A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Efficacy and Safety Study of Tezepelumab in Patients with Eosinophilic Esophagitis (CROSSING)

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This study has been transitioned to CTIS with ID 2023-504277-20-00 check the CTIS register for the current data. The aim of this global Phase III study is to investigate the use of tezepelumab as a treatment for patients with EoE. This study will...

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

Summary

ID

NL-OMON53940

Source
ToetsingOnline

Brief title
CROSSING

Condition

- Gastrointestinal inflammatory conditions

Synonym
eosinophilic esophagitis (EoE) / chronic inflammatory disorder of the esophagus

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Eosinophilic Esophagitis, tezepelumab, TSLP inhibitor

Outcome measures

Primary outcome

- To evaluate the effect of tezepelumab on the histologic response in adult and adolescent participants with symptomatic and histologically active EoE

- To evaluate the effect of tezepelumab on symptom improvement in adult and adolescent participants with symptomatic and histologically active EoE

Secondary outcome

Key Secondary

- To evaluate the effect of tezepelumab on the centrally-read EoE EREFS

- To evaluate the effect of tezepelumab on the centrally-read EoE-HSS

- To evaluate the long-term effect of tezepelumab on the histologic response

- To evaluate the long-term effect of tezepelumab on symptom improvement

- To evaluate the long-term effect of tezepelumab on the centrally-read EoE EREFS

- To evaluate the effect of tezepelumab on achievement of clinico-histological remission

see table 7 for all Objectives and Endpoints

Study description

Background summary

Eosinophilic esophagitis (EoE) is a rare, chronic inflammatory disorder triggered by an immune response to foods and aeroantigens and characterizedby a combination of esophageal dysfunction and eosinophilic infiltration of the esophagus. Thymic stromal lymphopoietin (TSLP) is produced in response to pro-inflammatory stimuli and drives allergic inflammatoryresponses, primarily through its activity on type 2 innate lymphoid cells, dendritic and mast cells, which release an abundance of mediators that attract and activate eosinophils as well as molecules that directly promote tissue remodeling including fibrosis. TSLP-driven eosinophilic inflammation is a central finding in EoE. Tezepelumab is a human immunoglobulin G (IgG)2* monoclonal antibody (mAb) that selectively blocks TSLP from interacting with its heterodimeric receptor. By blocking the interaction of TSLP with its heterodimeric receptor and interfering with multiple downstream inflammatory pathways, tezepelumab has the potential to reduce the initiation and persistence of esophageal eosinophilia, inflammation, and fibrosis, which are important factors in the pathogenesis of EoE.

Study objective

This study has been transitioned to CTIS with ID 2023-504277-20-00 check the CTIS register for the current data.

The aim of this global Phase III study is to investigate the use of tezepelumab as a treatment for patients with EoE. This study will evaluate the efficacy and safety of tezepelumab 210 mg every 4 weeks (Q4W) and tezepelumab 420mg Q4W administered subcutaneously (SC) using an accessorized pre-filled syringe (APFS) versus placebo in adult and adolescent participants with EoE. In 2021, tezepelumab was granted Orphan Drug Designation in the US by the FDA for the treatment of EoE

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Study design

Overall Design
This is a Phase III, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the efficacy and safety of repeat dosing of tezepelumab administered SC using an APFS versus placebo in adult and adolescent participants with EoE.

This study will randomize approximately 360 participants1:1:1 to receive either

210 mg tezepelumab, 420 mg tezepelumab, or placebo, administered SC Q4W. Randomization will be stratified by region (Asia vs Rest of World), age category (adults vs adolescents), and baseline swallowed topical corticosteroids (STC) use (yes vs no).

The study consists of a screening/run-in period of 2 to 8 weeks and a 52-week randomized double-blind placebo-controlled treatment period. After completion of the treatment period, participants will be eligible to participate in an active treatment extension period (lasting for a minimum of 24 weeks), followed by a 12-week off-treatment safety follow-up period. Participants who will not participate in the extension period will participate in a 12-week off-treatment safety follow-up period following completion of the 52-week treatment period.

Two interim analyses (IAs) for futility are planned for this study. The first IA will be performed after approximately 15% of study participants (approximately 54 adult participants) have completed Week 24. The second IA will be performed after approximately 40% of study participants (approximately 144 participants) have completed Week 24. The study team will remain blinded to the interim data. A Data Monitoring Committee (DMC) will review the unblinded efficacy and safety data and make recommendation to stop the 210 mg Q4W dose or both doses for futility. If the study is not stopped at the first IA for futility or safety, enrollment of adolescent participants will start following the recommendation of the DMC. Details of the 2 planned IAs are provided in Section 9.4. Further details of the role of the DMC are provided in Section9.5.

Intervention

Following informed consent or assent (if applicable), all participants will enter a screening/run-in period of 2 to 8 weeks. Following this, participants confirmed to be eligible will be randomized 1:1:1 to receive either 210 mg Q4W tezepelumab, 420 mg Q4W tezepelumab, or placebo administered by SC injections for 52 weeks. There will then be a 12-week off-treatment safety follow-up period for participants who do not continue in the active treatment extension period. For these participants, the maximum duration of the study will be 72 weeks in total.

Study burden and risks

During the double-blind treatment period, the subject is asked to visit the hospital at least 15 times. Each visit will last 1-3 hours and if an endoscopy is made 6 hours.
For the extended treatment period, the subject is asked to visit the hospital at least 12 times. Each visit will last 1-4 hours.
The subject will receive study drug 12 times during 52 weeks. If the subject participates in the extension of the study, the subject will receive the study drug 18 times during 78 weeks. The study drug may cause allergic reactions. A

study physician will be present at the time of study drug administration and will observe the subject for 1-2 hours after study drug administration. In addition, the test subject may experience side effects from the study drug.

Blood samples will be taken during the study. The total blood volume that will be collected during the first year is 266 ml.
The subject will have a physical examination during each visit.
The subject will undergo endoscopy including biopsies at least 4 times during the study. Endoscopies carry risks and inconveniences, but the number of endoscopies is equal to the number of endoscopies in standard practice.
An EKG is taken four times.
Women of childbearing potential will be required to provide a urine sample to perform a pregnancy test during the screening visit and each time before study drug administration (17 times).
The subject is asked to complete questionnaires during each hospital visit.
The subject will complete daily, weekly and monthly questionnaires in an electronic diary. This will take about 5 minutes per day.

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. Participant must be 12 to 80 years of age inclusive, at the time of signing the informed
consent/assent.The protocol indicated that subjects between 12 and 80 years old can participate. In the Netherlands it is decided that only subjects between the 18 and 80 can participate.
2. Weight >= 40 kg at Visit 1.
3. Previously established diagnosis of EoE by EGD and esophageal biopsy.
4. Participants who have symptomatic EoE as defined by a history of on average at least 2 episodes of dysphagia (any severity of food going down slowly or being stuck in the throat) per week in the 4 weeks prior to Visit 1.
5. Must have been on stabilized diet for at least 8 weeks prior to Visit 1 and be willing to remain on stabilized diet during the course of the study (stable diet is defined as no initiation of single or multiple elimination diets or reintroduction of previously eliminated food groups).
6 . May be on any background medication for EoE, for example PPI and/or STC, during the course of the study, as long as background medications have been stable for at least 8 weeks prior to the screening/run-in period (Visit 1) and there is agreement not to change background medication or dosage unless medically indicated, during the screening/run-in and treatment period.
7. Participants should have previously documented standard of care treatment, which could include PPI and/or STC and/or diet.
8. Participants currently on leukotriene inhibitors and/or steroid treatments for asthma or allergies that are inhaled or administered intranasally, must report a stable dose for at least 4 weeks prior to the screening/run-in period (Visit 1).
9. Participants with either of the following:
(a) If a medication for EoE (for example PPI and/or STC) is discontinued prior to the screening/run-in, there should be a washout period of at least 8 weeks prior to Visit 1.
(b) Discontinuation of any marketed biologic (monoclonal or polyclonal antibody) should have a washout period of 4 months or 5 half-lives prior to Visit 1, whichever is longer.

Exclusion criteria

1. Other gastrointestinal disorders such as active Helicobacter pylori

infection, history of achalasia, esophageal varices, Crohn's disease, ulcerative colitis, inflammatory bowel disease, celiac disease, EGE, EG, eosinophilic enteritis,colitis, diverticulitis, irritable bowel syndrome, or other clinically significant gastrointestinal conditions as per investigator discretion.
2. Eosinophilic granulomatosis with polyangiitis vasculitis.
3. Esophageal stricture that prevents the easy passage of a standard endoscope or any critical esophageal stricture that requires dilation at screening.
4. Use of a feeding tube, or having a pattern of not eating solid food >= 3 days of the week.
Solid food is defined as food that requires chewing before swallowing.
5. Hypereosinophilic syndrome
6. Esophageal dilation performed within 8 weeks prior to screening.

see section 5.2 of the protocol for a complete overview of all exclusion criteria.

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):	20-04-2023
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Tezpire
Generic name:	Tezepelumab

Ethics review

Approved WMO Date:	24-10-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-07-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2023
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
Other	IND 156401
EU-CTR	CTIS2023-504277-20-00
EudraCT	EUCTR2022-001294-31-NL
CCMO	NL82040.018.22