Lirentelimab (AK002) Safety and Efficacy in Patients with Higher Eosinophil Thresholds: Supplementary Analysis of Phase 2/3 EoE KRYPTOS Trial

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BACKGROUND

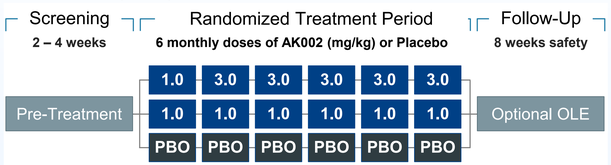
- In the KRYPTOS phase 2/3 randomized, double-blind, placebo controlled clinical trial of lirentelimab (AK002), an IgG1 Ab against Siglec-8, in EoE patients (NCT04322708), a significant histologic response was observed but the co-primary symptom endpoint was not met[1]
- Patients with higher esophageal eosinophil levels (>24/hpf) are better differentiated from other confounding conditions like GERD[2], and have more severe inflammatory disease

OBJECTIVE

- This supplementary analysis explores the effect of lirentelimab in a subpopulation of patients with EoE and baseline esophageal eos >24/hpf, a threshold previously suggested to differentiate EoE from a cofounding condition like GERD

METHODS

- Multi-center, randomized, double-blinded, placebo-controlled
- Key inclusion criteria:
  - Male or female aged ≥12 and ≤80 years old
  - Biopsy confirmed EoE: ≥15 eos/high power field (hpf) in 1 hpf in esophagus
  - Active moderate to severe symptoms: Dysphagia Symptom Questionnaire (DSQ) score ≥12
- Key exclusion criteria:
  - Causes of esophageal eosinophilia other than EoE or one the following: hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, or peripheral blood absolute eosinophil count >1500 eosinophils/μL
  - History of inflammatory bowel disease, celiac disease, achalasia, and/or esophageal surgery
- 276 adult patients dosed (1:1:1 randomization)
  - High dose (HD) IV lirentelimab (n=91)
  - Low dose (LD) IV lirentelimab (n=93)
  - Placebo (n=92)



- Primary Objectives:
  - Histologic Co-Primary Endpoint: Proportion of tissue eosinophil responders (≤6 eos/hpf in peak esophageal hpf)
  - Symptom Co-Primary Endpoint: Absolute change in Dysphagia Symptom Questionnaire (DSQ) score
- Key Secondary Objectives:
  - Safety and tolerability
  - Proportion of treatment responders who achieved peak tissue eos count ≤6 eos/hpf AND >30% improvement in DSQ
  - Proportion of patients achieving peak tissue esophageal eos count ≤1 and <15 eos/hpf

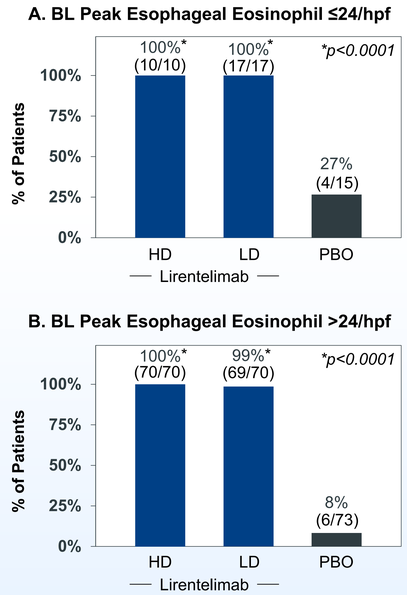
RESULTS

Table 1. Baseline Characteristics by Peak Eos

Patient Characteristics	Peak Esophageal Eosinophils ≤24/hpf			Peak Esophageal Eosinophils >24/hpf		
	HD n=14	LD n=18	PBO n=16	HD n=77	LD n=75	PBO n=76
Age, median years (range)	35.5 (15 - 67)	33.5 (15 - 67)	43.5 (20 - 68)	29 (12 - 69)	34 (12 - 67)	30 (12 - 70)
Female sex, n (%)	6 (43%)	8 (44%)	6 (38%)	20 (26%)	32 (43%)	31 (41%)
History of EoE, n (%)	11 (79%)	15 (83%)	15 (94%)	70 (91%)	69 (92%)	71 (93%)
Duration of EoE, median years (range) [mean]	4 (1 - 19) [6.5]	4 (0 - 11) [5.0]	4 (0 - 12) [4.9]	4 (0 - 38) [6.3]	5 (0 - 56) [7.7]	5 (0 - 18) [5.2]
History of atopy[a], n (%)	11 (79%)	12 (67%)	9 (56%)	58 (75%)	54 (72%)	64 (84%)
History of esophageal dilatations, n (%)	2 (14%)	3 (17%)	1 (6%)	2 (3%)	3 (4%)	6 (8%)
Number of prior esophageal dilatations, mean ± SD	3 ± 1	3 ± 2	2 ± 0	2 ± 1	2 ± 1	1 ± 1
Peak esophageal eos counts/hpf mean ± SD in distal location, mean ± SD in proximal/mid location, mean ± SD	20 ± 3 15 ± 7 13 ± 9	19 ± 3 17 ± 4 7 ± 9	20 ± 3 17 ± 7 10 ± 9	66 ± 31 54 ± 32 48 ± 29	71 ± 32 59 ± 31 54 ± 37	67 ± 30 55 ± 29 46 ± 35
Peripheral blood eosinophils cells/μL, median (IQR)	310 (213-430)	175 (143-245)	220 (98-400)	300 (240-470)	300 (210-500)	380 (240-455)
Serum IgE, kU/L, median (IQR)	83 (33-348)	64 (21-168)	65 (24-140)	105 (54-349)	117 (46-314)	98 (33-255)
Baseline DSQ [0-84], mean ± SD	34 ± 10	38 ± 11	36 ± 10	34 ± 12	36 ± 12	35 ± 13

a Asthma, allergic rhinitis, atopic dermatitis and/or food allergy

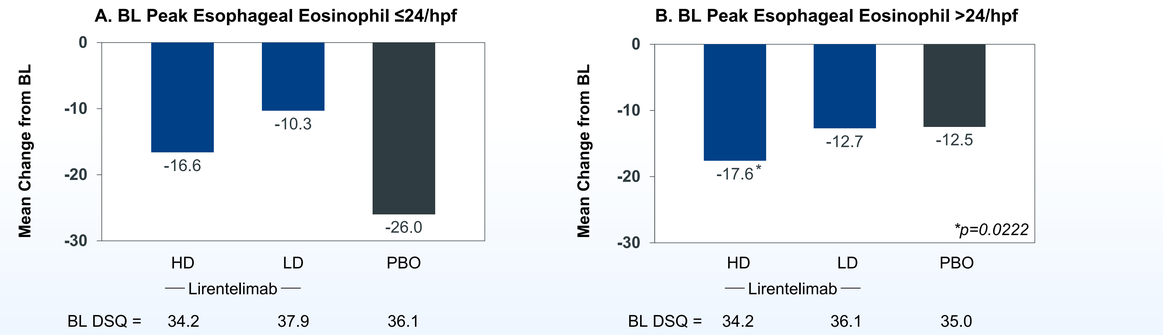
Figure 1. Proportion of Tissue Eosinophil Responders[a] by Baseline Peak Eosinophil Count



Lirentelimab achieved histologic co-primary endpoint regardless of baseline peak eosinophil count

a Tissue eosinophil responders defined as those who achieved ≤6 eos/hpf in peak esophageal hpf. Observed data

Figure 2. Change in DSQ at Weeks 23-24 by Baseline Eosinophil Counts



Among those with BL esophageal eos count >24/hpf, patients on lirentelimab had significant symptom improvement vs. patients on placebo

* HD lirentelimab from placebo p-values derived from MMRM model

Figure 3. Percent Change in DSQ at Weeks 23-24 by Baseline Eosinophil Counts

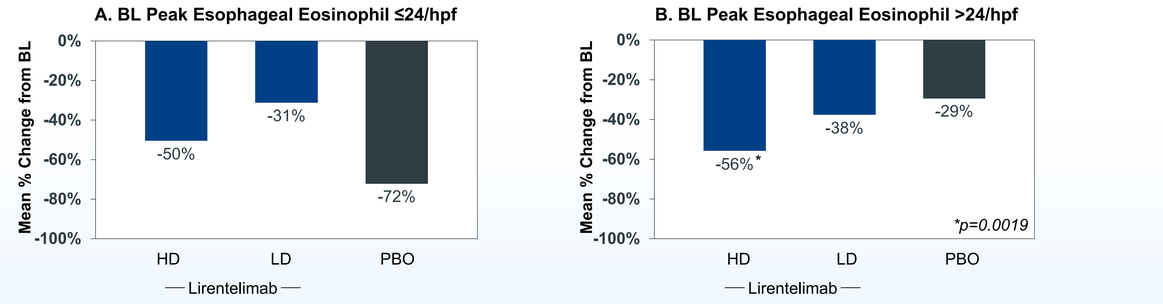


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Table 3. KRYPTOS Safety Summary

Treatment-Emergent Adverse Events (TEAEs) in ≥5% of Patients

n (%) of Patients	HD Lirentelimab (n=91)	LD Lirentelimab (n=93)	PBO (n=92)
≥1 Treatment-Emergent Adverse Event (TEAE)	61 (67.0%)	65 (69.9%)	53 (57.6%)
Infusion related reaction	35 (38.5%)	24 (25.8%)	11 (12.0%)
Headache	6 (6.6%)	8 (8.6%)	6 (6.5%)

- Drug-related Serious AEs: 2 patients on on High Dose lirentelimab[a], 1 patient on placebo[b]
- Safety risk profile overall was consistent with previously reported safety profile in ENIGMA1 and other lirentelimab studies to date

a HD lirentelimab: Patient 1 with moderate severity IRR post dose 1, occurred over 2 days then recovered; Patient 2 with two moderate severity IRRs post dose 1 and 2, recovered from each within the same day.
b Placebo SAE: Patient with moderate severity angioedema, lasted 2 days then recovered.

CONCLUSIONS/DISCUSSION

- Supplementary analysis of the KRYPTOS phase 2/3 EoE trial revealed that patients with BL esophageal eos counts >24/hpf had a decrease in DSQ with lirentelimab compared to placebo
- Lirentelimab was of greater benefit for patients with eos >24/hpf, suggesting that this population included potentially more severe EoE or fewer confounding esophageal conditions
- The safety profile of lirentelimab was consistent with previous reports with the majority of TEAEs being mild to moderate IRRs
- Further study is warranted to identify patients with EoE who may be more likely to respond to treatment with lirentelimab

Reference: (1) ACG 2022 Poster #D0201, Dellon et al.; (2) Rothenberg ME. J Allergy Clin Immunol 2001;108:891-4.

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