A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of AK002 in Adult and Adolescent Subjects with Active Eosinophilic Esophagitis

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To evaluate the efficacy of AK002 in adult and adolescent subjects with active EoE when compared to placebo, efficacy endpoints will be co-primary:1) The proportion of subjects who achieve a peak esophageal intraepithelial count of

Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal signs and symptoms
Study type	Interventional

Summary

ID

NL-OMON55008

Source
ToetsingOnline

Brief title
AK002 in EoE

Condition

- Gastrointestinal signs and symptoms

Synonym
active Eosinophilic Esophagitis (EoE)

Research involving
Human

Sponsors and support

Primary sponsor: Allakos Inc.
Source(s) of monetary or material Support: The Sponsor: Allakos Inc.

Intervention

Keyword: Active Eosinophilic Esophagitis (EoE), AK002, immunoglobulin G1 (IgG1) antibody, Siglec-8

Outcome measures

Primary outcome

Co-Primary Efficacy Endpoints

1) The proportion of patients who achieve a peak esophageal intraepithelial

count of <=6 eosinophils/hpf at Week 24.

2) Mean change in DSQ score from Baseline to Weeks 23-24.

Secondary outcome

Secondary Efficacy Endpoints

To further evaluate the efficacy of AK002 in adult and adolescent subjects with

active EoE when compared to placebo as measured by:

• Percent change in peak esophageal intraepithelial eosinophil count at Week 24.

• Proportion of subjects achieving peak esophageal intraepithelial eosinophil

count of <=1 eosinophil/hpf at Week 24.

• Proportion of subjects achieving peak esophageal intraepithelial eosinophil

count of <= 15 eosinophil/hpf at Week 24.

• Proportion of treatment responders where a responder is a subject achieving

> 30% reduction in symptoms (DSQ) at Weeks 23-24 and achieving a peak

esophageal intraepithelial count of <=6 eosinophils/hpf at Week 24.

• Proportion of subjects with 50% reduction in DSQ score from Baseline to

Weeks 23-24.

• Percent change in DSQ score from Baseline to Weeks 23-24.

• Change in biweekly mean DSQ over time.

• Change in EoE Endoscopic Reference Score (EREFS) from Baseline to at Week 24.

Exploratory Endpoints

• Change in EoE Histology Scoring System (EoEHSS) score from Baseline to Week 24.

• Change in health-related quality of life as measured by SF-36 from Baseline to Week 24.

• Change in mast cell counts from Baseline to Week 24.

Safety Endpoints

The safety and tolerability of AK002 will be assessed by determining the following:

• Physical examination

• Changes in vital signs

• Hematology

• Changes in concomitant medication use due to adverse events

• Blood chemistry

• Urinalysis

• ADA

• Adverse events.

Study description

Background summary

See paragraph 2 and 3 of protocol (version 7 May 2020)

Study objective

To evaluate the efficacy of AK002 in adult and adolescent subjects with active EoE when compared to placebo, efficacy endpoints will be co-primary:
1) The proportion of subjects who achieve a peak esophageal intraepithelial count of <=6 eosinophils/hpf at Week 24.
2) Mean change in Dysphagia Symptom Questionnaire (DSQ) score from Baseline to Weeks 23-24.

The secondary objectives are:
• Percent change in peak esophageal intraepithelial eosinophil count at Week 24.
• Proportion of subjects achieving peak esophageal intraepithelial eosinophil count of <= 1 eosinophil/hpf at Week 24.
• Proportion of subject achieving peak esophageal intraepithelial eosinophil count of < 15 eosinophil/hpf at Week 24.
• Proportion of treatment responders where a responder is a subject achieving > 30% reduction in symptoms (DSQ) at Weeks 23-24 and achieving a peak esophageal intraepithelial count of <=6 eosinophils/hpf at Week 24.
• Proportion of subjects with >50% reduction in DSQ score from Baseline to Weeks 23-24.
• Percent change in DSQ score from Baseline to Weeks 23-24.
• Change in biweekly mean DSQ over time.
• Change in EoE Reference Score for Endoscopic Abnormalities (EREFS) from baseline to week 24.

The exploratory objectives are:
• Change in EoE Histology Scoring System score from Baseline to Week 24.
• Change in health-related quality of life as measured by SF-36 Health and Well-Being Survey from Baseline to Week 24.
• Change in mast cell counts from Baseline to Week 24.

To evaluate the safety and tolerability of AK002 in adult and adolescent subjects with active EoE.

Study design

This is a randomized, double-blind, placebo-controlled phase 2/3 study in 1 hospital in the Netherlands and several centers in the United States.

After screening, 300 eligible participants are randomized 1: 1: 1 to be treated 6 times every 4 weeks with a low dose of AK002, a high dose of AK002 or placebo.

Subjects will be stratified at randomization based on
- age (12-17 and >=18 years) and
- baseline DSQ score (<=30 and >30).

An evaluation will take place after the treatments.

There is the possibility of a follow-up participation in an open-label study with the AK002 low or high dose 6 times every 4 weeks.

The participants will come back twice more for a Follow-up visit.

Intervention

One group will be treated with the low dose regimen: 1 mg/kg AK002 administered every 4 weeks for 6 doses.

One group will be treated with the high dose regimen: 1 mg/kg AK002 for the first dose followed by 3 mg/kg AK002 administered every 4 weeks for 5 subsequent doses.

One group will be traeated with the placebo regimen administered every 4 weeks for 6 doses

The randomization is 1:1:1.

After the controlled randomized double blind part of the study, there is the possibility to participate in the open- label part of the study: 6 infusion doses every 4 weeks with a first infusion dose of 1 mg/kg followed by 5 infusion doses of 1 mg/kg or 3 mg/kg.

Study burden and risks

See paragraph 7 (page 83-84) of the IB version November 2019

The patient will be burdened with 13-19 visits to the hospital. Also 260 to 404 ml of blood is taken, and they perform a EGD with biopsy twice, the patient collects faces once and they have to complete a questionnaire daily.
There seems a small risk for serious adverse events.

The patient could benefit from the medication or new EoE patients could benefit from the results of this study.

The participating patients may be eligible for an open-label treatment after

treatment with 6 infusions.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1) Male or female aged >=12 and <=80 years at the time of signing ICF.
2) Confirmed diagnosis of EoE and intraepithelial eosinophilic infiltration of >=15 eosinophils/hpf in 1 hpf from the biopsy collected during the Screening EGD without any other cause for the esophageal eosinophilia.
3) Baseline DSQ (biweekly mean DSQ) score of >=12 from the last 2 weeks of Screening (the 14 days prior to the first dose). per the validated Algorithm in Appendix 11.
4) History (by subjject report) of an average of >=2 episodes of dysphagia with intake of solid foods per week during the 4 weeks prior to Screening.
5) Subjects must have failed or not be adequately controlled on standard of

care treatments for EoE symptoms, which could include PPI, systemic or topical corticosteroids, and/or diet, among others.
6) If on an allowed treatment for EoE (per Section 8), stable dose for at least 4 weeks prior to Screening and willingness to continue that dose for the study duration.
7) If subject is on pre-existing dietary restrictions, willingness to maintain dietary restrictions throughout the study, as much as possible.
8) Able and willing to comply with all study procedures.
9) Female subjects must be either post-menopausal for at least 1 year with FSH level >30 mIU/mL at Screening or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative pregnancy test and either agree to use dual methods of contraception, have a
partner who had a vasectomy, or agree to abstain from sexual activity from screening until the end of the study, or for 120 days following the last dose of study drug, whichever is longer.
Non-vasectomized male subjects with female partners of childbearing potential must agree to either abstain from sexual activity or agree to a highly effective method of contraception from Screening until the end of the study or for 120 days following the last dose of study drug, whichever is longer. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant at any time during study participation.

Exclusion criteria

1) Concomitant moderately or severely symptomatic EG and/or (with or without EoD*,) defined as
• >=30 eosinophils/hpf in 5 hpf in the stomach (EG) and/or >=30 eosinophils/hpf in 3 hpf in the duodenum (EoD) without any other cause for eosinophilia as determined by central histology assessment of biopsies collected during the Screening EGD

and
• an EG/EoD PRO Questionnaire weekly average single symptom score of >=3 during the last 2 weeks of Screening for 1 of the following symptoms: abdominal pain, nausea, and/or diarrhea.

* This exclusion criterion is only applicable to sites actively enrolling patients in the AK002-016 study. If a site is not actively screening and enrolling subjects in the AK002-016 study, then this exclusion criterion is not applicable.

2) Causes of esophageal eosinophilia other than EoE or one the following: hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, or

peripheral blood absolute eosinophil count of >1500 eosinophils/µL.
3) History of inflammatory bowel disease, celiac disease, achalasia, and/or esophageal surgery.
4) Any esophageal stricture unable to be passed with a standard diagnostic 9 mm to 10 mm upper endoscope or any critiacal esophageal stricture that requires dilatation during screening.
5) History of bleeding disorders or esophageal varices.
6) History of malignancy; except carcinoma in situ, early stage prostate cancer, or non-melanoma skin cancers. However, cancers that have been in remission for more than 5 years and are considered cured, can be enrolled (with the exception of breast cancer). All history of malignancy (including diagnosis, dates, and compliance with cancer screening recommendations) must be documented and certified by the Investigator, along with the statement that in their clinical judgment the tissue eosinophilia is attributable to EGID, rather than recurrence of malignancy.
7) Active Heliobacter pylori infection as determined by central histology staining of the biopsy collected during the Screening EGD, unless treated and confirmed to be negtive prior to randomization and symptoms remain consistent.
8) Positive Ova and Parasite (O&P) test at Screening, seropositive for Strongyloides stercoralis at Screening, and/or treatment for a clinically significant helminthic parasitic infection within 6 months of Screening.
9) Seropositive for HIV or hepatitis at Screening, except for vaccinated subjects or subjects with a history of hepatitis that has since resolved.
10) Prior exposure to AK002 or hypersensitivity to any constituent of AK002.
11) Change in dose of inhaled corticosteroids, nasal corticosteroids, PPI, and/or diet therapy within 4 weeks prior to Screening.
12) Use of oral corticosteroids (swallowed topical or systemic corticosteroids) within 8 weeks prior to Screening.
Exclusion Criteria cont.
13) Use of any biologics or medications that may interfere with the study, such as immunosuppressive or immunomodulatory drugs including azathioprine, JAK inhibitors, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, anti-TNF, anti-IL-4 receptor, e.g., dupilumab), anti-IL-5 (e.g., mepolizumab), anti-IL-5 receptor (e.g., benralizumab), anti-IL-13 (e.g., lebrikizumab), anti-IgE (e.g., omalizumab), within 12 weeks prior to Screening.
14) Participation in a concurrent interventional study with the last intervention occurring within 30 days prior to administration of study drug or 90 days or 5 half-lives, whichever is longer, for biologic products.
15) Vaccination with live attenuated vaccines <=30 days prior to initiation of treatment in the study, during the treatment period, or vaccination expected <=5 half-lives (<=4 months) following study drug administration. (with the exception of a COVID-19 vaccine authorized by the FDA or other applicable regulatory agency).

16) Treatment with chemotherapy or radiotherapy in the preceding 6 months.
17) Presence of abnormal laboratory values considered by the Investigator to be clinically significant.

18) Any disease, condition (medical or surgical), or cardiac abnormality, which in the opinion of the Investigator, would place the subject at increased risk.
19) Known history of alcohol, drug, or other substance abuse or dependence.
20) Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study.
21) Any other reason that in the opinion of the Investigator or Medical Monitor makes the subject unsuitable for enrolment.

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:	Completed
Start date (anticipated):	18-03-2021
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	AK002

Ethics review

Approved WMO

Date:	13-05-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-07-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2020
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:	15-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2022
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	EUCTR2019-004391-19-NL
ClinicalTrials.gov	NCT04322708
CCMO	NL73100.018.20

Study results

Date completed: 01-06-2022

Results posted: 05-02-2024

First publication
18-12-2023