A randomized, placebo-controlled, double-blind trial evaluating the efficacy, tolerability and safety of ESO-101 in adult patients with active eosinophilic esophagitis

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To evaluate the efficacy based on the histological response

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

Summary

ID

NL-OMON52665

Source
ToetsingOnline

Brief title
ACESO

Condition

- Gastrointestinal inflammatory conditions

Synonym
chronic inflammation of the esophagus, eosinophilic esophagitis

Research involving
Human

Sponsors and support

Primary sponsor: EsoCap AG

Source(s) of monetary or material Support: bedrijf

Intervention

Keyword: eosinophilic esophagitis, ESO-101, locoregional oesophagus-adjusted drug, mometasone furoate

Outcome measures

Primary outcome

To evaluate the efficacy based on the histological response:

- absolute change in peak eosinophil count from Baseline to EOT

Secondary outcome

To evaluate the efficacy based on histological response and clinical symptoms:

- Proportion of patients with histological remission, defined as the reduction

of peak eosinophil count in all esophageal samples to

<15 eosinophils/hpf at EOT, overall and determined differentially in each of

the 3 esophageal segments

- Proportion of patients with a peak eosinophil count in all esophageal samples

of <6 eosinophils/hpf at EOT, overall and determined differentially in each of

the 3 esophageal segments

- Proportion of patients with an improvement in the dysphagia severity score

from Baseline to EOT

- Absolute and relative change in mean eosinophil count from Baseline to EOT

- Proportion of patients with a relative reduction in peak eosinophil count of

>=30%, >=50%, or >=75% from Baseline to EOT

- Proportion of patients with histological remission and improvement in the

dysphagia severity score from Baseline to EOT

To evaluate the efficacy based on clinical response assessed by

patient-reported outcome:

- Absolute and relative change in dysphagia and odynophagia severity scores

from Baseline

- Time to achieve symptom relief (defined as 50% improvement in the dysphagia

or odynophagia symptoms on an NRS compared to Baseline)

To evaluate the efficacy based on endoscopic response

- Change in the EREFS1 from Baseline to EOT

To evaluate the safety and tolerability

- Incidence of treatment-emergent AEs and SAEs

- Incidence of AESI

- Local tolerability

To evaluate patient-reported treatment satisfaction

- Patient-reported treatment satisfaction at EOT based on questions about

handling, taste, and time necessary for administration

To evaluate the efficacy based on histological response

- Change in further histological parameters from Baseline to EOT

Study description

Background summary

Eosinophilic esophagitis (EoE) is a chronic, local immune-mediated esophageal disease, characterized by symptoms related to esophageal dysfunction and by eosinophil-predominant inflammation. Infiltration of the esophageal mucosa with eosinophils is the histologic hallmark of EoE. Because the esophagus does not usually harbor eosinophils, their infiltration in the epithelium, where they are found as isolated cells, in groups, or even in small abscesses, is abnormal. The incidence of EoE increases with age and peaks at 30-50 years. In clinical practice, EoE is suspected when a patient presents with symptoms of dysphagia, food impaction, and retrosternal pain or in children with feeding intolerance, abdominal pain, or vomiting. EoE can include various forms of esophageal dysfunction primarily associated with dysphagia. In adults and adolescents, dysphagia affects between 25% and 100% of EoE patients. EoE can be the cause of food impaction, which in rare cases may result in esophageal rupture.

ESO-101 consists of a hard gelatin capsule (Size 0) containing a mucoadhesive thin film loaded with 800 µg mometasone furoate. The film has a length of approximately 25 cm to enable a therapy for the entire length of the esophagus. The film is rolled up in a capsule. The capsule is
slit allowing the end of the rolled film to be threaded through the slit and attached to a retainer outside of the capsule. At the other end, the retainer is attached to the capsule holder. The capsule also contains a sinker to increase the weight of the capsule and thereby avoiding buoyancy of the capsule in the mouth during swallowing. Upon swallowing, the film unrolls and sticks to the mucosa where it dissolves slowly while releasing mometasone furoate. Mometasone furoate, a potent synthetic corticosteroid with anti-inflammatory activity, is a well-known active substance licensed since the early 1990s in various topical formulations (e.g. cream, ointment, lotion or emulsion) for the treatment of patients with inflammatory skin conditions such as psoriasis, eczema, atopic dermatitis, or seborrheic dermatitis. Mometasone furoate is also licensed as a spray for the treatment of symptoms of seasonal allergic or perennial rhinitis and nasal polyps, and as a powder for the treatment of astma. Mometasone furoate has a significantly lower systemic bioavailability (<1%) than older corticosteroids such as the oral agent budesonide. Unlike with other corticosteroids with low bioavailability, no activation by esterases is necessary for mometasone furoate. Hence, mometasone furoate is well-suited as a locoregional treatment.
Up until now, the use of mometasone furoate as a swallowed aerosol formulation has been studied in 3 trials assessing its effect on EoE in adults.
In all 3 trials, patients were treated with 200 µg mometasone furoate aerosol swallowed 4 times daily for 2 months. The results of these trials showed a significant improvement in the dysphagia scale scores and a reduced entry of eosinophils into the esophagus in EoE patients treated with mometasone.
The goal of EoE therapy is to maximize locoregional efficacy by an esophagus-adjusted drug delivery and drug formulation and increasing the

mucosal contact time while reducing systemic bioavailability and thus reducing systemic effects. The mode of delivery and the resulting mucosal contact time play an important role for the effectiveness of EoE therapy. The administration of ESO-101 ensures a targeted drug delivery to the esophagus allowing for a higher efficacy which should lead to histologic improvement directly related to higher mucosal contact time and subsequent clinical improvement of symptoms of EoE.
In contrast, esophageal transit times of tablets and capsules are shorter and depend on the swallowed water volume. Importantly, due to systemic side effects of corticosteroids, including hyperphagia, weight gain, and/or cushingoid features in patients receiving oral prednisone, systemic administration of corticosteroids is no longer recommended in the latest consensus guideline. Due to its efficient and targeted administration of a potent corticosteroid, ESO-101 is administered only once daily, unlike the only EoE treatment currently on the European market that requires twice daily administration (Jorveza®; an orodispersible tablet containing budesonide). The once-daily administration at bedtime also removes one major inconvenience for patients, which is the restriction in eating or drinking. It is also expected that fungal infections of the oral mucosa, one of the most common adverse reactions of Jorveza, can be avoided. A once-daily administration also minimizes the total time each day that steroids are taken, which could have a safety benefit for topical side effects such as oral and esophageal candidiasis, or throat irritation. Only minimal enteral absorption of mometasone furoate and systemic bioavailability is expected, and the portion of mometasone furoate dose that is swallowed and absorbed in the gastrointestinal tract is extensively metabolized primarily in the liver. Further, since mometasone furoate is highly lipophilic and binds strongly to its receptor, systemic side effects are expected to be uncommon.
The aim of this proof-of-concept trial is to investigate the efficacy, safety and tolerability of mometasone furoate administered via the ESO-101 delivery system.

Study objective

To evaluate the efficacy based on the histological response

Study design

This is a randomized, placebo-controlled, double-blind trial to evaluate the efficacy, tolerability, and safety of ESO-101 in adult patients with active eosinophilic esophagitis (EoE).

Patients will be screened at 2 visits (Visit 1 and Visit 2) during which their eligibility will be assessed based on endoscopy-independent criteria (Visit 1) and based on the histologic assessment of esophageal biopsy samples taken during the screening endoscopy (Visit 2).

Eligible patients will be randomized 2:1 to once-daily treatment with ESO-101 or placebo and treated for 28 days starting on Day 0. Further clinic visits will be performed at Day 14 (Visit 4) and Day 28 (Visit 5, end of treatment [EOT]) to assess the efficacy, tolerability, and safety. In addition, a safety follow-up call will be scheduled 2 weeks after the EOT (Day 42, Visit 6).

Intervention

Tested product:
ESO-101 is a unique drug delivery system for the upper gastrointestinal tract, consisting of a capsule holder containing a hard gelatin capsule with a rolled, thin mucoadhesive film, a sinker, and a dissolvable retainer. The capsule holder is screwed onto the lid of a drinking cup to facilitate swallowing while drinking from the cup. Upon swallowing, the film unrolls and sticks to the mucosa where it dissolves while slowly releasing mometasone furoate. In the tested product, ESO-101, the film is loaded with 800 µg mometasone furoate. Dosing: 1 capsule taken once daily in the evening at bedtime for 28 days.

Reference product:
The reference product (placebo) contains a thin adhesive film without active substance. The placebo is administered and dosed like ESO-101.

Study burden and risks

ESO-101 may have side effects. As nobody has been treated with ESO-101 to date, there is not yet any data about possible side effects or symptoms caused by taking ESO-101. The following unwanted side effects have been observed to date during treatment with other approved formulations containing mometasone furoate (nasal spray and powder for inhalation).

These side effects are common (occurs in 1 in 10 people or more):
- Fungal infection (candidiasis)
- Nosebleeds

These side effects occur, but not often (in 1-10% of people):
- Pharyngitis (inflammation in the troat)
- Headache
- Burning sensation in the nose, nose irritation, nasal ulcer
- Upper respiratory tract infection
- Hoarse voice
- Sore throat

The frequency of the following side effects is unknown:
- Blurred vision

- Glaucoma (increased pressure inside the eye)
- Cataract
- Altered smell and taste

ESO-101 may also cause side effects that are unknown.

In addition to the side effects described above, there are other risks that may in general be associated with the use of any medicine: itchy skin, shortness of breath, sensation of heat, nausea, and maybe even vomiting. Symptoms such as these typically suggest an allergic reaction. In rare cases, life-threatening conditions with severe breathing difficulties and circulatory shock may occur, requiring immediate medical intervention. .

The tests that will be performed in this study also include some risks:
- During the swallowing test, it is possible that the patient experiences problems swallowing the test tablet as a result of the disease.
- Collection of the blood samples may cause mild pain caused by the needle prick, and dizziness, local irritation, infection, bleeding or bruising have also been observed. There is also the risk of nerve damage with impaired sensation. In total, 30 mL blood will be collected. This amount should not cause any problems in adults. In comparison: at the blood bank, 500 mL of blood is collected at one time.
- During the imaging of the esophagus with sample collection, the endoscope may trigger the gag reflex of the patient as it is inserted. Hoarseness or problems swallowing may occur occasionally due to irritation of the voice box. More common complaints include flatulence and belching, as well as a feeling of fullness (caused by residual quantities of gas). There is also the risk of damage to the teeth, injury to the mucosa, or perforation (creation of a hole) in the wall of the esophagus, stomach or duodenum.

Possible benefit:
Decrease in dysphagia symptoms
Improvement in quality of life

Contacts

Public
EsoCap AG

Malzgasse 9
Basel 4052
CH
Scientific

EsoCap AG

Malzgasse 9
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CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Adult patients aged 18-70 years;
2. Confirmed clinicopathological diagnosis of EoE;
3. Active and symptomatic EoE, defined as:
a. peak eosinophil count >=15 eosinophils/high-powered field (hpf) at 2 levels of the
esophagus at the screening endoscopy (Visit 2) as measured in a total of 6 hpfs derived from 6 biopsies, 2 each from the proximal, mid, and distal segment of the
esophagus;
b. either a dysphagia or odynophagia severity sore of >=4 on a 11-point numeric rating
scale for >=1 day during the 7 days before Screening (Visit 1);
4. Written informed consent;
5. Willingness and ability to comply with the protocol for the duration of the trial;
6. Negative pregnancy test at Screening (Visit 1) and Day 0 (Visit 3) in women of
childbearing potential (i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include
hysterectomy, bilateral salpingectomy, and bilateral oophorectomy);
7. Women of childbearing potential must be willing to use (for a least 3 monthly cycles

before the screening endoscopy [Visit 2] and until 4 weeks after the last intake of IMP) a
highly effective method of contraception or birth control (failure rate less than 1% per
year when used consistently and correctly). Reliable methods for this trial are:
a. combined (estrogen and progestogen containing) hormonal contraception associated
with inhibition of ovulation (oral, intravaginal, transdermal);
b. progestogen-only hormonal contraception associated with inhibition of ovulation
(oral, injectable, implantable);
c. intrauterine device or intrauterine hormone-releasing system;
d. bilateral tubal occlusion;
e. a vasectomized sexual partner;
f. sexual abstinence (only accepted as true abstinence when this is in line with the
preferred and usual lifestyle of the patient; periodic abstinence [e.g. calendar,
ovulation, symptothermal, post-ovulation methods, and withdrawal] is not an
acceptable method of contraception).

Exclusion criteria

1. Women who are pregnant, lactating, possibly pregnant or planning a pregnancy during
the trial period;
2. Current or past (within the last 3 months) alcohol or drug abuse;
3. Initiation of a diet-modifying food restriction within 4 weeks before the screening
endoscopy (Visit 2) until EOT;
4. Use of systemic corticosteroids or biologic immunomodulators within 3 months before
the screening endoscopy (Visit 2) until the EOT;
5. History of non-response to treatment of EoE with topical corticosteroid drugs (defined as
no improvement of clinical symptoms of EoE after a minimum of 4 weeks corticosteroid
therapy used at appropriate doses according to the investigator*s judgment) or
requirement of cessation of corticosteroid therapy for EoE treatment due to oral
candidiasis or systemic corticosteroid side effects;
6. Use of corticosteroids for treatment of EoE within 4 weeks before the screening
endoscopy (Visit 2) until the EOT;
7. Use of inhalable (pulmonary or nasal) corticosteroids within 4 weeks before the screening

endoscopy (Visit 2) until the EOT;
8. Asthma requiring corticosteroid therapy in the seasonal allergy period according to the
investigator*s judgment based on anamnesis until the EOT;
9. Change in proton pump inhibitor (PPI) dosing regimen within 4 weeks before the
screening endoscopy (Visit 2) until the EOT;
10. Use of systemic leukotriene receptor antagonists, immunosuppressant therapy, or chronic
oral or systemic anticoagulants (such as coumarin derivates, novel oral and subcutaneous
anticoagulants) within 2 weeks before Screening (Visit 1) until the EOT;
11. Unable to swallow a test tablet of about the size of the IMP capsule used in the trial;
12. History of diabetes mellitus;
13. Other severe comorbid condition, concurrent medication, or other issue that renders the
patient unsuitable to participate in the trial in the judgment of the investigator, including
but not limited to: comorbid condition with an estimated life expectancy of <=12 months,
dialysis, severe pulmonary (requiring home oxygen, uncontrolled chronic obstructive
pulmonary disease Gold III/IV) or cardiovascular conditions (heart failure New York
Heart Association III and IV, uncontrolled hypertension systolic blood pressure by
repeated measurement >180mmHg);
14. History of cancer (except non-melanoma skin cancer, or carcinoma in situ of cervix) or
treatment with anticancer therapy (chemotherapy, immunotherapy, radiotherapy,
hormone therapy for cancer treatment, targeted therapy or gene therapy) within
12 months before Screening (Visit 1) until the EOT;
15. Known intolerability or hypersensitivity to mometasone furoate or any of the IMP
excipients (e.g. bovine gelatin, polyvinyl alcohol, polyvinyl acetate,
glycerol, sorbitol);
16. Systemic autoimmune disorders or any condition requiring immunosuppression (e.g.
methotrexate, cyclosporine, interferon alpha, tumor necrosis factor alpha inhibitors,
antibodies to immunoglobulin E) within 3 months before Screening (Visit 1);
17. Mental condition rendering the patient unable to understand the nature, scope, and
possible consequences of the trial or presence of any condition that impacts compliance
with the trial procedures;

18. Use of any investigational or non-registered product (medicinal product or medical
device) within 4 weeks before the screening endoscopy (Visit 2) until the EOT;
19. Employee at the trial center, spouse, partner or child of investigators or sub-investigators
or employee of the sponsor.
20. History of active eosinophilic gastroenteritis and colitis, inflammatory bowel disease, celiac disease, oral or esophageal
mucosal infection of any kind, and esophageal varices;
21. Gastroesophageal reflux disease with Los Angeles Grade B or higher, or erosive
esophagitis Grade 2 or above;
22. Presence of Barrett*s esophagus with a maximum length of >=3 cm with intestinal
metaplasia or dysplasia, peptic stricture, achalasia, significant hiatal hernia >3 cm,
esophageal scleroderma, or diagnosis of Lichen planus;
23. Emergency endoscopy for bolus impaction within 2 weeks before Screening (Visit 1);
24. Any mouth or dental condition that prevents normal eating;
25. History of (dilation within the previous 8 weeks) or current severe endoscopic structural
abnormality in esophagus (e.g. high-grade stenosis where an 8-10 mm endoscope cannot
pass without dilatation at the screening endoscopy [Visit 2]);
26. Diagnosed liver cirrhosis or portal hypertension;
27. History of upper gastrointestinal bleeding within 8 weeks before Screening (Visit 1);
28. Known allergy to β-lactoglobulin (cow milk protein).

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:	Recruiting
Start date (anticipated):	15-11-2021
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ESO-101
Generic name:	mometasone furoate

Ethics review

Approved WMO Date:	03-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	03-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	30-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2020-000082-16-NL
CCMO	NL73856.018.20

Study results

Results posted: 27-05-2024

First publication
30-04-2024