Lirentelimab (AK002), an Anti-Siglec-8 Antibody, Depletes Tissue Eosinophils and Improves Dysphagia Symptoms in Patients with Eosinophilic Esophagitis (ENIGMA Study; NCT03496571)

Ikuo Hirano[1], Kathryn A. Peterson[2], Joseph A. Murray[3], Evan S. Dellon[4], Gary W. Falk[5], Nirmala Gonsalves[1], Mirna Chehade[6], John Leung[7], Robert M. Genta[8], Paneez Khoury[9], Adam C. Bledsoe[3], Camilla Shaw[10], Bhupinder Singh[10], Alan T. Chang[10], Amol P. Kamboj[10], Henrik S. Rasmussen[10], Marc E. Rothenberg[11]

[1]Northwestern University, Chicago, IL; [2]University of Utah, Salt Lake City, UT; [3]Mayo Clinic Rochester, Rochester, MN; [4]University of North Carolina, Chapel Hill, NC; [5]University of Pennsylvania, Philadelphia, PA; [6]Icahn School of Medicine at Mount Sinai, New York, NY; [7]Tufts University, Boston, MA; [8]Baylor College of Medicine, Houston, TX; [9]NIAID/NIH, Bethesda, MD; [10]Allakos, Inc., Redwood City, CA.; [11]Cincinnati Children's Hospital, Cincinnati, OH;

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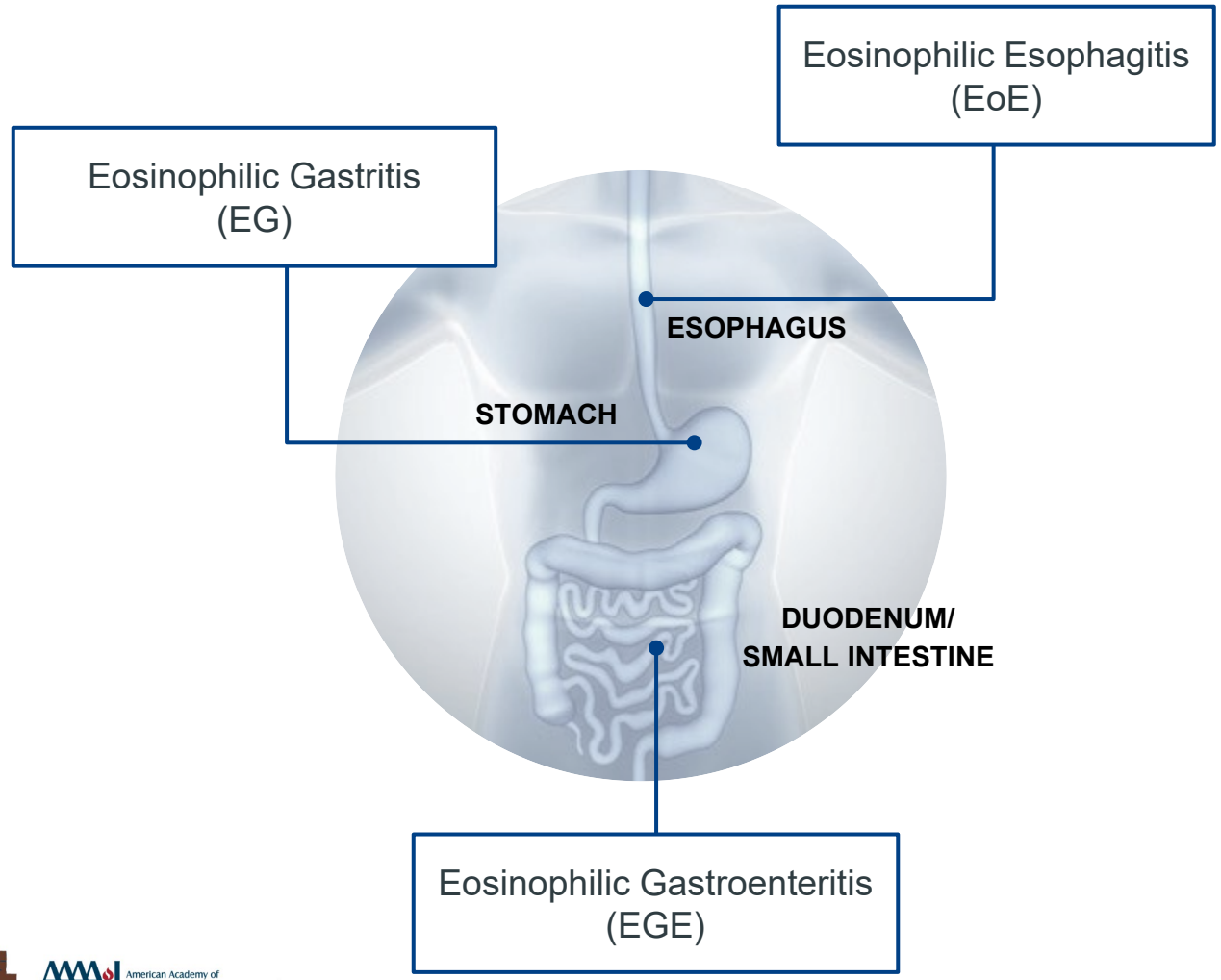
Disclosures

- Dr. Ikuo Hirano is a principal investigator in ENIGMA
- Lirentelimab (AK002) is an investigational drug candidate and is not FDA/EMA approved

Eosinophilic Gastrointestinal Diseases (EGIDs)

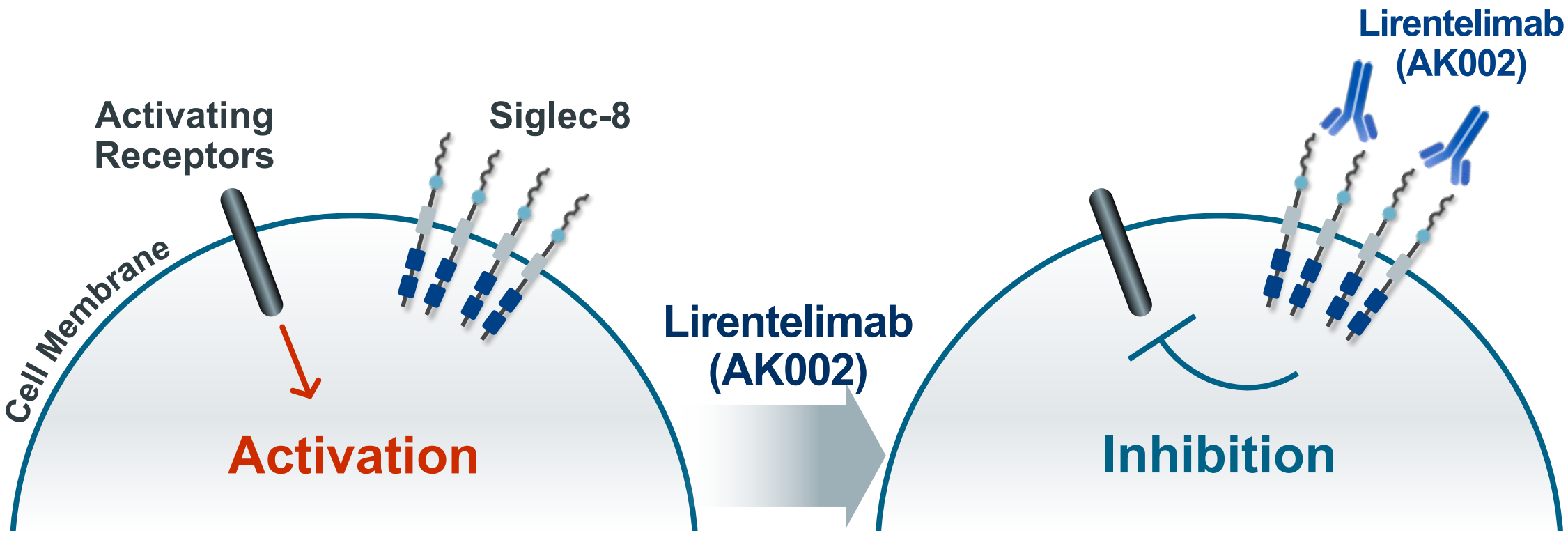


Chronic Eosinophilic Inflammation of the Stomach, Small Intestine, or Esophagus

- Eosinophils and mast cells are important drivers of disease
- Symptoms: abdominal pain, nausea, early satiety, loss of appetite, bloating, abdominal cramping, vomiting, diarrhea, and dysphagia
- No FDA approved treatment for EG, EGE, or EoE
- Current standard of care: diet and/or steroids

Source: Egan M, Furuta GT. Ann Allergy Asthma Immunol 121(2018) 162-167; Gonsalves M. Clin Rev. Allergy Immunol. 2019.

Lirentelimab (AK002) Targets Siglec-8 on Eosinophils and Mast Cells

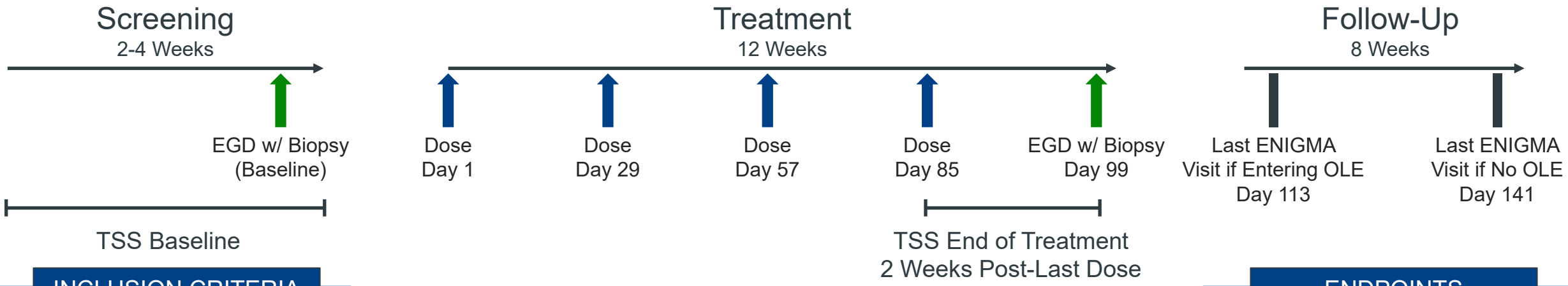


Mast Cell
Eosinophil
→ Inflammatory Response

Mast Cell → Inhibition
Eosinophil → ADCC[1]/Apoptosis

1 Antibody dependent cellular cytotoxicity

ENIGMA Phase 2 Study Design



INCLUSION CRITERIA

- Prior to endoscopy, active moderate-to-severe symptoms per daily diary
- Biopsy-confirmed
  - Stomach: ≥30 eos/hpf in 5 hpfs
  - Duodenum: ≥30 eos/hpf in 3 hpfs

Lirentelimab High Dose (N=21)
0.3 → 1.0 → 3.0 → 3.0 mg/kg

Lirentelimab Low Dose (N=22)
0.3 → 1.0 → 1.0 → 1.0 mg/kg

Placebo (N=22)

ENDPOINTS

- Primary: Mean % reduction in tissue eosinophils
- Secondary:
  - % Treatment responders[a]
  - Mean % reduction in Total Symptom Score[b] (TSS)
- Exploratory:
  - Proportion of patients with esophageal eos ≤6 eos/hpf
  - Mean % reduction in dysphagia severity scores

a: Treatment responder defined as: >75% reduction in tissue eosinophil counts AND >30% reduction in symptoms (TSS) from Baseline to End of Treatment
b: Total Symptom Score measured intensity of 8 symptoms on a 0-10 scale (TSS 0-80): abdominal pain, nausea, vomiting, early satiety, loss of appetite, abdominal cramping, bloating, and diarrhea

Symptoms Assessed Using Proprietary PRO

EG/EGE-SQ© Questionnaire

- Developed in accordance with FDA guidance on PRO development
- Captures the symptoms of patients on a daily basis
- Measures 8 symptoms each on a scale of 0-10; Total Symptom Score: (TSS) 80 points

  - Abdominal pain
  - Nausea
  - Vomiting
  - Early satiety
  - Loss of appetite
  - Abdominal cramping
  - Bloating
  - Diarrhea

- Patients with concomitant eosinophilic esophagitis received a daily question to report severity of dysphagia on a scale of 0-10

Prespecified Hierarchical Analysis Per Protocol

Primary Endpoint

- Mean percent change in gastrointestinal eosinophil counts from baseline to end of treatment[1]

Responder Secondary Endpoint

- Proportion of patients who have:
  - >75% decrease in tissue eosinophils AND >30% benefit in TSS

Symptoms Secondary Endpoint

- Mean percent change in TSS from baseline to end of treatment

Endpoints designed to show (1) tissue eosinophil depletion; (2) symptom improvement, and (3) that these effects occur in the same individuals

1 End of Treatment: two weeks post-last dose

Baseline Characteristics

		Lirentelimab (AK002) Dose Groups				
		High 0.3-3.0 mg/kg (n=20)	**Low** 0.3-1.0 mg/kg (n=19)	**Combined** High/Low (n=39)	**Placebo** (n=20)	**Total** (N=59)
Age, Mean (Range)		42 (20-67)	43 (18-74)	42 (18-74)	40 (18-67)	41 (18-74)
Female		60%	84%	72%	50%	64%
White		85%	95%	90%	100%	93%
Mean Gastrointestinal[1] Eosinophils/hpf		76	80	78	75	77
Mean Gastrointestinal[1] Mast Cells/hpf		59	70	64	56	62
Mean Total Symptom Score (TSS) [0-80]		34.1	34.7	34.4	30.1	32.9
% of Patients (n) by AEC[2]/μL	<500	80% (16)	68% (13)	74% (29)	60% (12)	70% (41)
	≥500	20% (4)	32% (6)	26% (10)	40% (8)	30% (18)

1 Gastric or duodenum site with highest eosinophil or mast cell counts
2 AEC: Absolute Eosinophil Count

Primary Endpoint

Treatment Arm	Baseline Eosinophil Counts / hpf	Mean %Δ in Eosinophil Counts	*p* - value
High Dose Lirentelimab (n=20)	76	-97%	**<0.0001**
Low Dose Lirentelimab (n=19)	80	-92%	**<0.0001**
Combined Lirentelimab (n=39)	78	-95%	**<0.0001**
Placebo (n=20)	75	+10%	-

p-value: ANCOVA

Treatment Responder Secondary Endpoint

Treatment Arm	Treatment Responders	*p* - value
High Dose Lirentelimab (n=20)	70%	**0.0009**
Low Dose Lirentelimab (n=19)	68%	**0.0019**
Combined Lirentelimab (n=39)	69%	**0.0008**
Placebo (n=20)	5%	-

Treatment responder defined as: >75% reduction in tissue eosinophil counts AND >30% reduction in symptoms (TSS)

p-value: MMRM

Patient Reported Symptoms Secondary Endpoint

Treatment Arm	Baseline TSS	Mean % Change in TSS	*p* - value
High Dose Lirentelimab (n=20)	34	-58%	**0.0012**
Low Dose Lirentelimab (n=19)	35	-49%	**0.0150**
Combined Lirentelimab (n=39)	34	-53%	**0.0012**
Placebo (n=20)	30	-24%	-

Statistically significant improvements in symptoms observed 1 day after first infusion and maintained throughout the study

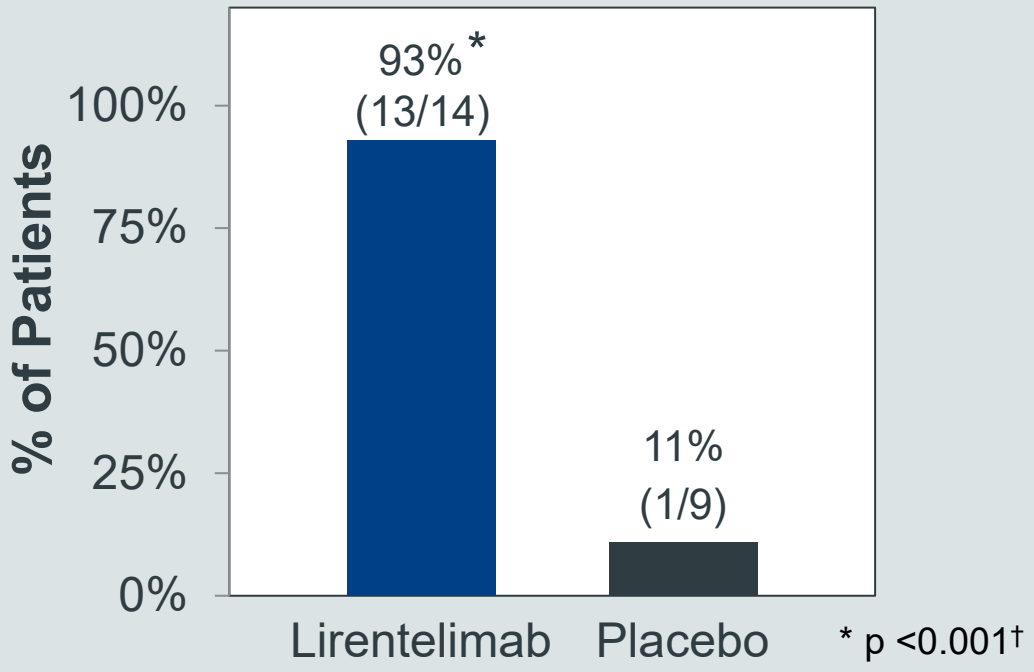
p-value: ANCOVA

Patients with Esophageal Involvement

	Lirentelimab (n=15)	Placebo (n=10)	Total (N=25)
Age, Median (Range)	34 (18-68)	34 (21-53)	34 (18-68)
Female	67%	40%	56%
Mean Blood Eosinophil Count eos/µL (Range)	623 (100-2880)	630 (30-1830)	626 (30-2880)
Mean Baseline Esophageal Eosinophils/hpf	46	79	58
Mean Baseline Esophageal Mast Cells/hpf	28	36	31
Mean Baseline Dysphagia Score [0-10]	4.0	4.4	4.2

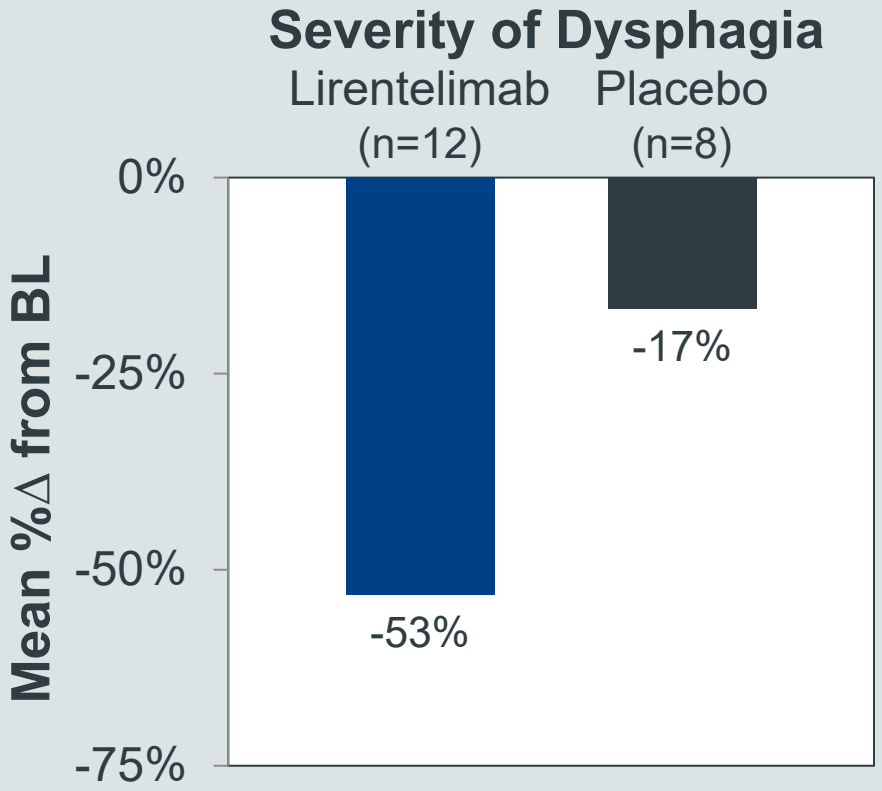
Exploratory: Histologic Response in Concomitant EoE[1]

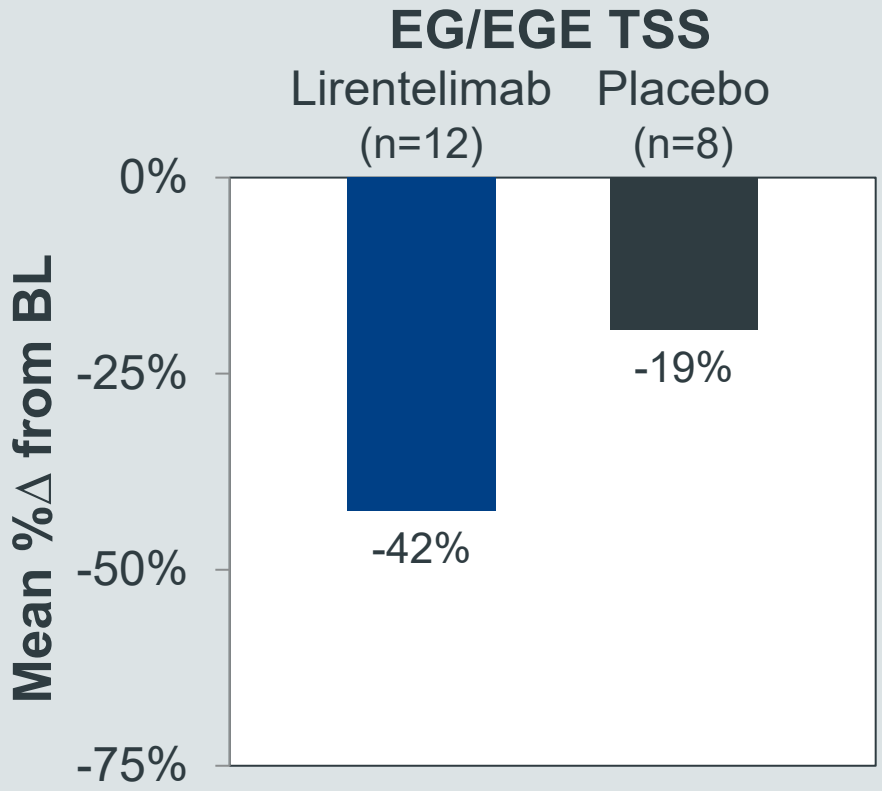
Esophageal Eos ≤ 6/hpf[2]



1 25 patients with concomitant EoE (≥15 eos/hpf or history of EoE) and baseline dysphagia
2 Excludes patients with eos < 6/hpf at baseline. At end of treatment, 10/14 AK002 patients had 0 eos/hpf; 2/14 AK002 patients had 1 eos/hpf; 1/14 AK002 patients had 3 eos/hpf; 1/14 AK002 patients had 105 eos/hpf (biopsy occurred 6 weeks post last dose instead of 2 weeks per protocol); 1/9 placebo patients had 2 eos/hpf; 8/9 placebo patients had 19 – 200 eos/hpf
† p = 0.00015

Symptomatic Response in Patients with Concomitant EoE[1]





1 All concomitant EoE (≥15 eos/hpf or history of EoE) patients with baseline and end of treatment dysphagia scores

Safety Summary

Treatment-Emergent AEs in ≥5% of Patients

% of Patients, (n)	AK002 (n=43)	Placebo (n=22)
Infusion related reaction	60% (26)	23% (5)
Headache	9% (4)	9% (2)
Upper respiratory tract infection	9% (4)	9% (2)
Urinary tract infection	9% (4)	5% (1)
Nausea	7% (3)	14% (3)
Fatigue	7% (3)	9% (2)
Diarrhea	5% (2)	9% (2)
Nasopharyngitis	5% (2)	9% (2)
Abdominal pain	2% (1)	9% (2)
Dehydration	2% (1)	9% (2)
Gastroenteritis viral	2% (1)	9% (2)
Pyrexia	2% (1)	9% (2)
Sinusitis	2% (1)	9% (2)
Cough	0% (0)	9% (2)
Influenza	0% (0)	9% (2)
White blood cell count increased	0% (0)	9% (2)

- Generally well tolerated
- Most common AE was mild to moderate infusion related reactions (IRR)
  - 93% mild to moderate (flushing, feeling of warmth, headache, nausea, dizziness)
  - Mostly on first infusion, greatly reduced or does not occur on subsequent infusions
  - 1 drug-related serious adverse event, an IRR which recovered within 24 hours with no further sequelae
- Treatment-emergent SAEs: 9% on AK002, 14% on Placebo
- No other significant AEs

Summary

- This was the first randomized study in eosinophilic gastritis and/or enteritis (duodenum)
- Study met all primary and secondary endpoints, demonstrating significant histologic and symptom improvements
- Strong histologic and symptom improvements in comorbid EoE
  - 13/14 (93%) patients with esophageal eos ≤ 6/hpf vs. 1/9 (11%) on placebo
  - 53% improvement in dysphagia symptom severity vs. 17% on placebo
- Generally well-tolerated
- These results build on clinical activity of lirentelimab (AK002) observed in chronic urticaria, severe allergic conjunctivitis, asthma, atopic dermatitis, and indolent systemic mastocytosis

We thank the patients who participated in this study, investigators, and study staff