A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Safety and Efficacy of Benralizumab 30 mg sc in Patients with Severe Asthma Uncontrolled on Standard of Care Treatment

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To determine the effect of benralizumab on the rate of asthma exacerbationsSubstudy: - To assess the potential for benralizumab treated patients to reduce their standard of care asthma controller regimen whilemaintaining asthma control.- To assess...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract infections
Study type	Interventional

Summary

ID

NL-OMON50740

Source
ToetsingOnline

Brief title
D3250C00045 (ANDHI)

Condition

- Respiratory tract infections

Synonym
Asthma

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: The pharmaceutical industry.

Intervention

Keyword: Asthma, uncontrolled

Outcome measures

Primary outcome

The annualized rate of asthma exacerbations between benralizumab and placebo.

Substudy:

Main outcome variables:

- Number of reductions in asthma controller medications from Visit 15 to the

end of study (EOS) Visit 27 (Day 560/Week 80).

- Number of adapted GINA step category reductions from baseline at Visit 15 to

the EOS Visit 27 (Day 560/Week 80).

Main outcome measures:

-Proportion of patients with at least one reduction in asthma controller

medication from Visit 15 to EOS (Visit 27);

- Proportions of patients with the number of adapted GINA step category

reductions from Visit 15 to EOS (Visit 27) * X, where X is ranging from 1 to 4.

- Distribution of the number of adapted GINA step reductions from Visit 15 to

EOS (Visit 27) (X) where X is ranging from 0c to 4.

Secondary outcome

The change from baseline (Visit 4) in Saint George Respiratory Questionnaire (SGRQ) to the EOT (Day 168/Week 24).

The change from baseline (Visit 4) in forced expiratory volume in first second (FEV1) over the treatment period (up to and including Day 168/Week 24).

The change from baseline (Visit 4) in Asthma Control Questionnaire 6 (ACQ6) to the EOT (Day 168/Week 24).

Time to first asthma exacerbation (treatment period 24 weeks).

The change from run-in baseline morning peak expiratory flow (PEF) to the EOT (Day 168/Week 24).

The change from baseline (Visit 4) SF 36v2 to the EOT (Day 168/Week 24).

The change from baseline (Visit 4) in PGI-S to the EOT (Day 168/Week 24).

The degree of change reported by the patient (PGI-C) and Investigator (CGI-C) expressed as a proportion of each of the 7 possible responses to the EOT (Day 168/Week 24).

The degree of change reported by the patient in their predominant symptom to the EOT (Day 168/Week 24).

The change from baseline (Visit 3) in the sino-nasal outcome test (SNOT-22) score to the EOT (Day 168/Week 24).

Safety: Adverse events (AEs), laboratory variables, physical examination.

Exploratory:

The change from baseline (Visit 4) in circulating biomarkers to each prespecified

scheduled assessment during the treatment period.

The proportion of time that that the patient's asthma is well-controlled based on composite diary measures.

Substudy:

- Change in continuous asthma efficacy measures (including ACQ6, SGRQ, pre-bronchodilator forced expiratory volume [pre-BD FEV1] and weekly mean morning peak expiratory flow [PEF]) from Visit 15 to the EOS Visit 27 (Day 560/Week 80).
- Change in continuous asthma efficacy measures(including ACQ6, SGRQ, FEV1 and morning PEF) from Visit 4 to the EOS Visit 27 (Day 560/Week 80).
- Degree of change reported by the patient (PGI-C) from Visit 13 and Investigator (CGI-C) from Visit 4 to the EOS Visit 27 (Day 560/Week 80).
- Clinically significant asthma exacerbations from Visit 15 to the EOS Visit 27 (exacerbation count and time to first exacerbation).

Study description

Background summary

Asthma is a syndrome characterized by airway inflammation, reversible airway obstruction, and airway hyperresponsiveness. Patients present clinically with recurrent wheezing, shortness of breath, cough, and chest tightness. Despite treatment per management guidelines, up to 50% of patients have asthma that is not well controlled. This results in considerable impact on quality of life, disproportionate use of healthcare resources, and adverse reactions from regular systemic steroid use. Therefore, there remains an unmet medical need for patients whose asthma is not controlled by existing therapies.

Study objective

To determine the effect of benralizumab on the rate of asthma exacerbations

Substudy:
- To assess the potential for benralizumab treated patients to reduce their standard of care asthma controller regimen while maintaining asthma control.
- To assess standard asthma efficacy measures for benralizumab treated patients when reducing their standard of care asthma controller regimen.
- Safety Objective: To assess the safety and tolerability of benralizumab during treatment period.

Study design

This is a Phase IIIb, randomized, double-blind, placebo-controlled, parallel-group study

Substudy: Open label

Intervention

Benralizumab 30 mg/mL solution for injection in an accessorized pre-filled syringe (APFS) will be administered at the study center subcutaneously (sc) for 4 doses: Day 0 (Week 0), Day 28 (Week 4), Day 56 (Week 8), and Day 112 (Week 16). A matching placebo will be used as comparator.

Substudy: one dose of study drug (30mg/ml) approximately every 4 weeks for the first three doses (Visits 13, 14, and 15) and then every 8 weeks, at Visits 17, 19, 21, 23, and 25.

Study burden and risks

Benralizumab is being studied in severe asthma where there are few treatment options for patients whose asthma remains uncontrolled on high dose ICS/LABA and/or oral corticosteroids. In adult patients whose asthma was poorly controlled by high dose ICS/LABA therapy, benralizumab 30 mg every 8 weeks produced improvements in multiple measures of asthma control including the annual rate of asthma exacerbations, lung function symptoms, and Asthma Control Questionnaire (ACQ) scores in two Phase III trials each approximately 1 year in duration.
Longerterm safety studies are presently ongoing.
The efficacy and safety data obtained to date support a favorable benefit/risk profile of benralizumab in severe asthma patients who manifest an eosinophilic phenotype.
A detailed assessment of the overall risk/benefit of benralizumab is given in

the Investigator*s Brochure.

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.Written informed consent for study participation must be obtained prior to any study related procedures being performed and according to international guidelines and/or applicable European Union (EU) guidelines.
2.Female and male patients aged 18 to 75 years inclusively at the time of Visit 1 with a history of physician-diagnosed asthma requiring treatment with medium-to-high dose ICS plus asthma controller, for at least 12 months prior to Visit 1. Other acceptable asthma controllers include a long acting bronchodilator (LABA or long-acting muscarinic antagonists [LAMA]), a leukotriene inhibitor, theophylline preparations or maintenance OCS (daily or

every other day OCS requirement in order to maintain asthma control; maximum total daily dose 20 mg prednisone or equivalent).
3.Documented current treatment with high daily doses of ICS plus at least one other asthma controller for at least 3 months prior to Visit 1; see inclusion criterion 2 for acceptable other asthma controllers.
* For ICS/LABA combination preparations, highest-strength maintenance doses approved in the given country will meet this criterion.
* If the ICS and the other asthma controller therapies are given by separate inhalers, then the patient must be on a high daily ICS dose.
4.History of at least 2 asthma exacerbations while on ICS plus another asthma controller (see inclusion criterion 2 for examples) that required treatment with systemic corticosteroids (IM, IV, or oral) in the 12 months prior to Visit 1. For patients receiving corticosteroids as a maintenance therapy, the corticosteroid treatment for the exacerbation is defined as a temporary increase of their maintenance dose.
5.ACQ6 score *1.5 at Visit 1.
6.Screening pre-bronchodilator (pre-BD) FEV1 of <80% predicted at Visit 2
Note: Spirometry testing should only be performed if the patient meets the asthma medication hold for lung function testing, the test should be postponed to another day prior to Visit 3 to improve the chances of achieving a qualifying FEV1 that is not affected
by bronchodilator medication.
7. Evidence of asthma as documented by excessive variability in lung function by satisfying *1 of the criteria below: a) Airway reversibility (FEV1 *12%) using a short-acting bronchodilator demonstrated at Visit 2 or Visit 3. b) Airway reversibility to short-acting bronchodilator (FEV1
12%) documented during the 12 months prior to enrolment Visit 1. c) Daily diurnal peak flow variability of >10% when averaged over 7 continuous days during the study run-in period. d) An increase in FEV1 of *12% and 200 mL after a therapeutic trial of systemic corticosteroid (eg, OCS), given outside of an asthma exacerbation, documented in the 12 months prior enrolment Visit 1. e) Airway hyper-responsiveness documented in the 24 months prior to randomization Visit 4.
8. Peripheral blood eosinophil count either: *300 cells/*L assessed by central laboratory at either Visit 1 or Visit 2 OR *150 to <300 cells/*L assessed by central laboratory at either Visit 1 or Visit 2, IF *1 of the following 5 clinical criteria (a to e) is met: a) Using maintenance OCS (daily or every other day OCS requirement in order to maintain asthma control; maximum total daily dose 20 mg prednisone or equivalent) at screening. b) History of nasal polyposis. c) Age of asthma onset *18 years. d) Three or more documented exacerbations requiring systemic corticosteroid treatment during the 12 months prior to screening. e) Pre- bronchodilator forced vital capacity <65% of predicted, as assessed at Visit 2.
9. Women of childbearing potential (WOCBP) must use at least one acceptable and effective form of birth control (confirmed by the Investigator). Women of childbearing potential must agree to use birth control, as defined above, from enrolment, throughout the study duration and until 16 weeks (approximately 5

half-lives) after last dose of investigational product (IP). Women of childbearing potential must also have negative serum pregnancy test result on Visit 1.
10.Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. 11.All male patients who are sexually active must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of IP until 16 weeks after their last dose.
12.Weight of *40 kg.
For Inclusion Criteria for ANDHI in Practice Sub Study please see Page 47 of protocol.

Exclusion criteria

1.Clinically important pulmonary disease other than asthma (eg, active lung infection, chronic obstructive pulmonary disease [COPD], bronchiectasis, pulmonary fibrosis, cystic fibrosis), or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).
2.Acute upper or lower respiratory infections within 30 days prior to the date informed consent is obtained or during the screening/run-in period.
3.Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:
Affect the safety of the patient throughout the study.
Influence the findings of the studies or their interpretations.
Impede the patient's ability to complete the entire duration of study.
4.Known history of allergy or reaction to any component of the IP formulation.
5.A helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy.
6.Any clinically significant abnormal findings in physical examination, vital signs, hematology, or clinical chemistry during screening period, which in the opinion of the Investigator may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study.
7.Any clinically significant cardiac disease or any electrocardiogram (ECG) abnormality obtained during the screening/run-in period, which in the opinion

of the Investigator may put the patient at risk or interfere with study assessments.
8.History of alcohol or drug abuse within 12 months prior to the date informed consent is obtained.
9.A history of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test.
10.Current smokers or former smokers with a smoking history of *10 pack years. A former smoker is defined as a patient who quit smoking at least 6 months prior to Visit 1.
11.Current malignancy, or history of malignancy, except for:
Patients who have had non-melanoma skin cancers or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent is obtained.
Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent is obtained.
12.Approved or off-label use of systemic immunosuppressive medications within 3 months prior to the date informed consent is obtained. These include but are not limited to small molecules such as methotrexate, cyclosporine, azathioprine, and immunosuppressive/immunomodulating biologics such as tumor necrosis factor (TNF) blockers. Regular use of systemic (oral) corticosteroids is also excluded except for the indication of asthma.
13.Concurrent biologics for asthma are not allowed except for stable allergen immunotherapy (defined as a stable dose and regimen at the time of Visit 1).
Acceptable washout periods for other asthma biologics:
Other eosinophil lowering products indicated for asthma (including mepolizumab or reslizumab): at least 4 months.Prior omalizumab use: at least 1 month.
14.Previously received benralizumab (MEDI-563).
15.Receipt of any investigational medication as part of a research study within approximately 5 half-lives prior to randomization.
16.ALT or AST level >3 times the upper limit of normal (ULN) confirmed during screening period.
17.Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent is obtained.
18.Receipt of live attenuated vaccines 30 days prior to the date of randomization; other types of vaccines are allowed.
19.Planned surgical procedures during the conduct of the study.
20.Currently breastfeeding or lactating women.
21.Pevious randomization in the present study.
22.Concurrent enrolment in another interventional or post-authorization safety study.
23.AstraZeneca staff involved in the planning and/or conduct of the study.
24.Employees of the study center or any other individuals involved with the conduct of the study or immediate family members of such individuals.
For Exclusion Criteria for ANDHI in Practice Sub Study please see Page

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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:	Recruitment stopped
Start date (anticipated):	26-03-2018
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not applicable
Generic name:	Benralizumab

Ethics review

Approved WMO Date:	05-09-2017
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	03-10-2017

Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	31-10-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	02-11-2017
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	13-02-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	20-02-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	25-04-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	20-09-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	29-11-2018

Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	13-12-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	12-03-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	01-05-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	21-05-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	05-08-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	28-08-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	02-09-2020

Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2017-001040-35-NL
ClinicalTrials.gov	NCT03170271
CCMO	NL62422.075.17