High Discovery Rate of Previously Undiagnosed Patients with Eosinophilic Gastritis and Duodenitis Using a Systematic Endoscopic Biopsy Protocol: Screening Data Analysis from ENIGMA, a Randomized Controlled Trial

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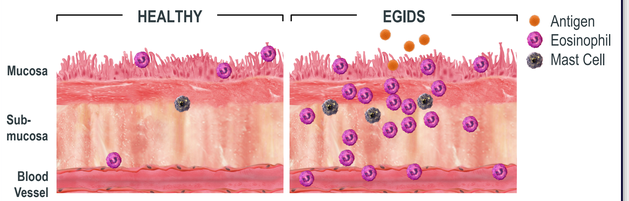
BACKGROUND

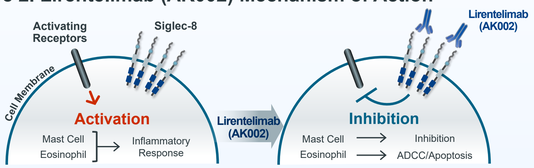
- Pathologic accumulation and over-activation of eosinophils and mast cells are implicated in multiple chronic inflammatory diseases in the gastrointestinal (GI) tract including eosinophilic esophagitis (EoE), gastritis (EG), duodenitis (EoD), and colitis - collectively termed eosinophilic gastrointestinal diseases (EGIDs)[1,2]
- Patients with EGIDs have decreased quality of life due to chronic debilitating and often nonspecific symptoms such as dysphagia, abdominal pain, bloating, nausea, vomiting, & diarrhea

Figure 1. Pathogenesis of EGIDs



- EG and EoD is thought to affect 45,000 - 50,000 patients in the US, though this number may be significantly underestimated and new evidence suggests it may be as common as inflammatory bowel disease (IBD)[3,4]
- Current treatment options such as diet restriction and corticosteroids have limited efficacy and/or are inappropriate for chronic use
- There is a significant unmet need for novel therapies

Figure 2. Lirentelimab (AK002) Mechanism of Action



- Siglec-8 is an inhibitory receptor selectively expressed on mature human eosinophils and mast cells, and is a novel target for the treatment of EGIDs
- AK002 is a humanized, non-fucosylated IgG1 monoclonal Siglec-8 antibody
- Engagement of Siglec-8 receptor by AK002 triggers:
  - Antibody dependent cell mediated cytotoxicity (ADCC, blood) and apoptosis (tissue) of eosinophils
  - Inhibition of mature mast cells in tissue
- Results from a phase 2 study of AK002 in patients with EG/EoD has been previously presented; 13/65 (20%) enrolled patients did not have a previous diagnosis of EG/EoD[5]
- A subgroup analysis was conducted to characterize these newly diagnosed EG/EoD patients and to compare to those with an established diagnosis

OBJECTIVES

- To evaluate the discovery rate of EG/EoD among previously undiagnosed patients with chronic non-specific GI symptoms who enrolled in ENIGMA
- To compare treatment response of AK002 in patients with newly established diagnosis of EG/EoD and patients with a previous diagnosis of EG/EoD

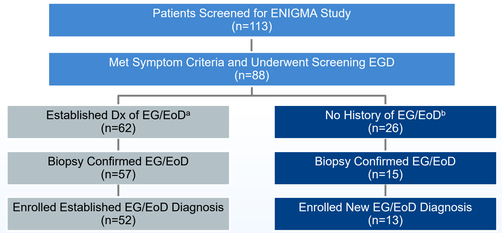
METHODS

- ENIGMA was a phase 2 multi-center, randomized, double-blind, placebo-controlled study of 4 monthly doses of AK002 in 65 EG and/or EoD patients
  - Patients were eligible for the study if they had
    - Active moderate-to-severe symptoms[a] per a daily EG/EoD Symptom Questionnaire©, which assessed 8 symptoms, each on a scale of 0-10; Total Symptom Score (TSS) 0-80
    - Confirmed EG/EoD, based on 8 biopsies from the stomach (≥30 eos/hpf in 5 hpfs) and/or 4 from the duodenum (≥30 eos/hpf in 3 hpfs)
  - Patients were randomized 1:1:1 to groups that received placebo, a low-dose AK002 regimen (first dose 0.3 mg/kg, last 3 doses 1.0 mg/kg), or a high-dose AK002 regimen (0.3 mg/kg, 1.0 mg/kg, and last 2 doses 3.0 mg/kg)
- 58 of 59 eligible patients who completed the ENIGMA study chose to enter the open-label extension (OLE) and receive AK002
  - As many as 26 monthly AK002 infusions every 28 days, titrated to 3.0 mg/kg
  - Upper endoscopy with biopsy collection on Day 323 after entering ENIGMA
  - Symptoms assessed with the daily patient-reported EG/EoD-SQ© Questionnaire
- A subgroup analysis was performed on patients with a newly or previously established diagnosis of EG/EoD to compare baseline characteristics, medical history, and response to treatment as measured by the TSS

a PRO entry criteria: average weekly score over ≥2 weeks of ≥3 for either abdominal pain, diarrhea and/or nausea

RESULTS

Figure 3. ENIGMA Screening Data Point to Significant Undiagnosed EG/EoD Population



- 113 patients entered screening, 88 met moderate-to-severe symptom criteria and underwent screening endoscopy with biopsy, 72 met histologic criteria for EG/EoD, and 65 were randomized to AK002 (low-dose n=22, high-dose n=21) or placebo (n=22)
- 51 patients entered screening without an established diagnosis of EG/EoD; 29% (n=15) were diagnosed with moderate-severe EG/EoD

a Consortium of Eosinophilic Gastrointestinal disease Researchers (CEGIR) sites; n=62 entered screening
b General gastrointestinal practices and professional GI research centers; n=51 entered screening

Table 1. Baseline Characteristics by History of EG/EoD Diagnosis

EG/EoD Patients (N=72)		New Diagnosis (n=15)	Established (n=57)
Age (years), Mean (Range)		48 (20-74)	40 (18-68)
Female		67% (10)	58% (33)
White		93% (14)	91% (52)
Immunoglobulin E (IU/mL), Mean (Range)		127 (10-898)	665 (10-7240)
Absolute Eosinophil Count /µL	Mean (Range)	133 (30-340)	791 (40-4900)
	% (n) with < 250	87% (13)	25% (14)
	% (n) with ≥ 250	13% (2)	75% (43)
Gastrointestinal Eosinophils/hpf, Mean (Range)		54 (36-117)	92 (33-300)
Gastrointestinal Mast Cells/hpf, Mean (Range)		51 (35-84)	67 (20-139)
Total Symptom Score (TSS) [0-80], Mean		31.7	31.3
History of	EoE	27% (4)	61% (35)
	Asthma	40% (6)	39% (22)
	Atopic Dermatitis	20% (3)	18% (10)

Table 2. Medical History of GI Diagnoses or Symptoms

Number (%) of subjects with	Met Symptom Criteria n=88	Met EG/EoD Histologic Criteria n=72	Established Diagnosis n=57	New Diagnosis n=15
Functional abdominal pain	7 (8%)	7 (10%)	7 (12%)	0 (0%)
Functional constipation	10 (11%)	8 (11%)	5 (9%)	3 (20%)
Functional diarrhea	20 (23%)	18 (25%)	11 (19%)	7 (47%)
Irritable bowel syndrome (IBS)	3 (3%)	3 (4%)	2 (4%)	1 (7%)
Gastroesophageal/acid reflux (GER/GERD)	26 (30%)	24 (33%)	16 (28%)	8 (53%)
Peptic ulcer	9 (10%)	9 (13%)	8 (14%)	1 (7%)
Chronic gastritis/duodenitis	6 (7%)	4 (6%)	0 (0%)	4 (27%)
One or more of the above	48 (55%)	43 (60%)	30 (53%)	13 (87%)

Figure 4. Patients With a New Diagnosis of EG/EoD Have Similar Symptom Intensity as Patients With a Previous Diagnosis

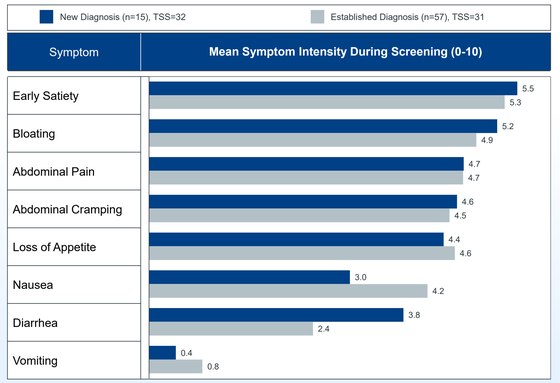
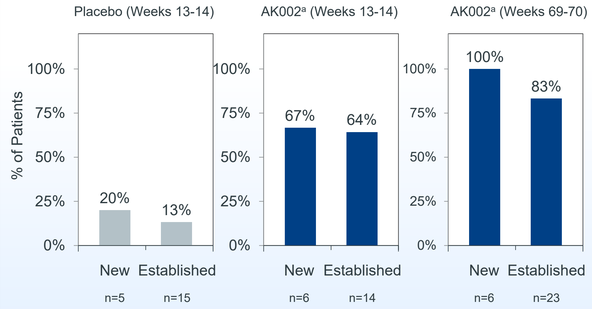


Figure 5. Newly Diagnosed EG/EoD Patients Responded Similarly to AK002 As Those With Established EG/EoD



a AK002 High dose regimen

Safety Summary

- Generally well tolerated
- Most common adverse event was infusion-related reaction (IRR)
  - Most are mild to moderate (flushing, feeling of warmth, headache, nausea, dizziness)
  - Mostly on first infusion, greatly reduced or does not occur on subsequent infusions
  - No IRRs in 20 patients who received single-dose oral prednisone night before first infusion in OLE
  - 1 drug-related serious adverse event in ENIGMA, an IRR which recovered within 24 hours with no further sequelae
- No drug-related serious adverse events in OLE
- No other significant adverse events

CONCLUSIONS/DISCUSSION

- 15 of 51 (29%) of patients entering ENIGMA without an established diagnosis of EG/EoD were diagnosed with moderate-severe EG/EoD
- Most of the newly diagnosed EG/EoD patients had a previous history of GER/GERD, peptic ulcer disease, or a functional GI disorder
- Newly diagnosed patients had a similar symptom response to AK002 in ENIGMA as patients with an established diagnosis of EG/EoD
- Long-term treatment of AK002 in OLE led to further improvement in symptoms and was generally well-tolerated
- These data suggest that EG/EoD may be more common than previously reported, and that EG/EoD should be considered in patients with chronic, moderate to severe GI symptoms
- Upper endoscopy with multiple gastric and duodenal biopsies may be indicated for patients with chronic nonspecific GI symptoms

Presented at the American Partnership For Eosinophilic Disorders (APFED), July 14th – 16th, 2021

Acknowledgements: We thank the patients who participated in this study, investigators, and study staff. This study was funded by Allakos, Inc. and in part by Division of Intramural Research, NIAID, NIH

Reference: (1) Caldwell JM, et al. J Allergy Clin Immunol. 2014.; (2) Youngblood BA, et al. Gastroenterology. 2019.; (3) Jensen ET, et al. J Pediatr Gastroenterol Nutr. 2016.; (4) Licari AL, et al. JACI. 2020.; (5) Dellon ES, et al. ACG. 2019.