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Intraepithelial Mast Cells are Elevated in Active Eosinophilic Esophagitis and Correlate with Eosinophils: Baseline Data from a Randomized Controlled Trial of Barzolvolimab

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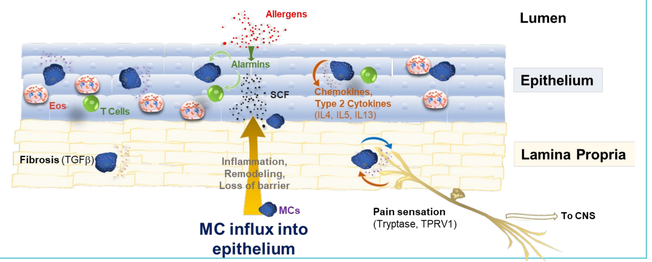
INTRODUCTION

- Mast cells (MCs) have been implicated in the pathogenesis of eosinophilic esophagitis (EoE). MC numbers are increased and activated in the esophageal epithelium of EoE biopsy specimens [1-11], are important sources of inflammatory cytokines[2,9] and are associated with disease features of EoE including histological abnormalities and pain [5,7,12,13,15].
- MCs persist in patients who are refractory to topical corticosteroid therapy, even when eosinophils regress[13].
- We hypothesized that barzolvolimab, a monoclonal antibody (mAb) against c-KIT previously shown to deplete cutaneous MCs [17], would deplete esophageal MCs and lead to clinical improvement in EoE.
- We present the design, baseline characteristics, and baseline peak esophageal epithelial MC count (PMC) and eosinophil (Eos) count (PEC) from an ongoing, fully-enrolled Phase 2 trial.



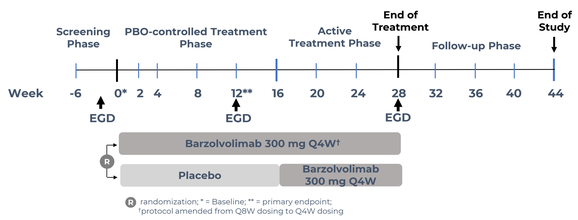
METHODS AND STUDY SCHEMA

Clinical Trial Design:

- The "EvolvE" study is a 28-week, Phase 2 randomized, double-blind, placebo controlled clinical trial of barzolvolimab (NCT05774184)
- 300 mg of barzolvolimab or matching placebo is administered subcutaneously every 4 or 8 weeks in 86 randomized participants with known EoE.
- Eligible participants have at least 15 Eos/high power field (hpf) in 2 of 3 segments of the esophagus and at least 4 dysphagia days in the 2 weeks prior to baseline (dysphagia symptom questionnaire [DSQ] score ≥ 8).
- The primary endpoint of this study is reduction in the PMC at 12 weeks, with key secondary endpoints of reduction in PEC and reduction in DSQ at 12 weeks.

Baseline histological measurements:

- Pinch biopsies from 151 screened participants were obtained by esophagogastroduodenoscopy (EGD) at screening from three different esophageal segments (proximal, middle, distal).
- PEC was assessed by hematoxylin and eosin (H&E) staining, and MCs were enumerated separately by tryptase and CD117 immunohistochemistry (IHC), using a central pathology laboratory.
- PMC and PEC correlations overall and by esophageal level were determined by Pearson analysis.



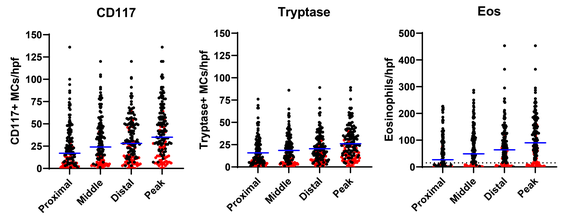
RESULTS

Demographics and Baseline Characteristics

Randomized participants, n	86
Age, years	40 (18-65)
Male, n (%)	47 (55)
BMI	29 (17-55)
EoE duration, years	6 (0.3-20)
DSQ score	37 (20-64)
Total EREFS	7.7 (0-14)
Proximal EREFS	3.4 (0-7)
Distal EREFS	4.3 (0-8)
Prior swallowed TCS, n (%)	38 (44)
Prior esophageal dilation, n (%)	45 (52)

BMI = body mass index
DSQ = dysphagia symptom questionnaire
EREFS = endoscopic reference score
TCS = topical corticosteroids
Data shown are mean (range) unless otherwise specified and for randomized participants only

Increased Number of Intraepithelial MCs in Screened Participants



Histological screen pass (N=104)*
Histological screen fail (N=47)
* 86 of 104 were randomized. 18 additional screen failures were due to other inclusion/exclusion requirements.

Intraepithelial MCs (Tryptase and CD117 positive) and Eos counts per hpf from screening biopsies were enumerated by IHC and H&E staining, respectively. Similar numbers of cells are observed across the three biopsy sites, with a trend towards greater numbers in the distal esophagus. Participants who failed screening due to low Eos counts (red) also tended to have lower tryptase⁺ and CD117⁺ MC counts. Median values are shown as a blue line.

Baseline MC and Eos Counts in Histologically-Eligible Participants

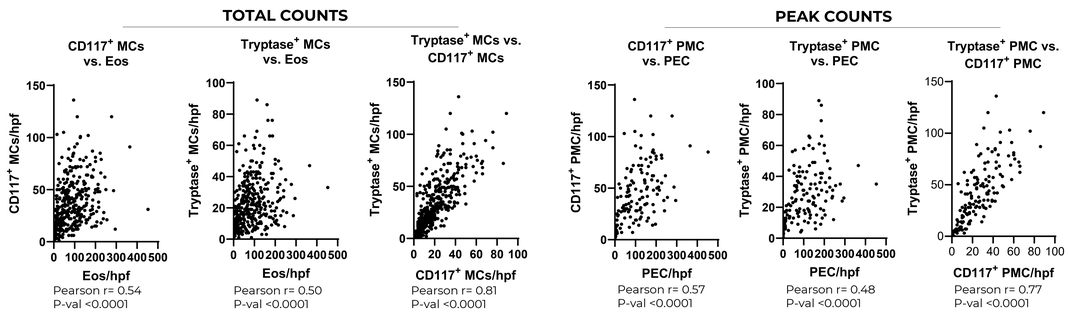
Mean (SD), range	Tryptase⁺ MCs	CD117⁺ MCs	Eosinophils
Proximal counts/hpf	**20.6** (16.3), 1-76	**31.8** (24.5), 1-136	**73.6**(61.1), 0-227
Medial counts/hpf	**24.8** (15.2), 1-86	**41.3** (24.6), 1-120	**103.0** (66.5), 2-287
Distal counts/hpf	**25.0** (16.4), 1-89	**40.6** (23.4), 3-120	**103.7** (74.0), 0-453
Peak counts/hpf	**32.6** (17.4), 4-86	**51.9** (26.7), 7-136	**140.0** (74.7), 26-365
Peak count/mm²	**130.4**	**207.7**	**560.0**

Baseline MC and Eos Counts in All Participants

Mean (SD), range	Tryptase⁺ MCs	CD117⁺ MCs	Eosinophils
Proximal counts/hpf	**15.8** (15.6), 0-76	**24.0** (23.7), 0-136	**52.2** (60.4), 0-227
Medial counts/hpf	**18.5** (15.9), 0-86	**30.6** (26.2), 0-120	**71.7** (72.2), 0-287
Distal counts/hpf	**20.4** (16.0), 0-89	**32.5** (24.4), 0-120	**76.7** (75.5), 0-453
Peak counts/hpf	**26.0** (18.1), 0-89	**40.8** (28.8), 0-136	**102.8** (85.2), 0-453
Peak count/mm²	**104**	**163.2**	**411**

Mean intraepithelial cell counts at screening with standard deviations (SD) and ranges are shown. Peak counts by hpf and mm² are presented, where 1 mm² = 4hpf.

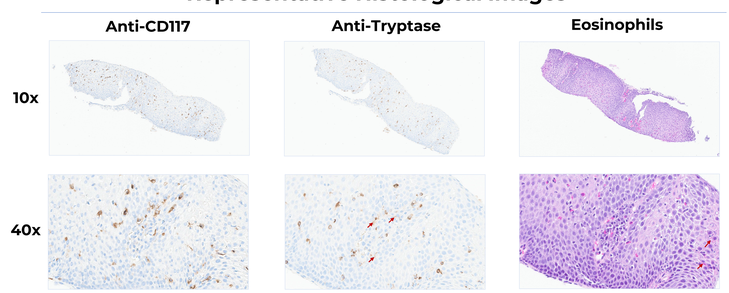
Significant Correlation between Total and Peak Intraepithelial MC and Eos Counts



Pearson correlations show a strong association between total CD117⁺ or tryptase⁺ MCs and eosinophils, as well as between CD117⁺ and tryptase⁺ MCs. Correlations include all screening biopsies – histological screen pass and fail.

Pearson correlations show a strong association between CD117⁺ or tryptase⁺ PMCs and PECs, as well as between CD117⁺ and tryptase⁺ PMCs. Correlations include all screening biopsies – histological screen pass and fail.

Representative Histological Images



Representative IHC images showing clear intraepithelial infiltration of CD117⁺ MCs (left), tryptase⁺ MCs (middle) and Eos (right) at 10x (top) and 40x (bottom) magnification. Evidence of MC and Eos degranulation is denoted by the arrows.

CONCLUSIONS

- Intraepithelial MC infiltration has been associated with EoE pathogenesis and may represent an important therapeutic target
- This ongoing Phase 2 trial is designed to test the hypothesis that the anti-KIT mAb barzolvolimab would lead to esophageal MC depletion and clinical improvement
- Screening histology data from this trial demonstrate that intraepithelial MCs are elevated in participants with active EoE and correlate with Eos counts.
- The primary analysis timepoint will be reached in 2025. Data from the analysis will be presented at a scientific meeting later in 2025.

REFERENCES

[1]Tappata et al. Allergy 2018; [2]Aceves et al., JACI 2010; [3]Abonia et al. JACI 2010; [4]Colombo et al. WJGPT 2013; [5]Dellon et al. AJG 2011; [6]Lomazi et al. Arq Gast 2017; [7]Zhang et al. JACI 2024; [8]Kleuskens et al. Muc Imm, 2023; [9] Ben-Baruch Morgenstern et al. JACI 2022; [10]Dunn et al. JACI 2020; [11]Kirsch et al. JPGN 2007; [12]Alvarado et al. Allergy 2023; [13]Bolton et al. AMJ 2020; [14]Collins et al. JPGN 2020; [15]Zhang et al. Allergy 2022; [16]Hsu Blatman et al. JACI 2011,[17] Terhorst-Molawi et al. Allergy 2023.

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