A Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Study to Investigate the Use of Benralizumab for Eosinophilic Esophagitis (MESSINA)

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The objective of this Phase 3 study is to investigate the safety and efficacy of benralizumab as a treatment for patients with eosinophilic esophagitis.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON55048

Source
ToetsingOnline

Brief title
MESSINA

Condition

- Gastrointestinal inflammatory conditions

Synonym
allergic oesophagitis, Eosinophilic oesophagitis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Benralizumab, Eosinophilic Esophagitis, IL-5R&alfa, monoclonal antibody

Outcome measures

Primary outcome

Primary objective: To evaluate the effect of benralizumab 30 mg Q4W on histologic signs and symptoms of EoE in patients with symptomatic and histologically active EoE.

Dual-primary endpoints/variables: Proportion of patients with a histologic response at Week 24, defined as a peak esophageal intraepithelial eosinophil count <= 6 eos/hpf and Changes from baseline in DSQ score at Week 24.

Secondary outcome

Secondary objectives:

To evaluate the effect of benralizumab 30 mg Q4W on clinical features of EoE and disease activity.

Endpoints/variables:

- Key secondary endpoint: Changes from baseline in centrally-read EoE EREFS at Week 24.
- Centrally-read biopsies for additional histopathology and tissue eosinophil counts, including EoE-HSS, at Week 24.
- Dysphagia-free days as captured by the DSQ.
- Frequency of dysphagia episodes as captured by the EoE-3D.
- Changes from baseline in dysphagia associated pain, discomfort, and overall severity as captured by the EoE-3D at Week 24.

- Changes from baseline in abdominal pain and nausea as captured by the daily diary at Week 24.

To evaluate the effect of benralizumab 30 mg Q4W on patient reported QOL measures.

Endpoints/variables:

- Changes from baseline in EoE-QoL-A at Week 24.
- SF-36 v2 Health Survey at Week 24.

To evaluate the effect of benralizumab 30 mg Q4W on healthcare resource utilization due to EoE.

Endpoint/variable:

- Percent of patients with relevant concomitant procedures and healthcare resource utilization during the study through Week 24.

To evaluate the effect of benralizumab 30 mg Q4W on patient reported measures of disease severity and health status.

Endpoints/variables:

- PGI-S at Week 24.
- PGI-C at Week 24.

To assess the PK and immunogenicity of benralizumab 30 mg Q4W in patients with EoE.

Endpoints/variables:

- Serum benralizumab concentration.

- ADA and nAb.

Study description

Background summary

Eosinophilic esophagitis is a chronic allergic inflammatory disorder of the esophagus, defined histologically by esophageal inflammation of >=15 eosinophils per high power field (eos/hpf). Typical symptoms include dysphagia and food impaction in adolescents and adults.
There is a clinical unmet need for new therapies for use in patients with EoE. Jorveza® (orodispersible budesonide tablet) was approved in the EU for the treatment of EoE in adults in 2018, and there are no approved products for the treatment of EoE in the paediatric population. Additionally, most current treatment approaches are either burdened with compliance problems, and/or limited efficacy, or reserved for the treatment of complications.
Benralizumab is a humanized, afucosylated, monoclonal antibody that binds specifically to the IL-5Rα on the target cell and directly depletes eosinophils through ADCC. The mechanism of action of benralizumab makes it a potential treatment option for the high unmet need in patients with symptomatic and histologically active EoE. Benralizumab has been or is being investigated in patients with asthma, chronic obstructive pulmonary disease (COPD), HES, nasal polyposis, eosinophilic granulomatosis with polyangiitis (EGPA), eosinophilic chronic rhinosinusitis, and eosinophilic gastritis/gastroenteritis. The present study (D3255C00001 [MESSINA]) represents the first clinical study dedicated to the assessment of benralizumab in patients with EoE.

Study objective

The objective of this Phase 3 study is to investigate the safety and efficacy of benralizumab as a treatment for patients with eosinophilic esophagitis.

Study design

This is a randomized, placebo-controlled, DB, parallel-group, multicenter, Phase 3 study to compare the efficacy and safety of repeat dosing of benralizumab versus placebo in male and female patients 12 to 65 years of age with symptomatic and histologically active eosinophilic esophagitis (EoE). Approximately 170 eligible patients with symptomatic and histologically active EoE before randomization will be randomized in a 1:1 ratio to receive either 30 mg of benralizumab or placebo at 4-week intervals for a 24-week treatment period (DB period). The randomization for adults will be stratified by region

(North America vs Rest of World [ROW]) and baseline steroid use. Patients who complete the DB, placebo-controlled treatment period on investigational product (IP) will continue into an OL treatment period with benralizumab 30 mg Q4W until Week 52 (OL period). All compliant patients who complete the 52-week treatment period (the 24-week DB treatment period and the 28-week OL treatment period; DB+OL treatment periods) on IP will be eligible to continue into a 52-week OLE period on benralizumab 30 mg Q4W (OLE). The OLE is intended to allow each patient 1 year of treatment with OL benralizumab after completion of the 52-week DB+OL treatment periods. All eligible patients will be invited to participate in the OLE. Patients who do not enroll in the OLE will have a follow-up visit 12 weeks after their last dose of IP.

Intervention

Eligible patients with symptomatic and histologically active EoE before randomization will be randomized in a 1:1 ratio to receive either 30 mg of benralizumab or placebo at 4-week intervals for a 24-week treatment period (DB period). Patients who complete the DB, placebo-controlled treatment period on investigational product (IP) will continue into an OL treatment period with benralizumab 30 mg Q4W until Week 52 (OL period). All patients considered compliant to the protocol and treatment by the Investigator who complete the 52-week treatment period (the 24-week DB treatment period and the 28-week OL treatment period; DB+OL treatment periods) on IP will be eligible to continue into a 52-week or longer OLE period on benralizumab 30 mg Q4W (OLE).

Study burden and risks

For the double-Blind treatment period the subject is asked to visit the site at least 8 times. The visit time will last 1 - 4 hours.
For the Open-label treatment period the subject is asked to visit the site at least 7 times. The visit time will last 1 - 4 hours.
For the Open-label extension treatment period the subject is asked to visit the site at least 12 times The visit time will last 1 - 4 hours.

The subject will receive the study medication 13 times in 48 weeks. In case the subject participates in the extension, the subject will receive study medication 26 times in 100 weeks. The study medication may cause allergic reactions. A study physician will supervise the administration of the study drug and will observe the subject at the study center for 1- 2 hours after each injection. Additionally, subject may experience side effects of the study medication.

Blood samples will be taken in this study. The total volume of blood that will be collected during the first year of the study is 322 ml. In case the subject continues with the second year of the study there will be an additional 70ml blood samples taken. As an indication, people who donate blood give 500ml of

blood each time.
The subject will undergo physical examinations at every hospital visit.
The subject will undergo endoscopy including biopsy at least 3 times during the study. Endoscopies have risks and they can cause discomforts, but the number of endoscopies is similar as the number of endoscopies in standard practice.
An ECG will be made during 1 visit.
Woman of child bearing potential have to provide a urine sample to test for pregnancy at screening and each time before administration of study medication (13 or 26 times).
The subject will be asked to fill out questionnaires at all hospital visits.
The subject must fill out daily, weekly and monthly questionnaires in an e-Diary. This takes approximately 5 minutes a day.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1) Patients 12 to 65 years of age, inclusive, at the time of signing the informed consent or assent (if applicable) form.
2) Documented previous diagnosis of EoE by endoscopy (documented diagnosis defined as an esophageal count of >=15 eos/hpf on at least 1 esophageal level) and confirmed diagnosis by a centrally-read esophageal biopsy for the purposes of this study (confirmed diagnosis defined as an esophageal count of >=15 eos/hpf at 2 or more esophageal levels). Two to 4 biopsies should be obtained from both the proximal and distal esophagus. Biopsies can be taken from the mid-esophagus for additional evaluation.
3) Must be symptomatic at Visit 1 (screening) and Visit 2 :
(a) A patient reported average of at least 2 days per week with an episode of dysphagia over the 4 weeks prior to the run-in period
AND
(b) At least 2 days with an episode of dysphagia (Daily DSQ >=2) per week between Visit 1 and the Visit 2 (randomization).
4) Must be adherent to daily diary assessments:
(a) Must complete 70% of daily diaries between Visit 1 and Visit 2; AND
(b) Must have completed at least 8 of 14 daily diaries in the 14 days prior to randomization.
5) May be on background medications for EoE and related treatments during the study as long as the background medications have been stable for at least 4 weeks (8 weeks for PPI) prior to screening and there is agreement not to change type of background medication or dosage for the first 52 weeks of the study unless medically indicated. If a medication for EoE (including swallowed steroids, systemic steroids and PPI) is discontinued prior to screening, there should be a washout period of at least 8 weeks.
6) Negative serum pregnancy test for women of childbearing potential at Visit 1.
7) Women of childbearing potential must agree to use a highly effective form of birth control (confirmed by the Investigator) from randomization throughout the study duration and within 12 weeks after last dose of IP.

Exclusion criteria

1) Other GI disorders such as active Helicobacter pylori infection, history of achalasia, esophageal varices, Crohn's disease, ulcerative colitis, inflammatory bowel disease, or celiac disease.
2) Esophageal stricture that prevents the easy passage of a standard endoscope or any critical esophageal stricture that requires dilation during the run-in period.
3) Use of a feeding tube, or not eating solid food daily during the run-in period.
4) Hypereosinophilic syndrome, defined by multiple organ involvement and

persistent blood eosinophil count >1500 eos/µL.
5) EGPA vasculitis.
6) Eosinophilic gastritis, gastroenteritis, enteritis, or colitis documented by biopsy.
7) Current malignancy, or history of malignancy with some specific exceptions.
8) History of anaphylaxis to any biologic therapy or vaccine.
9) Current active liver disease:
*Chronic stable hepatitis B and C (including positive testing for hepatitis B surface antigen [HBsAg] or hepatitis C antibody), or other stable chronic liver disease are acceptable if patient otherwise meets eligibility criteria.
*Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level >=3 times the upper limit of normal (ULN), confirmed by repeated testing during the run-in period.
10) Helminth parasitic infection diagnosed within 24 weeks prior to screening that has not been treated with or has failed to respond to standard of care therapy.
11) History of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test.
12) use of immunosuppressive medication within 8 weeks prior to screening
13) Initiation or change of a food-elimination diet regimen or reintroduction of a previously eliminated food group in the 6 weeks prior to start of the run-in period.
14) Currently pregnant, breastfeeding, or lactating women.
15) Esophageal dilation performed within 8 weeks prior to screening.

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):	23-11-2020
Enrollment:	9
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:	08-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-03-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	24-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2021
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:	25-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-05-2022
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
EudraCT	EUCTR2019-002871-32-NL
ClinicalTrials.gov	NCTvolgt
CCMO	NL71639.056.19