Long-Term Treatment With Lirentelimab, a Monoclonal Antibody Against Siglec-8, in Patients With Eosinophilic Gastritis and/or Duodenitis

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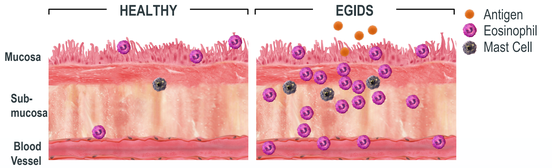
BACKGROUND

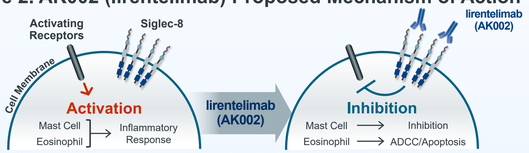
- Pathologic accumulation and over-activation of eosinophils and mast cells are implicated in multiple chronic inflammatory diseases in the gastrointestinal (GI) tract, including eosinophilic esophagitis (EoE), gastritis (EG), duodenitis (EoD), and colitis—collectively termed eosinophilic gastrointestinal 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, and diarrhea[3]

Figure 1. Pathogenesis of EGIDs



- EG and EoD are thought to affect 45,000–50,000 patients in the US, although this number might be underestimated; there is evidence that EG and EoD are as common as inflammatory bowel diseases (IBD)[4,5]
- Current treatment options, such as diet restriction and corticosteroids, have limited efficacy and/or are inappropriate for chronic use
- There is an unmet need for novel therapies

Figure 2. AK002 (lirentelimab) Proposed Mechanism of Action



- Siglec-8 is an inhibitory receptor selectively expressed on mature human eosinophils and mast cells and is a therapeutic target for EGIDs
- Lirentelimab (AK002), an investigational medicine, is a humanized, non-fucosylated IgG1 monoclonal antibody against Siglec-8*
- Engagement of Siglec-8 receptor by lirentelimab induces:
  - Antibody-dependent cell-mediated cytotoxicity (ADCC, of blood eosinophils) and apoptosis (of tissue eosinophils)
  - Inhibition of mature mast cells in tissues
- Results from a phase 2 study of lirentelimab (ENIGMA) in patients with EG and/or EoD (EG/EoD) have been published[6]; 58 of 59 patients who completed ENIGMA chose to enter the open-label extension (OLE) and receive lirentelimab
- We present interim results (as of 7/72021) from this OLE study

- ENIGMA was a phase 2, multi-center, randomized, double-blind, placebo-controlled study in 65 patients with EG/EoD that included patients with:
  - Active moderate–severe symptoms[a] in the daily 8-symptom EG/EoD-SQ© Questionnaire (the patient-reported outcome [PRO] questionnaire)
  - Biopsy confirmed EG/EoD
    - Stomach: ≥30 eos/hpf in 5 hpfs
    - Duodenum: ≥30 eos/hpf in 3 hpfs
- Lirentelimab met the primary and secondary endpoints and was generally well tolerated[5]

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

OBJECTIVE

- To determine the safety and efficacy of long-term lirentelimab in patients with EG/EoD

METHODS

- Patients who completed ENIGMA had the option to receive lirentelimab in the OLE
- Patients enrolled in the OLE received up to 26 monthly infusions of AK002, administered intravenously every 28 days, titrated up to 3.0 mg/kg
- Patients underwent an upper endoscopy with biopsy on day 323 (week 46) and day 659 (week 94) after entering ENIGMA
- Symptoms assessed with daily PRO questionnaire (0 –10 scale)

RESULTS

Table 1. Baseline Characteristics

Patient Characteristics		OLE Patients (n=58)
Age, Mean (Range)		41 (18–74)
Female		60%
White		93%
GI[a] Eosinophils/hpf, Mean (Range)		74 (33–201)
GI[a] Mast Cells/hpf, Mean (Range)		60 (20–114)
Total Symptom Score [0-80], Mean (Range)		32 (6–61)
% of Patients (n) by blood AEC[b]/μL	<500	69% (40)
	≥500	31% (18)

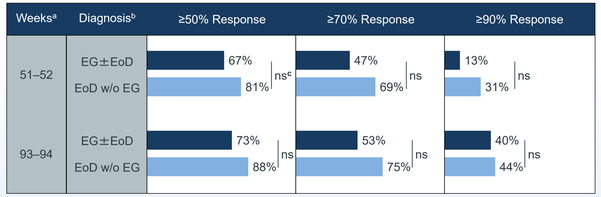
a Gastrointestinal; gastric (5 hpfs) or duodenum (3 hpfs) site with highest eosinophil or mast cell counts
b AEC, absolute eosinophil count

Table 2. Continued Symptom Reduction Through 94 Weeks

Lirentelimab Exposure (Weeks)[a]	Diagnosis	Baseline[b] TSS	Change in TSS	Percent change in TSS
51–52 (n=31)	EG±EoD (n=15)	35	–20	–61%
	EoD without EG (n=16)	34	–26	–73%
	P value[c]	0.8705	0.1567	0.2500
93–94 (n=31)	EG±EoD (n=15)	35	–23	–70%
	EoD without EG (n=16)	34	–28	–80%
	P value	0.8705	0.1763	0.2512

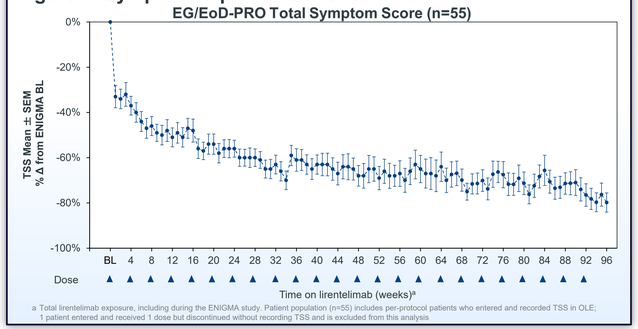
a Total AK002 exposure, including exposure during the ENIGMA study
b Baseline refers to ENIGMA (if randomized to treatment arm) or OLE (if randomized to placebo in ENIGMA)
c Unpaired 2-tailed *t* test

Figure 3. Proportions of Patients With TSS Improvements



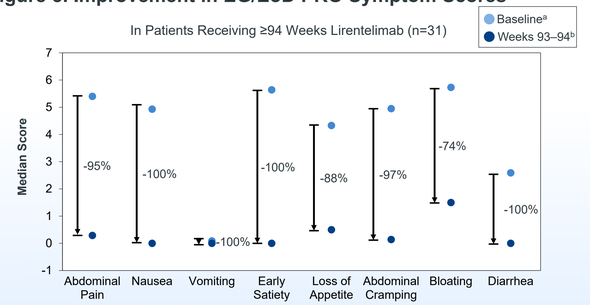
a Total lirentelimab exposure, including during the ENIGMA study
b EG ± EoD n=14, baseline TSS=36; EoD without EG n=16, baseline TSS=34
c Fisher's exact test; ns = not significant

Figure 4. Symptom Improvement Over Time



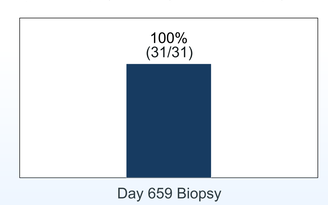
a Total lirentelimab exposure, including during the ENIGMA study. Patient population (n=55) includes per-protocol patients who entered and recorded TSS in OLE; 1 patient entered and received 1 dose but discontinued without recording TSS and is excluded from this analysis

Figure 5. Improvement in EG/EoD PRO Symptom Scores



a Baseline refers to ENIGMA (if randomized to treatment arm) or OLE (if randomized to placebo in ENIGMA)
b Total lirentelimab exposure, including during the ENIGMA study

Figure 6. Proportion of Patients Meeting Histologic Remission Criteria[a]



- Lirentelimab produced sustained depletion of tissue eosinophils; 45/48 (94%) patients at day 323 and 31/31 (100%) at day 659 were in histologic remission[b]

a Histologic remission was defined as eosinophils ≤4/hpf (stomach) and/or ≤15/hpf (duodenum)
b By day 659, 29 patients were no longer in treatment in the OLE (8 patients completed the study and 21 patients discontinued for reasons not related to study drug)

Table 3. OLE Safety Summary

Treatment-emergent Adverse Events in >5% of Patients

% of Patients, (n)	Total (n=58)
Infusion-related reaction	34% (20)
Nasopharyngitis	17% (10)
Headache	16% (9)
Nausea	12% (7)
Rash	10% (6)
Influenza	10% (6)
Diarrhea	10% (6)
Anxiety	10% (6)
Blood creatine phosphokinase increased	10% (6)
Sinusitis	9% (5)
Fatigue	9% (5)
Vomiting	9% (5)
Anemia	9% (5)
Urinary tract infection	9% (5)
Abdominal pain	7% (4)
Neutrophilia	7% (4)
Hypertension	7% (4)
Oropharyngeal pain	7% (4)
Chest pain	7% (4)

a Symptoms included flushing, feeling of warmth, headache, nausea, and/or dizziness

- Lirentelimab was generally well tolerated
- Most common adverse event was mild to moderate infusion-related reaction[a]; mostly occurred on first infusion, greatly reduced or did not occur on subsequent infusions
- No drug-related serious adverse events in the OLE as of 7/7/2021

CONCLUSIONS/DISCUSSION

- Long-term treatment with lirentelimab resulted in histologic & symptomatic improvements in patients with EG and/or EoD through week 94
  - Symptomatic responses improved with increased duration of treatment
- Response was similar across patients with EG and/or EoD
- Long-term lirentelimab was generally well tolerated; OLE results help characterize its safety profile in the studied patient populations
- Additional studies of lirentelimab are ongoing:
  - Phase 3 randomized trial in patients with EG/EoD (NCT04322604)
  - Phase 2/3 randomized trial in patients with EoE (NCT04322708)

Reference: (1) Caldwell JM, et al. J Allergy Clin Immunol. 2014; (2) Youngblood BA, et al. Gastroenterology. 2019; (3) Chehade M, et al. JACI in Practice 2020; (4) Jensen ET, et al. J Pediatr Gastroenterol Nutr. 2016; (5) Licari AL, et al. JACI. 2020; (6) Dellon ES, et al. NEJM. 2020. *Lirentelimab is an investigational medicine, its efficacy and safety profile have not been established, and it has not been approved by the FDA

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