use of immunosuppressive medication or expected need for chronic use during the study.
25. Chronic use of antibiotics if duration of treatment is <9 months prior to randomization. Chronic macrolide or other antibiotic therapy is allowed provided the patient has been on stable dose/regimen for >=9 months prior to randomization and has had >=2 COPD exacerbations while on stable therapy.
26. Receipt of any investigational non-biologic product within 30 days or 5 half-lives prior to enrollment.
27. Receipt of benralizumab within 12 months prior to enrollment.
28. Known history of allergy or reaction to any component of the IP formulation.

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):	22-01-2021
Enrollment:	15
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	02-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-05-2020
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	12-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-12-2022
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
EU-CTR	CTIS2022-503050-39-00
EudraCT	EUCTR2019-001800-39-NL
ClinicalTrials.gov	NCT04053634
CCMO	NL72848.056.20