Endoscopy and Systematic Biopsy of Patients with Chronic Gastrointestinal Symptoms Leads to High Discovery Rate of Patients Who Meet Histologic Criteria for Eosinophilic Gastritis and/or Eosinophilic Duodenitis

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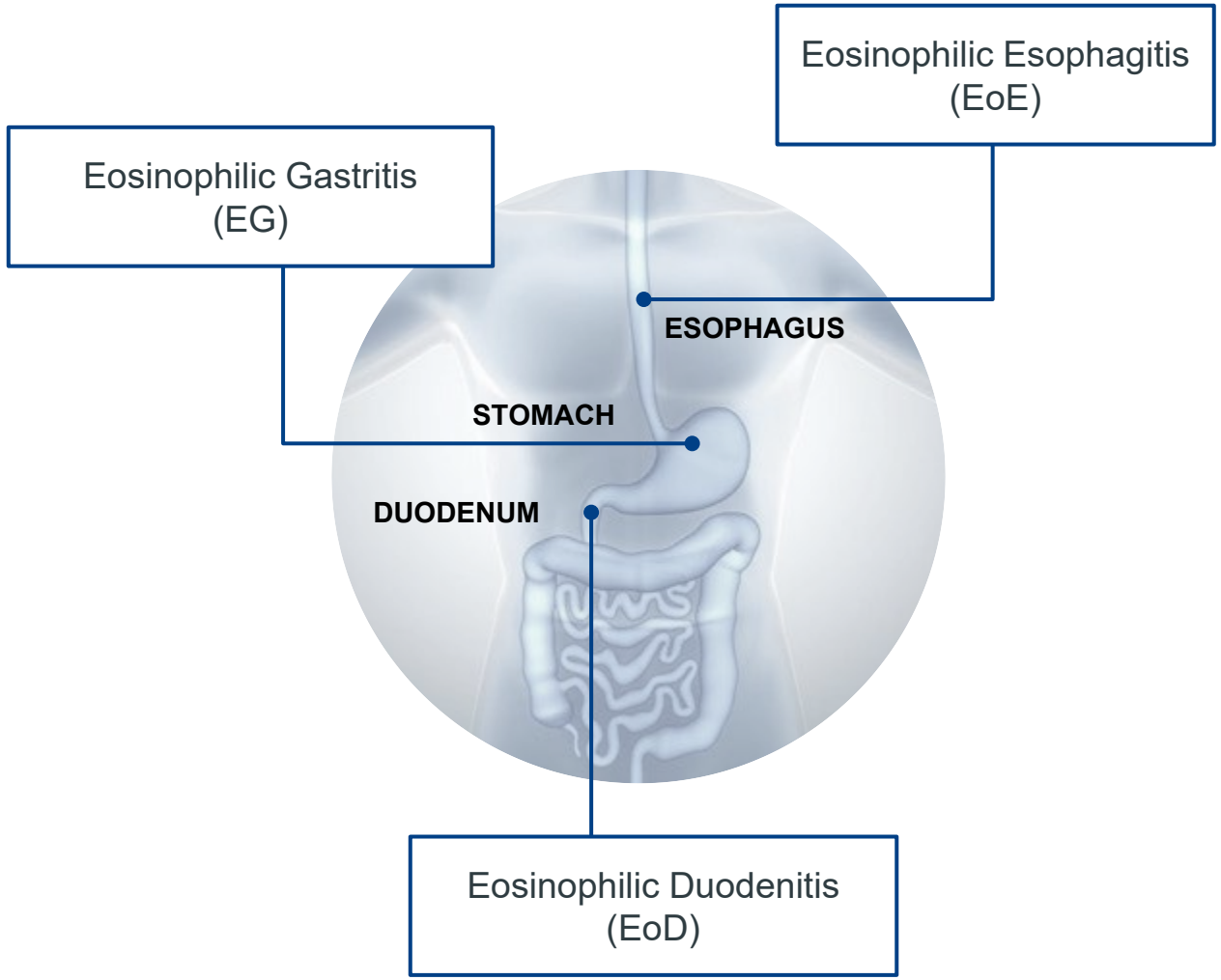
Disclosures

- Dr. Nicholas Talley is a consultant for Allakos, Inc.
- Lirentelimab (AK002) is an investigational drug candidate and is not FDA/EMA approved

Eosinophilic Gastrointestinal Diseases (EGIDs)



EG, EoD, EoE

Chronic Eosinophilic Inflammation of the Stomach, Duodenum, 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, EoD, 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.

ENIGMA: Phase 2 Study of Lirentelimab in EG and/or EoD

INCLUSION CRITERIA

- Patient-reported active moderate-to-severe symptoms per the **EG/EoD Questionnaire©**
  - Captures the symptoms of EG/EoD 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
  - Symptom criteria: weekly average ≥3 to 10 for abdominal pain, nausea, or diarrhea for at least 2 weeks
- Biopsy-confirmed EG and/or EoD
  - **EG:** ≥30 eos/hpf in 5 hpfs (stomach)
  - **EoD**: ≥30 eos/hpf in 3 hpfs (duodenum)

STUDY DESIGN

- Phase 2 multi-center, randomized, double-blind, placebo-controlled study
- 65 Patients – 3 arms, 4 monthly doses
  - 21 patients 0.3, 1.0, 3.0, 3.0 mg/kg lirentelimab
  - 22 patients 0.3, 1.0, 1.0, 1.0 mg/kg lirentelimab
  - 22 patients placebo
- Primary endpoint: Mean % reduction in tissue eosinophils from baseline to day 99
- Secondary endpoints
  - % Treatment responders (>75% reduction in tissue eosinophil counts AND >30% reduction in symptoms (TSS) from baseline to 2 weeks post-last dose)
  - Mean % reduction in TSS from baseline to 2 weeks post-last dose

RANDOMIZED STUDY RESULTS

Prespecified Endpoints		lirentelimab (n=39)	Placebo (n=20)
1° - Tissue Eosinophils	% Δ	-95%	+10%
	p-value	**<0.0001**	-
2° - Treatment Responders	%	69%	5%
	p-value	**0.0008**	-
2° - TSS	% Δ	-53%	-24%
	p-value	**0.0012**	-

- All primary and secondary endpoints met in the first randomized trial in patients with EG and EoD
- Generally well tolerated

SOURCE: Dellon ES, et al. New England Journal of Medicine. 2020;383:1624-34.

ENIGMA: Unexpectedly High Diagnosis Rate of EG and/or EoD Among Previously Undiagnosed Patients

51 patients without history of EG and/or EoD entered ENIGMA screening

↓

51% (26/51) met symptom criteria for endoscopy and biopsy

↓

58% (15/26) EG and/or EoD

- 29% (15/51) received a de novo diagnosis of EG and/or EoD
- Majority of patients without a previous diagnosis of EG and/or EoD came from general GI practices
- These patients had a history of chronic nonspecific functional GI symptoms or diagnoses

Suggests significant underdiagnosis of EG and/or EoD

SOURCE: Peterson KA et al. AJG. 2020 (ACG 2020 presentation)

EG and/or EoD Prevalence Study Aim & Design

- **Study Design**
  - Prospective, multi-center study to assess the prevalence of EG and/or EoD in symptomatic patients with chronic functional GI symptoms
    - At least a 6-month history of abdominal pain, abdominal cramping, nausea, vomiting, diarrhea, bloating or early satiety without identifiable cause and unresponsive to pharmacologic or dietary intervention

    and/or

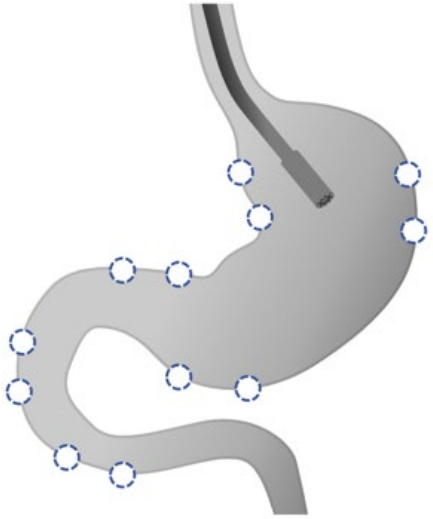
    - a diagnosis of IBS or functional dyspepsia (FD), indicating a chronicity of symptoms
  - **An asymptomatic healthy volunteer study was conducted for comparison**
- **Co-Primary Endpoints**
  - Proportion of symptomatic patients that underwent biopsy and met the histologic criteria for EG and/or EoD (≥30 eos/hpf in 5 gastric or 3 duodenal hpf)
  - Proportion of symptomatic patients that underwent biopsy with ≥30 mast cells/hpf in 5 gastric hpfs and/or ≥30 mast cells/hpf in 3 duodenal hpfs and < 30 eos/hpf

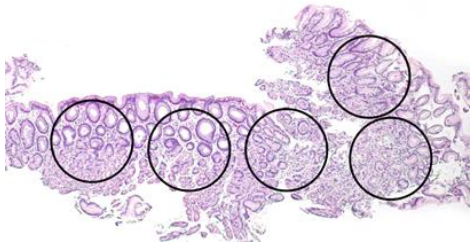
Symptoms Assessed With the Same PRO Questionnaire Used in ENIGMA

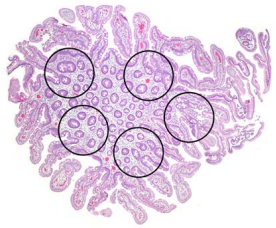
GI Symptom Questionnaire

- Developed in accordance with FDA guidance on PRO development
- Captures the GI symptoms of patients on a daily basis
- Measures symptoms each on a scale of 0-10 for the following:
  - Abdominal pain
  - Nausea
  - Vomiting
  - Early satiety
  - Loss of appetite
  - Abdominal cramping
  - Bloating
  - Diarrhea
- Average daily score of ≥3 (on a scale from 0-10) for any individual symptom and a Total Symptom Score ≥10
- Same PRO used for asymptomatic controls who had to have an average daily score ≤1 for all symptoms and no daily score ≥3 on any day for any symptom

Systematic Biopsy and Histopathologic Assessment Protocol for Patients and Controls







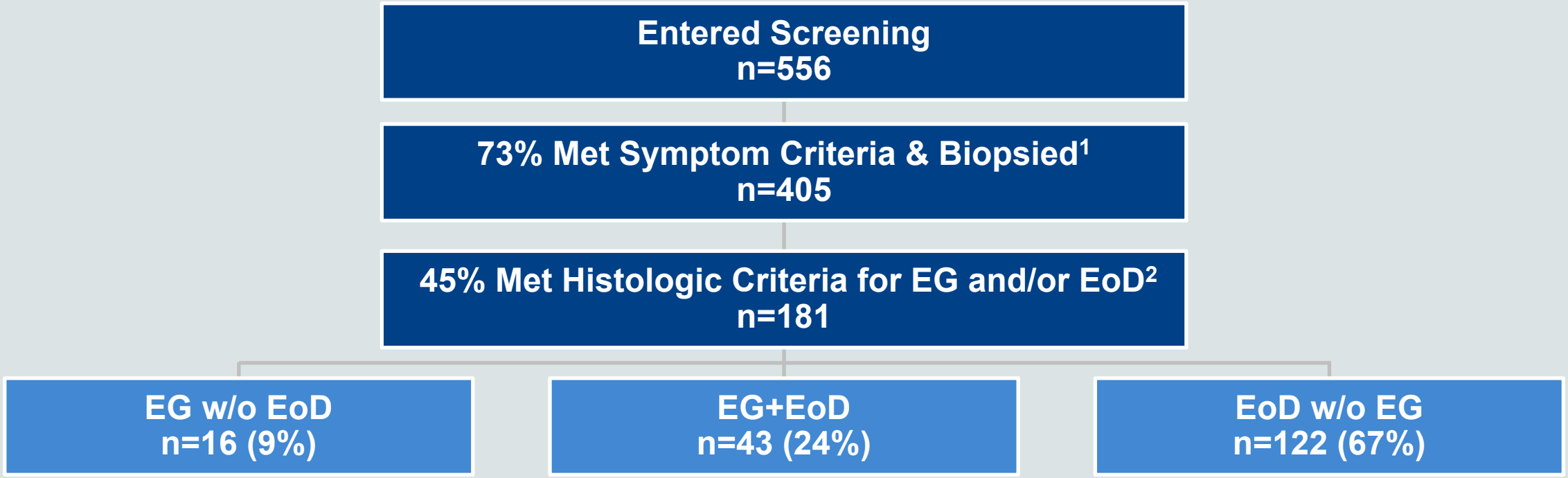
Biopsy Protocol

Stomach	• **GASTRIC ANTRUM: 4 biopsies** (2-5 cm proximal to the pylorus) • **GASTRIC CORPUS: 4 biopsies** (2 from the proximal lesser curvature and 2 from the greater curvature)
Duodenum	• **4 biopsies** from the duodenum, 2 each from the descending and horizontal parts

Assessment Protocol

- Biopsy samples were collected and sent to the central lab for fixing and staining and then evaluated by an external expert pathologist, who was blinded to all patient demographic, clinical, and endoscopic data
- Eosinophils and mast cells were counted systematically in a minimum of 5 non-overlapping hpfs in at least 12 biopsies to avoid missing areas of infiltration
- Gastric biopsies were graded using the Sydney System on inflammation, metaplasia, atrophy, and reactive gastropathy; the Marsh Scale Classification was used to grade duodenal samples

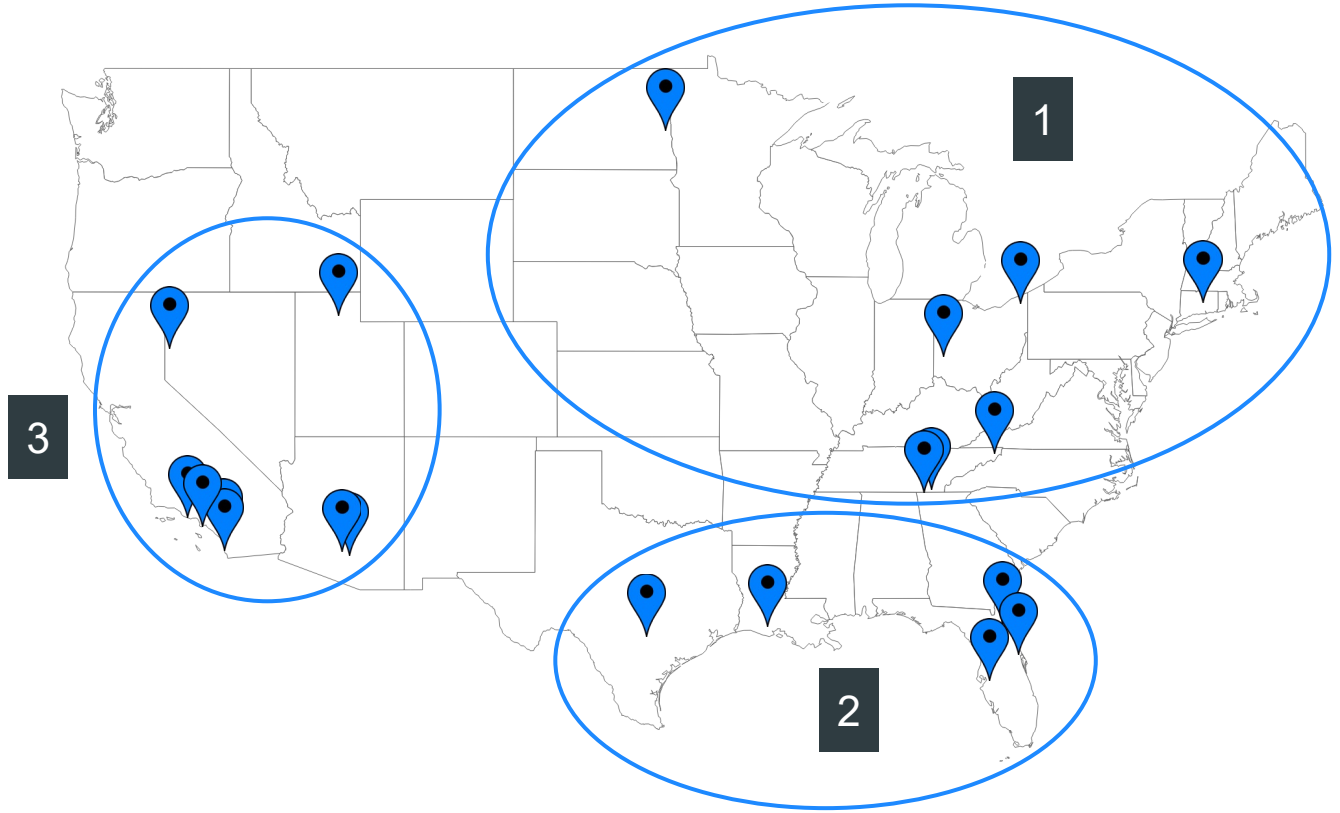
High Prevalence of EG and/or EoD in Patients with Chronic GI symptoms



33% (181/556) of patients with chronic functional GI symptoms and 45% (181/405) of patients with moderate-severe symptoms undergoing biopsy met histologic criteria for EG and/or EoD

1 378/405 (93%) of patients met mast cell histologic criteria of ≥30 mast cells in 5 gastric and/or 3 duodenal hpfs
2 Patients who met symptom criteria and ≥30 eos/hpf in 5 gastric hpfs and/or ≥30 eos/hpf in 3 duodenal hpfs; 7 patients did not meet mast cell histologic criteria

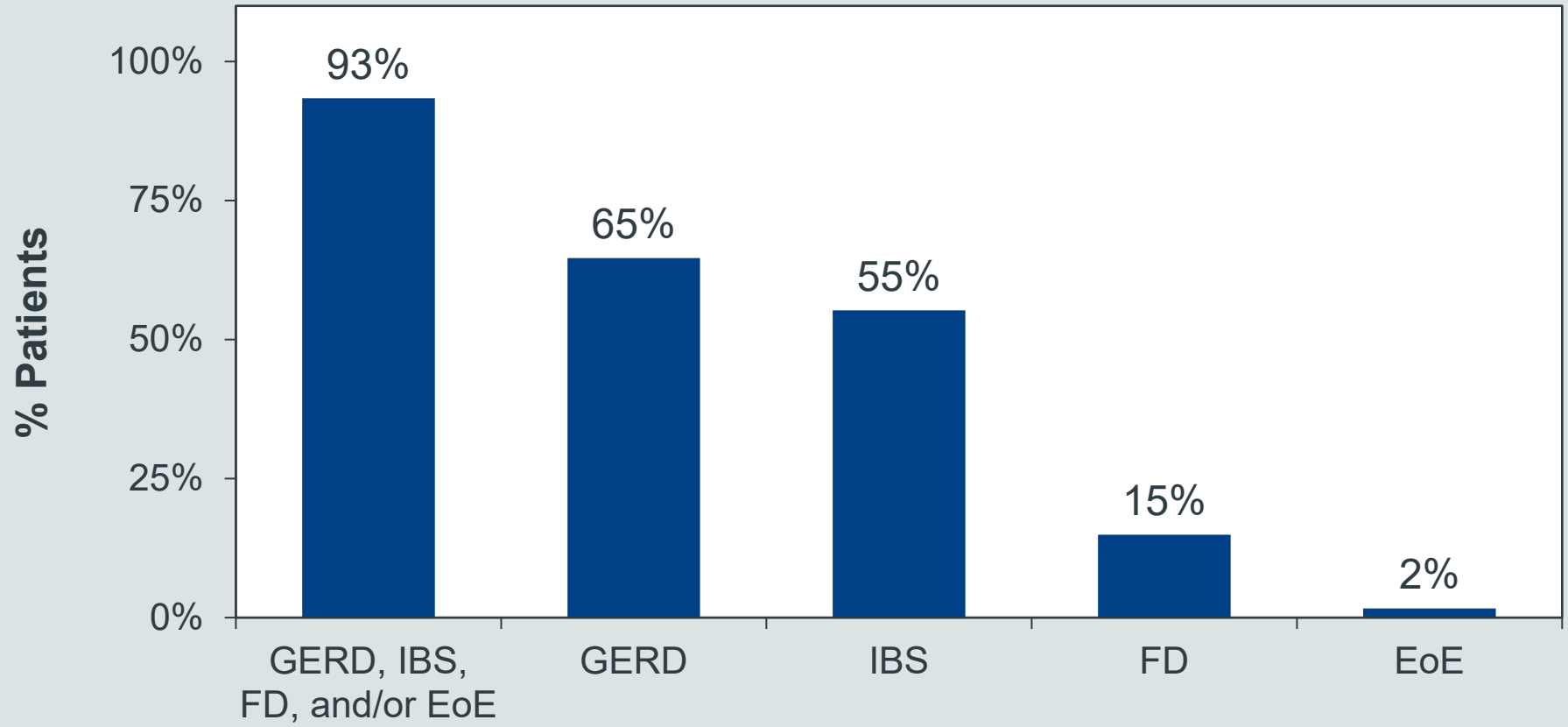
Consistent EG and/or EoD Discovery Rate Across Sites



Region	# Sites	Total Patients	EG and/or EoD Pts	EG and/or EoD Rate
1	7	131	66	50%
2	5	123	60	49%
3	8	151	55	36%

These Patients had Previously Been Diagnosed with Functional Disorders

Past GI Diagnoses[a] in Patients Who Met Histologic Criteria for EG and/or EoD (n=181)



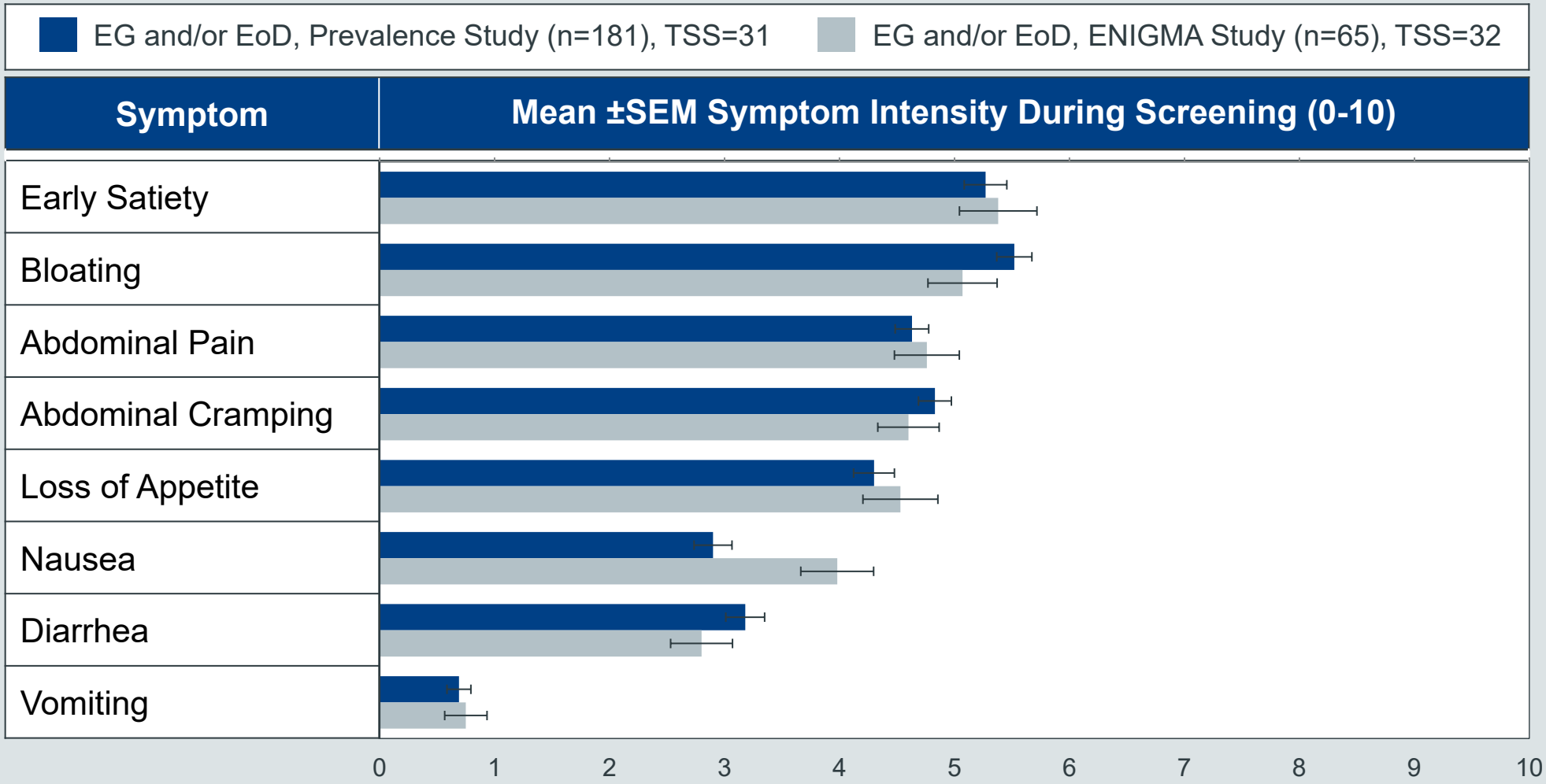
a Other prior GI diagnoses included other functional GI disorders, such as chronic abdominal pain or functional diarrhea

Characteristics of EG and/or EoD Patients

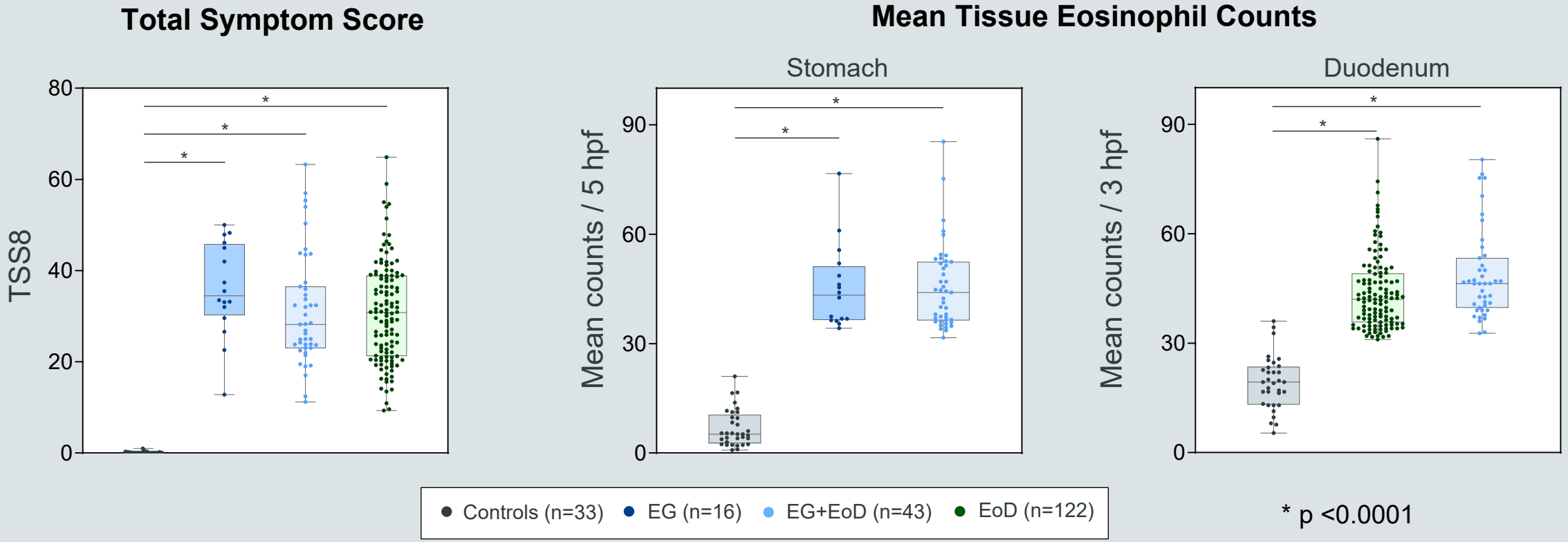
Patient Characteristics		Met Histologic[a] Criteria for EG and/or EoD n=181	ENIGMA n=65
Mean age, years (range)		45 (19-78)	41 (18-74)
Female sex, %		73%	62%
White, %		85%	92%
Weight, median, kg		83	80
Blood eosinophils	Cells/μL, median (IQR)	170 (100-250)	330 (160-720)
	Blood eos ≥250 cells/μL, %	27%	65%
	Blood eos ≥500 cells/μL, %	4%	35%
	Blood eos ≥1500 cells/μL, %	0%	11%
Immunoglobin E	kU/μL, median (IQR)	34 (14-103)	141 (44-361)
	IgE ≥70 kU/μL, %	36%	67%
TSS [0-80], mean ±SD		31.3 ±11.2	31.9 ± 13.6
History of	GI symptoms, mean years	11	9
	Atopy[b], %	48%	69%
	EoE, %	2%	54%

a Patients who met symptom criteria and ≥30 eos/hpf in 5 gastric hpfs and/or ≥30 eos/hpf in 3 duodenal hpfs
b Asthma, allergic rhinitis, atopic dermatitis and/or food allergy

Comparable Symptom Profile in EG and/or EoD Patients



Total Symptom Scores and Mean Eosinophil Counts in Patients vs. Controls



45% (181/405) of patients and 6% (2/33) of asymptomatic controls met histologic criteria for EG/EoD (Odds ratio=12.52; 95% CI, 3.0–53.0; *P*<0.001)

a Patients and controls used the same PRO questionnaire and underwent identical biopsy protocols. Histologic evaluation for both groups were performed by the same central pathologists

Under-Recognition of EG/EoD in Patients with Chronic GI Symptoms

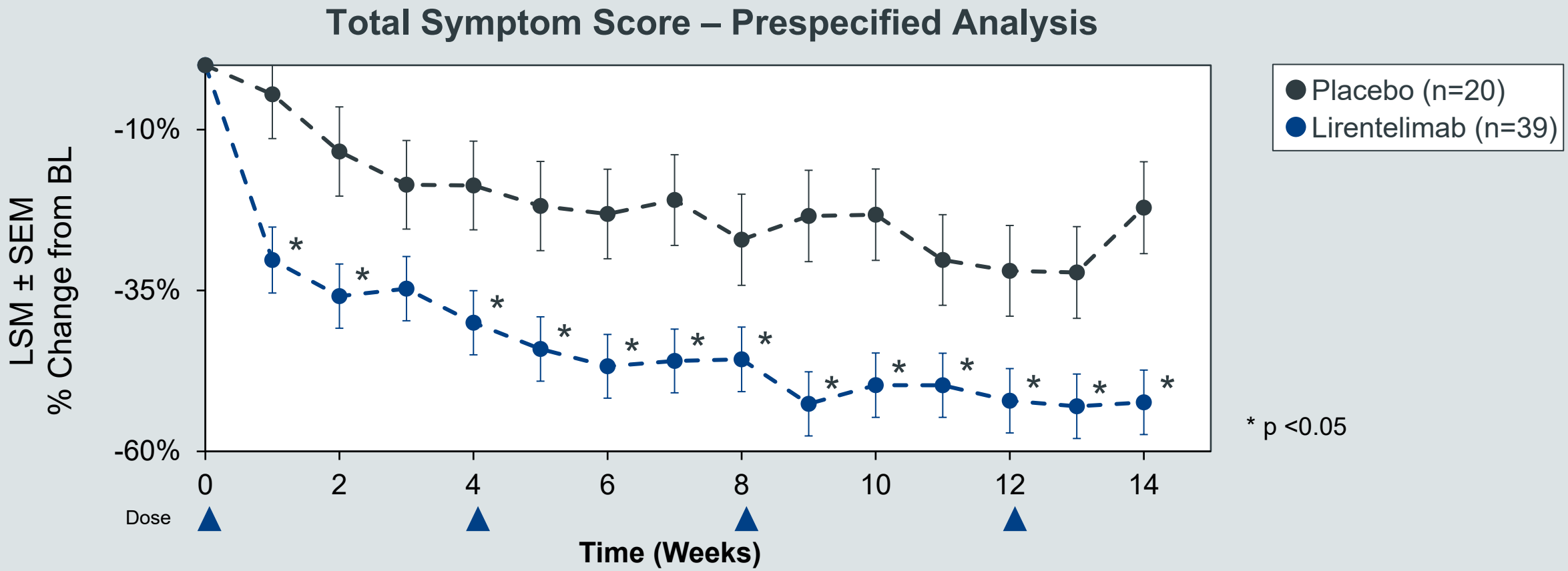
181 of 405 (45%) patients biopsied with moderate-severe unexplained GI symptoms met strict histologic criteria for EG and/or EoD

EG and/or EoD appear to be more common than previously thought, and should be considered in patients with moderate-severe unexplained GI symptoms

Patients with moderate-severe unexplained GI symptoms are currently not well managed, likely because no approved therapies target cellular drivers of disease

Diagnosis of EG/EoD could lead to targeted therapies addressing pathogenic drivers of symptoms and disease

ENIGMA: Changes in Total Symptom Score



In ENIGMA, patients with EG and/or EoD had a meaningful response to lirentelimab, which continued to improve in an open-label extension

SOURCE: Dellon ES, et al. New England Journal of Medicine. 2020;383:1624-34.

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