Double-blind, randomized, placebo-controlled, phase III study on the efficacy and tolerability of a 48-week treatment with two different doses of budesonide effervescent tablets vs. placebo for maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis

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Primary:* To assess the efficacy of a 48-week treatment with 2 x 0.5 mg/d or 2 x 1 mg/d budesonide effervescent tablets vs. placebo for the maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis (EoE).Secondary…

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

Summary

ID

NL-OMON47207

Source
ToetsingOnline

Brief title
BUL2

Condition

- Gastrointestinal infections

Synonym
oesophageal inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Dr. Falk Pharma GmbH
Source(s) of monetary or material Support: Dr. Falk Pharma GmbH

Intervention

Keyword: EoE, eosinophilic, oesophagitis, remission

Outcome measures

Primary outcome

* Rate of patients free of treatment failure after 48 weeks of treatment.

Treatment failure after 48 weeks of treatment is *yes*, if at least one of the following criteria is met at any time during the DB treatment phase:

- Clinical relapse, i.e., experiencing dysphagia or pain during swallowing in the past seven days (7-day recall period) of a severity of *4 points on a 0*10 NRS for dysphagia or pain during swallowing, respectively, confirmed by a severity of *4 points on at least 1 day during the subsequent week on the respective 0 10 NRS for dysphagia or pain during swallowing (24-hours recall period).

- Histological relapse, i.e., a peak of *48 eos/mm2 hpf at DB V6/EOT,

- Experiencing a food impaction which needed endoscopic intervention,

- Need for an endoscopic dilation,

- Premature withdrawal for any reason.

Secondary outcome

A priori ordered key secondary endpoints (DB-phase [48 weeks]):

1. Rate of patients with histological relapse, defined as peak of *48 eos/mm2 hpf at week 48 DB,

2. Change in the peak eos/mm2 hpf from DB V1 to week 48 DB,

3. Rate of patients with a clinical relapse, have experienced a food impaction which needed endoscopic intervention, or needed an endoscopic dilation during the DB treatment phase,

4. Rate of patients with a total weekly Eosinophilic Esophagitis Activity Index (EEsAI) * Patient-Reported Outcome (EEsAI-PRO) score of *20 at week 48 DB.

Further exploratory secondary endpoints (DB-phase [48 weeks]):

* Rate of patients with histological remission, defined as a peak of <16 eos/mm2 hpf at week 48 DB,

* Course and change from DB V1 in total modified EEsAI endoscopic instrument score,

* Course and change from DB V1 in the *inflammatory signs* subscore of the modified EEsAI endoscopic instrument score,

* Course and change from DB V1 in the *fibrotic signs* subscore of the modified EEsAI endoscopic instrument score,

* Rate of patients with *none* or only *mild* endoscopic findings (endoscopist*s overall assessment of EoE activity) at week 48 DB,

* Course and change from DB V1 in blood eosinophil counts,

* Course and change from DB V1 in the Physician*s Global Assessment of EoE activity (0-10 NRS),

* Course and change from DB V1 in the dysphagia rating (0 10 NRS, 7-day recall

period) in the week prior to a visit,

* Course and change from DB V1 in the pain during swallowing rating (0 10 NRS, 7-day recall period) in the week prior to a visit,

* Rate of patients with increase of *3 points from DB V1 in the PatGA concerning the severity of EoE symptoms (0-10 NRS) in the course of the DB treatment phase,

* Rate of patients with PatGA concerning the severity of EoE symptoms of *2 points (0 10 NRS) in the course of the DB treatment phase,

* Course and change from DB V1 in the PatGA concerning the severity of EoE symptoms (0-10 NRS),

* Rate of patients with a total weekly EEsAI-PRO score of *20 in the course of the DB treatment phase,

* Rate of patients with deterioration in the total weekly EEsAI-PRO score of >20 points compared to DB V1 for at least 2 consecutive weeks,

* Course and change from DB V1 in the total weekly EEsAI-PRO score and its individual components,

* Course and change from DB V1 in the Adult EoE-QoL questionnaire (EoE-QoL-A),

* Course and change from DB V1 in modified Short Health Scale (modSHS),

* Time in DB-phase,

* Time to relapse (clinical or histological), experiencing a food impaction which needed endoscopic intervention, or need for an endoscopic dilation,

* Time to treatment failure,

* Time to first occurrence of clinical relapse,

* Rate of patients experiencing a food impaction during the DB treatment phase

which needs endoscopic intervention,

* Rate of patients needing endoscopic dilation during the DB treatment phase,

* Patient*s Global Satisfaction at the end of the DB treatment phase,

* Course and change from DB V1 in esophageal distensibility (i.e., minimum esophageal diameter at 40 mmHg distending pressure as measured by Endo FLIP®),

* Course and change from DB V1 of potential biomarkers (e.g., eotaxin-3).

OLE-phase (if applicable and optional up to 96 weeks):

* Course and change from baseline of DB and OLE phase, respectively in blood eosinophil counts,

* Course and change from baseline of DB and OLE phase, respectively in the Physician*s Global Assessment of EoE activity (0-10 NRS),

* Course and change from baseline of DB and OLE phase, respectively in the dysphagia rating (0 10 NRS, 7-day recall period) in the week prior to a visit,

* Course and change from baseline of DB and OLE phase, respectively in the pain during swallowing rating (0-10 NRS, 7-day recall period) in the week prior to a visit,

* Rate of patients with a clinical relapse, experiencing a food impaction which needed endoscopic intervention, or need for an endoscopic dilation during the OLE treatment phase,

* Rate of patients with increase of *3 points from baseline of DB and OLE phase, respectively in the PatGA concerning the severity of EoE symptoms (0-10 NRS) in the course of the OLE treatment phase,

* Rate of patients with PatGA concerning the severity of EoE symptoms of *2 points (0-10 NRS) in the course of the OLE treatment phase,

* Course and change from baseline of DB and OLE phase, respectively in the PatGA concerning the severity of EoE symptoms (0-10 NRS),

* Rate of patients with a total weekly EEsAI-PRO score of *20 in the course of the OLE treatment phase,

* Course and change from baseline of DB and OLE phase, respectively in the total weekly EEsAI-PRO score and its individual components,

* Rate of patients with deterioration in the total weekly EEsAI-PRO score of >20 points compared to baseline of DB and OLE phase, respectively,

* Course and change from baseline of DB and OLE phase, respectively in the adult EoE-QoL-A,

* Course and change from baseline of DB and OLE phase, respectively in the modSHS,

* Time in OLE-phase,

* Time to clinical relapse, experiencing a food impaction which needed endoscopic intervention, or need for an endoscopic dilation,

* Patient*s Global Satisfaction at OLE V4/EOT and OLE V8/EOT resepctively,

* Course and change from baseline of DB and OLE phase, respectively in potential biomarkers,

* Rate of patients with histological relapse, defined as a peak of *48 eos/mm² hpf, at OLE V4/EOT and OLE V8/EOT,

* Change in the peak eos/mm² hpf from baseline of DB phase and (where available) from baseline of OLE phase, respectively to OLE V4/EOT and OLE V8/EOT,

* Rate of patients with histological remission, defined as a peak of <16

eos/mm2 hpf, at OLE V4/EOT and OLE V8/EOT,

* Course and change from baseline of DB phase and (where available) from baseline of OLE phase, respectively in the total modified EEsAI endoscopic instrument score,

* Course and change from baseline of DB phase and (where available) from baseline of OLE phase, respectively in the *inflammatory signs* subscore of the modified EEsAI endoscopic instrument score,

* Course and change from baseline of DB phase and (where available) from baseline of OLE phase, respectively in the *fibrotic signs* subscore of the modified EEsAI endoscopic instrument score,

* Rate of patients with *none* or only *mild* endoscopic findings (endoscopist*s overall assessment of EoE activity) at OLE V4/EOT and OLE V8/EOT.

OLRI-phase:

* Rate of patients with resolution of symptoms (i.e., no or only minimal problems) defined as a severity of *2 points (0-10 NRS, 7-day recall period) for dysphagia AND a severity of *2 points (0-10 NRS, 7-day recall period) for pain during swallowing in the week prior to OLRI V1/EOT (LOCF),

* Rate of patients with no or only minimal problems in dysphagia defined as a severity of *2 points (0-10 NRS, 7-day recall period) for dysphagia in the week prior to OLRI V1/EOT (LOCF),

* Rate of patients with no or only minimal problems in pain during swallowing defined as a severity of *2 points (0-10 NRS, 7-day recall period) for pain during swallowing in the week prior to OLRI V1/EOT (LOCF),

* Rate of patients with total weekly EEsAI-PRO score of *20 points at OLRI V1/EOT (LOCF),

* Rate of patients with clinical response (decrease in the total weekly EEsAI-PRO score of *20 points) at OLRI V1/EOT (LOCF) compared to EOT/withdrawal DB visit,

* Patient*s Global Satisfaction at OLRI V1/EOT (LOCF).

OLI-phase:

* Rate of patients with clinico-pathological remission at OLI V4/EOT (LOCF),

* Rate of patients with histological remission, defined as a peak of <16 eos/mm2 hpf at OLI V4/EOT (LOCF),

* Change in the peak eos/mm2 hpf from OLI V1 to OLI V4/EOT (LOCF),

* Rate of patients with resolution of symptoms (i.e., no or only minimal problems) defined as a severity of *2 points (0-10 NRS, 24-hours recall period) for dysphagia AND a severity of *2 points (0-10 NRS, 24-hours recall period) for pain during swallowing on each day in the week prior to OLI V4/EOT (LOCF),

* Course and change from OLI V1 in the Physician*s Global Assessment of EoE activity (0-10 NRS),

* Rate of patients with PatGA concerning the severity of EoE symptoms of *2 points (0-10 NRS, 7-days recall period) in the course of the OLI phase,

* Course and change from OLI V1 in the PatGA concerning the severity of EoE symptoms (0-10 NRS, 7-days recall period),

* Rate of patients with total weekly EEsAI-PRO score of *20 at OLI V4/EOT (LOCF),

* Course and change from baseline in the total weekly EEsAI-PRO score and its

individual components,

* Course and change from baseline in time to eat a regular meal (last 7 days;

EEsAI Further Item),

* Rate of patients with Patient*s Response Assessment (PRA) of at least: *A

little improved*, *moderately improved*, or *much improved*, respectively (on a

7-point Likert scale) compared to OLI V1 in the course of the OLI-phase,

* Course and change from OLI V1in the adult EoE-QoL-A,

* Course and change from OLI V1 in the modSHS,

* Patient*s Global Satisfaction at OLI V4/EOT (LOCF).

Study description

Background summary

Recent studies suggest that swallowing of budesonide is effective in the treatment of EoE,and can bring the disease in remission, and possibly maintains this for a longer period of time, while it might not be associated with the toxicities of long term use of systemic corticosteroids.

Study objective

Primary:
* To assess the efficacy of a 48-week treatment with 2 x 0.5 mg/d or 2 x 1 mg/d budesonide effervescent tablets vs. placebo for the maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis (EoE).

Secondary:
* To study safety and tolerability in the form of adverse events and laboratory parameters,
* To assess patients* quality of life.

Open-label re-induction and open-label extension phase:
* To study re-induction of clinical response in patients with a clinical or histological relapse or having experienced a food impaction which needed endoscopic intervention,

* To study maintenance of clinical remission in patients who completed the double-blind phase without a clinical or histological relapse.

Exploratory:
* To study biomarkers in EoE.

Study design

This is a double-blind, randomized, multicenter, placebo-controlled, comparative, comfirmatory Phase III clinical trial with a 48-weeks double-bline (DB) treatment period.

Intervention

The trial will be conducted with three treatment groups in the form of a parallel group comparison and will serve to compare oral treatment with either 2 x 0.5 mg/d or 2 x 1 mg/d budesonide effervescent tablets vs. placebo for the maintenance of remission in EoE.

Study burden and risks

physical examination 3-9 x
oesophageal endoscopy 2 x
questionnaires related to complaints and disease: 8 vragenlijsten, per questionnaire variable amount
blood sampling 12-21 x
urine sampling 9 -15 x
examination of the eyes 4-6 x

The adverse events are characteristic for steroid medication, and can occur depending on the dosage, treatment period, whether the subject is or has been taking other corticosteroid preparations, and the individual sensitivity.

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

- Signed informed consent,
- Male or female patients, 18 to 75 years of age,
- Confirmed clinico-pathological diagnosis of EoE according to established diagnostic criteria ,
- Clinico-pathological remission of EoE
- A documented trial with proton pump inhibitors (PPIs) in order to rule out PPI-responsive esophageal eosinophilia,
- Negative pregnancy test in females of childbearing potential at baseline visit

Exclusion criteria

- Clinical signs (i.e., acid regurgitation and/or heart burn) and/or endoscopic signs (at least Los Angeles Classification of Esophagitis Grade A) of gastroesophageal reflux disease (GERD),
- History of abnormal results in case of an optionally performed pH monitoring of the distal esophagus,
- Patients with PPI-responsive esophageal eosinophilia
- Achalasia, scleroderma esophagus, or systemic sclerosis,
- Other clinically evident causes than EoE for esophageal eosinophilia,
- Any concomitant esophageal disease and relevant gastro-intestinal disease (celiac disease, inflammatory bowel disease, oropharyngeal or esophageal bacterial, viral, or fungal infection [candida esophagitis]),
- Any relevant systemic disease (e.g., AIDS, active tuberculosis),
- If careful medical monitoring is not ensured: cardiovascular disease, diabetes mellitus, osteoporosis, active peptic ulcer disease, glaucoma, cataract, or infection,

- Liver cirrhosis or portal hypertension,
- History of cancer in the last five years, except for non-metastatic cancers, e.g. basalioma.
- History of esophageal surgery at any time or of esophageal dilation procedures within the last 8 weeks prior to screening visit,
- Upper gastrointestinal bleeding within 8 weeks prior to screening visit,
- Existing or intended pregnancy or breast-feeding.

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):	07-09-2016
Enrollment:	18
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	02-05-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-08-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-10-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	27-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-08-2020
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2014-001485-99-NL
ClinicalTrials.gov	NCT02493335
CCMO	NL56616.041.16