AK002 (Lirentelimab) in Adult Patients with Active Eosinophilic Gastritis and/or Eosinophilic Gastroenteritis: Primary Results from a Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial (ENIGMA Study; NCT03496571)

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ACG 2019

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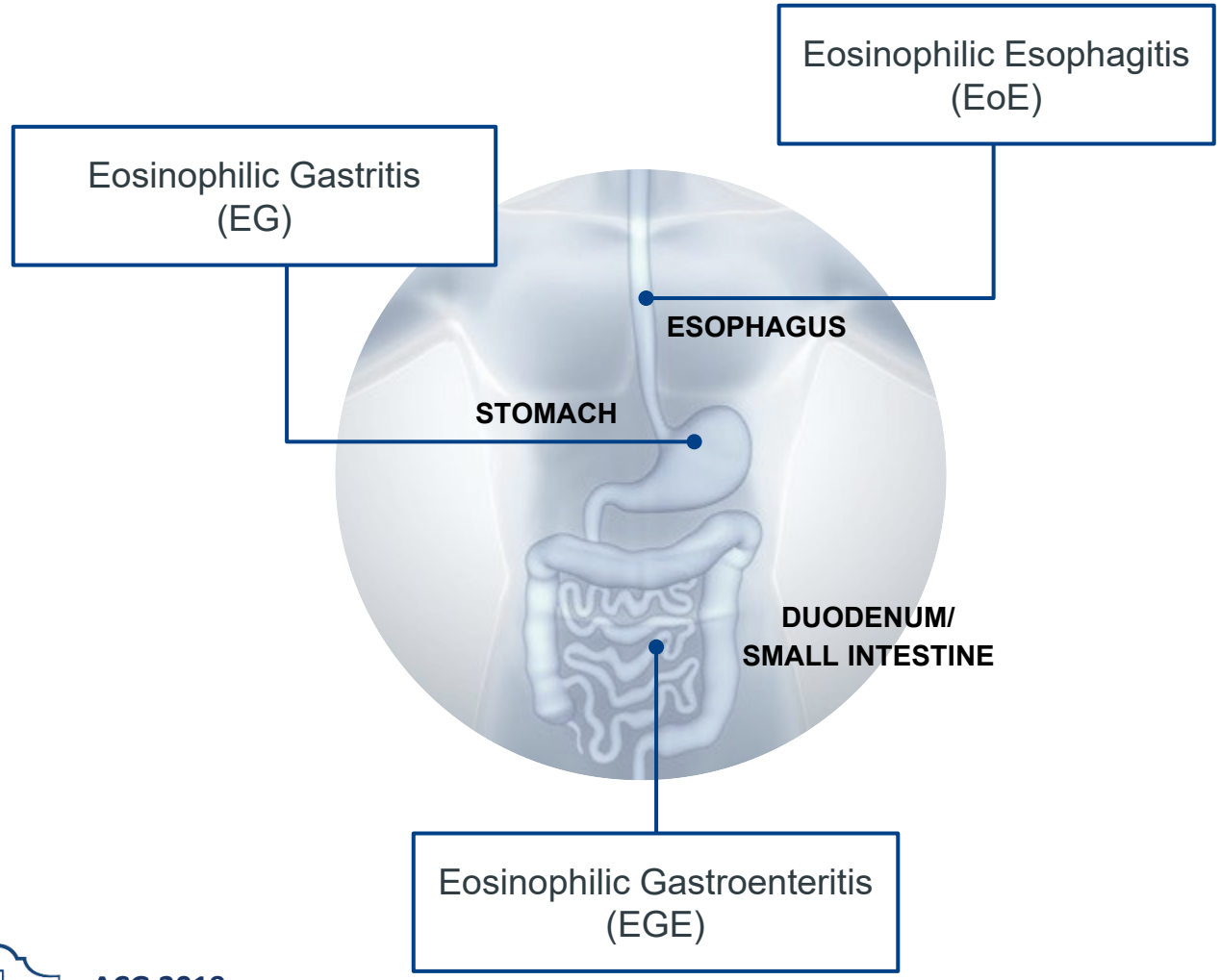
Eosinophilic Gastrointestinal Diseases (EGIDs)

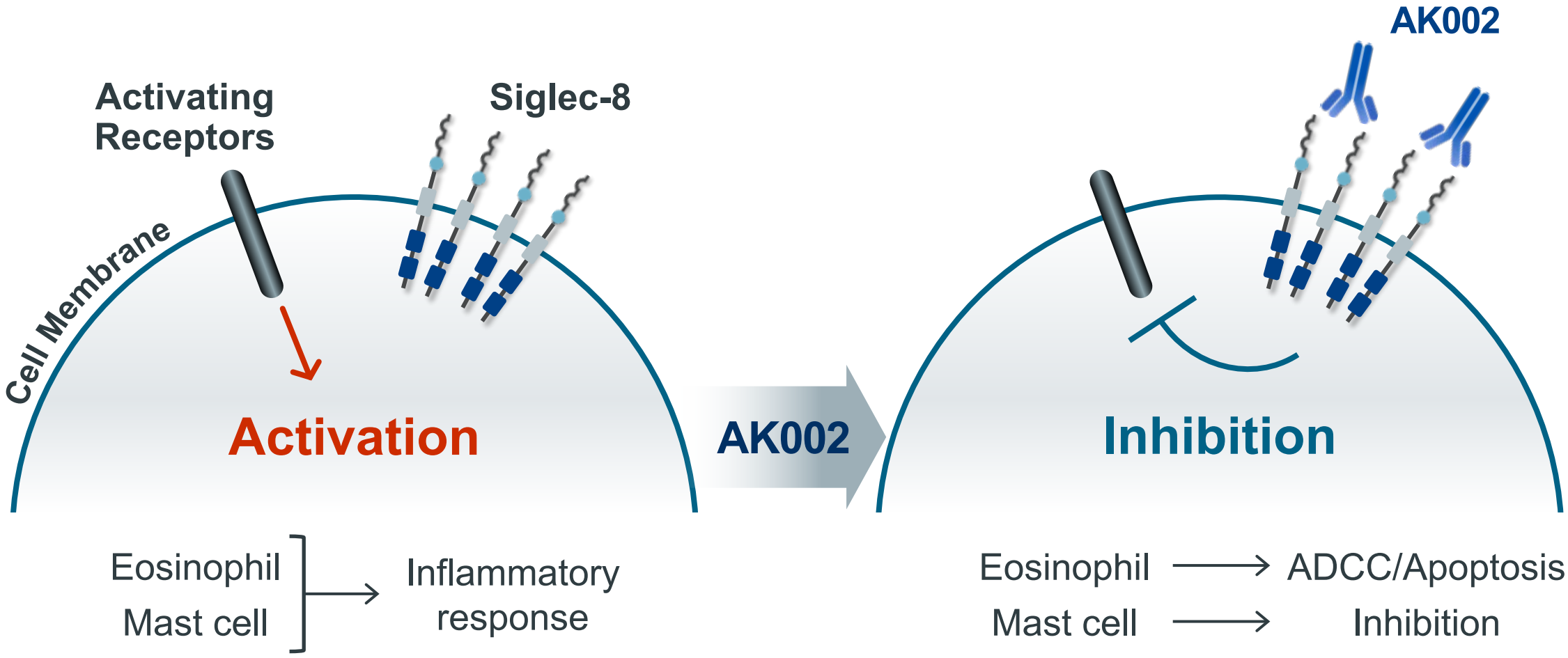


EG, EGE, EoE

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

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

AK002 Targets Siglec-8 on Eosinophils and Mast Cells



ENIGMA Phase 2 Study Aim and Inclusion

Study Aim

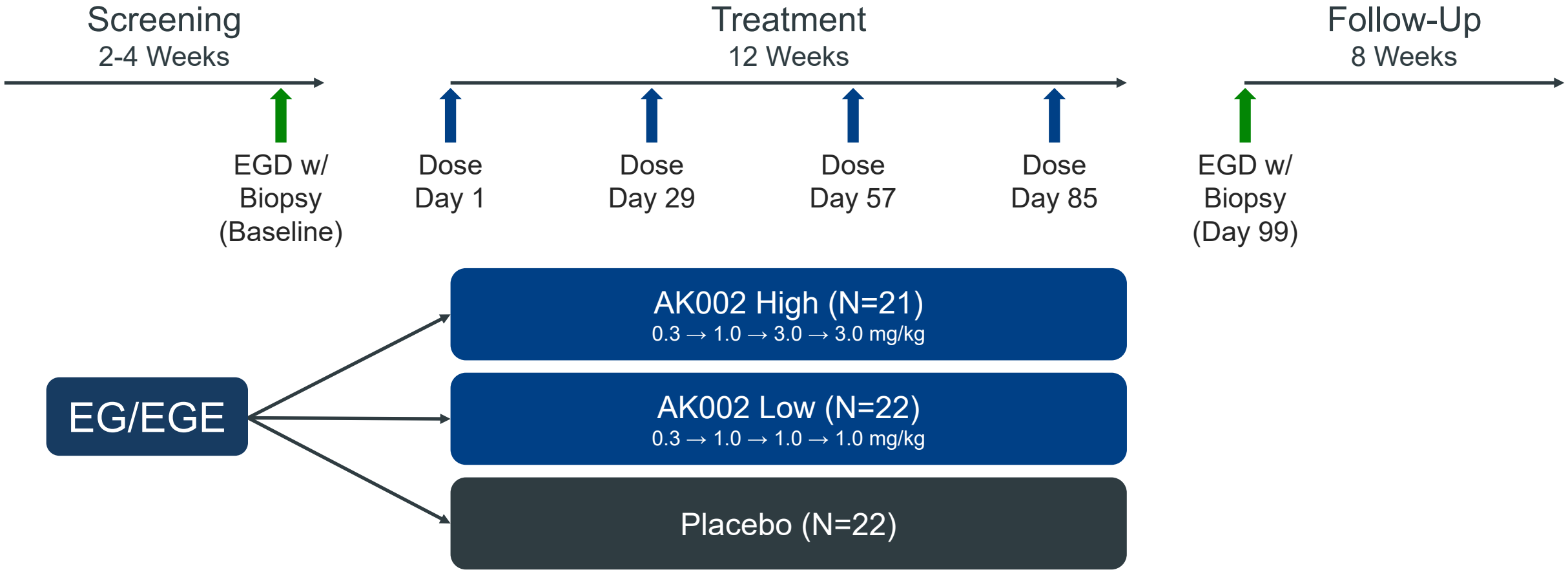
- Determine safety and efficacy of AK002 for treatment of EG and/or EGE

Key Inclusion Criteria

- Active moderate to severe symptoms[1] using the daily 8 symptom EG/EGE-SQ© Questionnaire
- Biopsy confirmed EG/EGE
  - Stomach: ≥30 eos/hpf in 5 hpfs
  - Duodenum: ≥30 eos/hpf in 3 hpfs

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

ENIGMA Phase 2 Study Design



Endpoints

Primary Endpoint

- Mean percent change in gastrointestinal eosinophil counts from baseline

Symptoms Secondary Endpoint

- Mean percent change in Total Symptom Score (TSS) from baseline

Responder Secondary Endpoint

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

Primary analysis with a pre-specified hierarchical per protocol approach

- Sensitivity analyses: ITT; subgroup with no steroid use

Baseline Characteristics

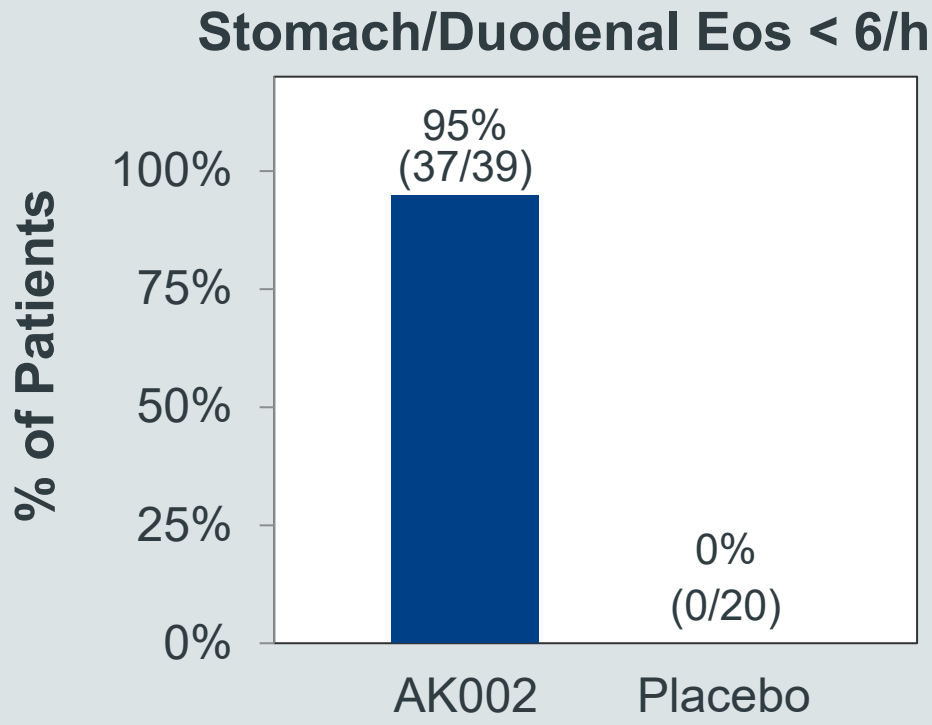
		AK002 Dose Groups			Placebo (n=20)	Total (N=59)
		High 0.3-3.0 mg/kg (n=20)	Low 0.3-1.0 mg/kg (n=19)	Combined High/Low (n=39)		
Age, Mean (Range)		42 (20-67)	43 (18-74)	42 (18-74)	40 (18-67)	41 (18-74)
Female		60%	84%	72%	50%	64%
White		85%	95%	90%	100%	93%
Mean Gastrointestinal[1] Eosinophils/hpf		76	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	<250	45% (9)	26% (5)	36% (14)	45% (9)	39% (23)
	250 to <500	35% (7)	42% (8)	38% (15)	15% (3)	31% (18)
	500 to <1500	20% (4)	21% (4)	21% (8)	35% (7)	25% (15)
	≥1500	0%	11% (2)	5% (2)	5% (1)	5% (3)

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

Primary Endpoint – Mean % Change in Eosinophil Count

Treatment Arm	Baseline Eosinophil Counts / hpf	Mean %Δ in Eosinophil Counts	*p* - value
High Dose AK002 (n=20)	76	-97%	**<0.0001**
Low Dose AK002 (n=19)	80	-92%	**<0.0001**
Combined AK002 (n=39)	78	-95%	**<0.0001**
Placebo (n=20)	75	+10%	-

Tissue Eosinophil Depletion

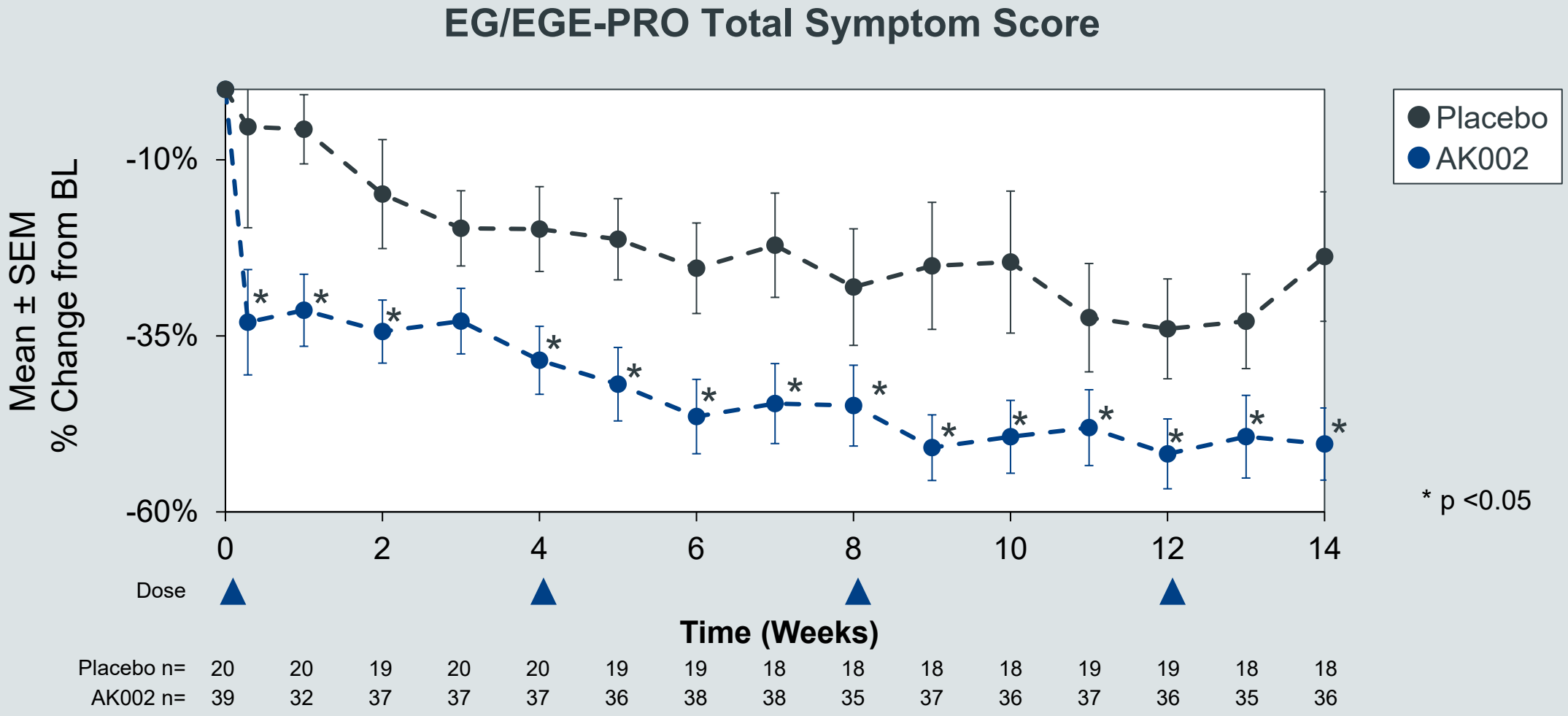


37 of 39 patients had < 6 eos/hpf; 31/39 had 0 eos/hpf

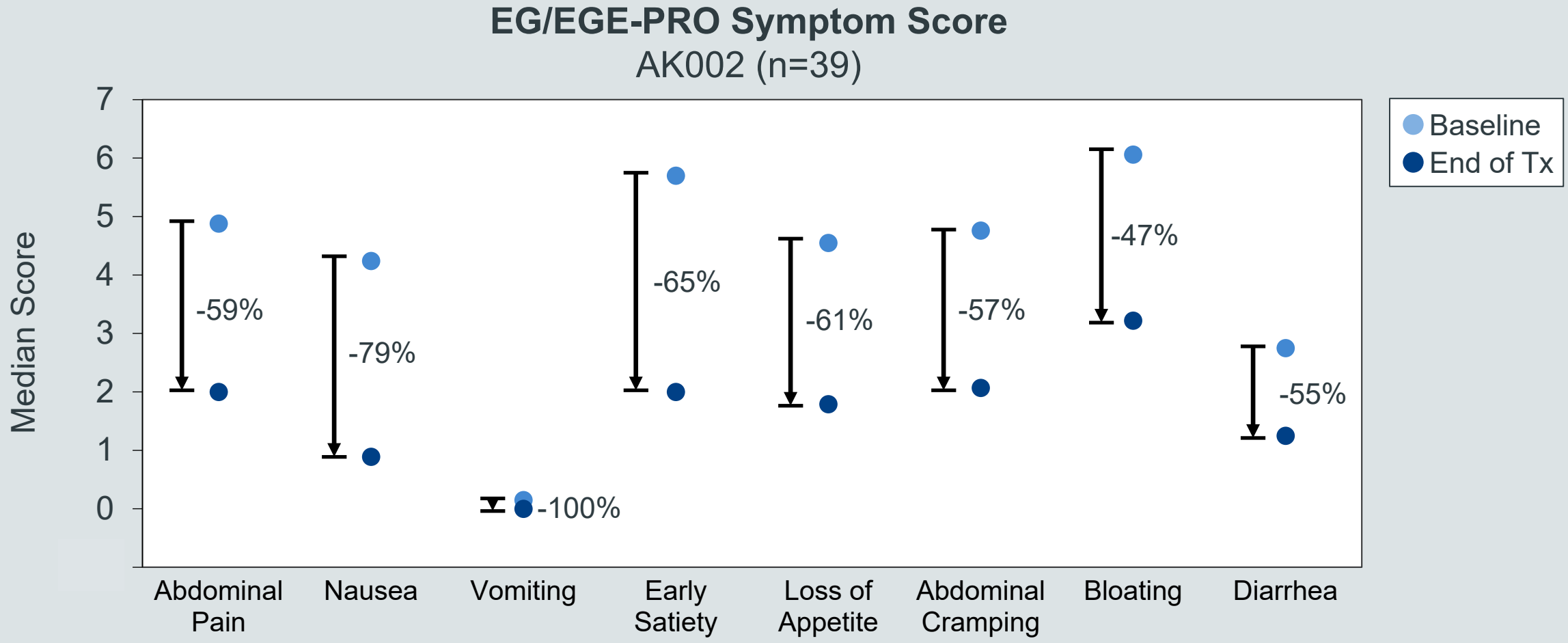
Patient Reported Symptoms Secondary Endpoint

Treatment Arm	Baseline TSS	Mean % Change in TSS	*p* - value
High Dose AK002 (n=20)	34	-58%	**0.0012**
Low Dose AK002 (n=19)	35	-49%	**0.0150**
Combined AK002 (n=39)	34	-53%	**0.0012**
Placebo (n=20)	30	-24%	-

Rapid & Sustained Improvement in Symptoms



Improvement Across All Symptoms



Improvements in TSS Were Not Driven by Any Single Symptom

Mean Reduction in TSS	Combined AK002 (N=39)	Placebo (N=20)	*p* - value
Total Score	**-53.5%**	**-24.3%**	**0.0012**
Minus Abdominal Pain	-53.1%	-22.5%	0.0010
Minus Nausea	-53.2%	-23.9%	0.0009
Minus Vomiting	-53.0%	-24.9%	0.0018
Minus Satiety	-51.8%	-25.4%	0.0019
Minus Loss of Appetite	-53.0%	-24.9%	0.0009
Minus Abdominal Cramping	-53.0%	-22.4%	0.0011
Minus Bloating	-55.9%	-26.9%	0.0029
Minus Diarrhea	-54.9%	-24.0%	0.0010

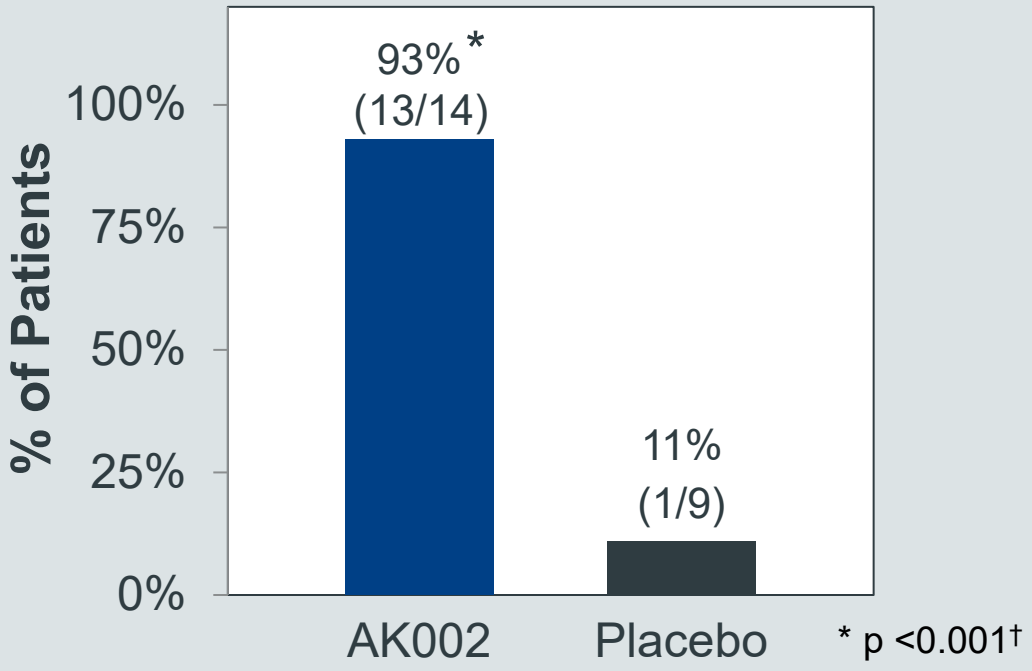
AK002 Met Treatment Responder Secondary Endpoint

Treatment Arm	Treatment Responders	*p* - value
High Dose AK002 (n=20)	70%	**0.0009**
Low Dose AK002 (n=19)	68%	**0.0019**
Combined AK002 (n=39)	69%	**0.0008**
Placebo (n=20)	5%	-

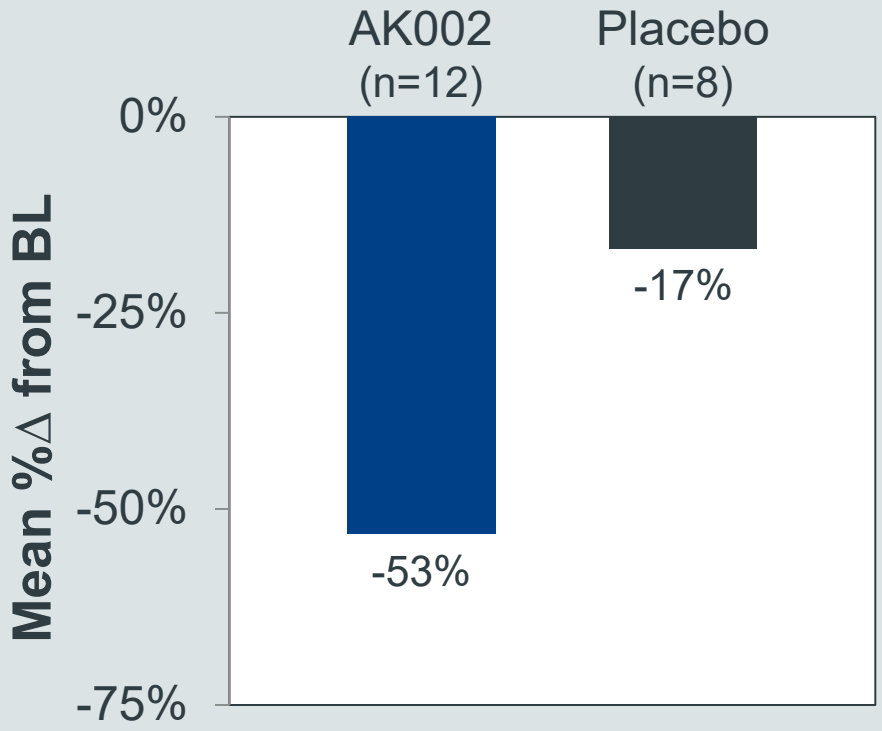
Treatment responder defined as: >75% reduction in tissue eosinophil counts AND >30% reduction in symptoms (TSS)

Response in Concomitant EoE[1]

Esophageal Eos ≤ 6/hpf[2]



Severity of Dysphagia[3]



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
3 All EoE patients with end of treatment dysphagia scores
† p = 0.00015

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

ENIGMA Summary

- This was the first randomized study in EG/EGE
- Study met all primary and secondary endpoints, demonstrating significant histologic and symptom improvements in EG/EGE
- Strong histologic and symptom improvements in EoE
- Generally well-tolerated
- These results build on clinical activity of AK002 observed in other atopic and mast cell disorders (chronic urticaria, severe allergic conjunctivitis, asthma, atopic dermatitis, and indolent systemic mastocytosis)
- Further development of AK002 for EG/EGE is appropriate

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