

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 met¹
- Patients with higher esophageal eosinophil levels (>24/hpf) are better differentiated from other confounding conditions like GERD², 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)

Screening 2-4 weeks | Randomized Treatment Period 6 monthly doses of AK002 (mg/kg) or Placebo | Follow-Up 8 weeks safety



- 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

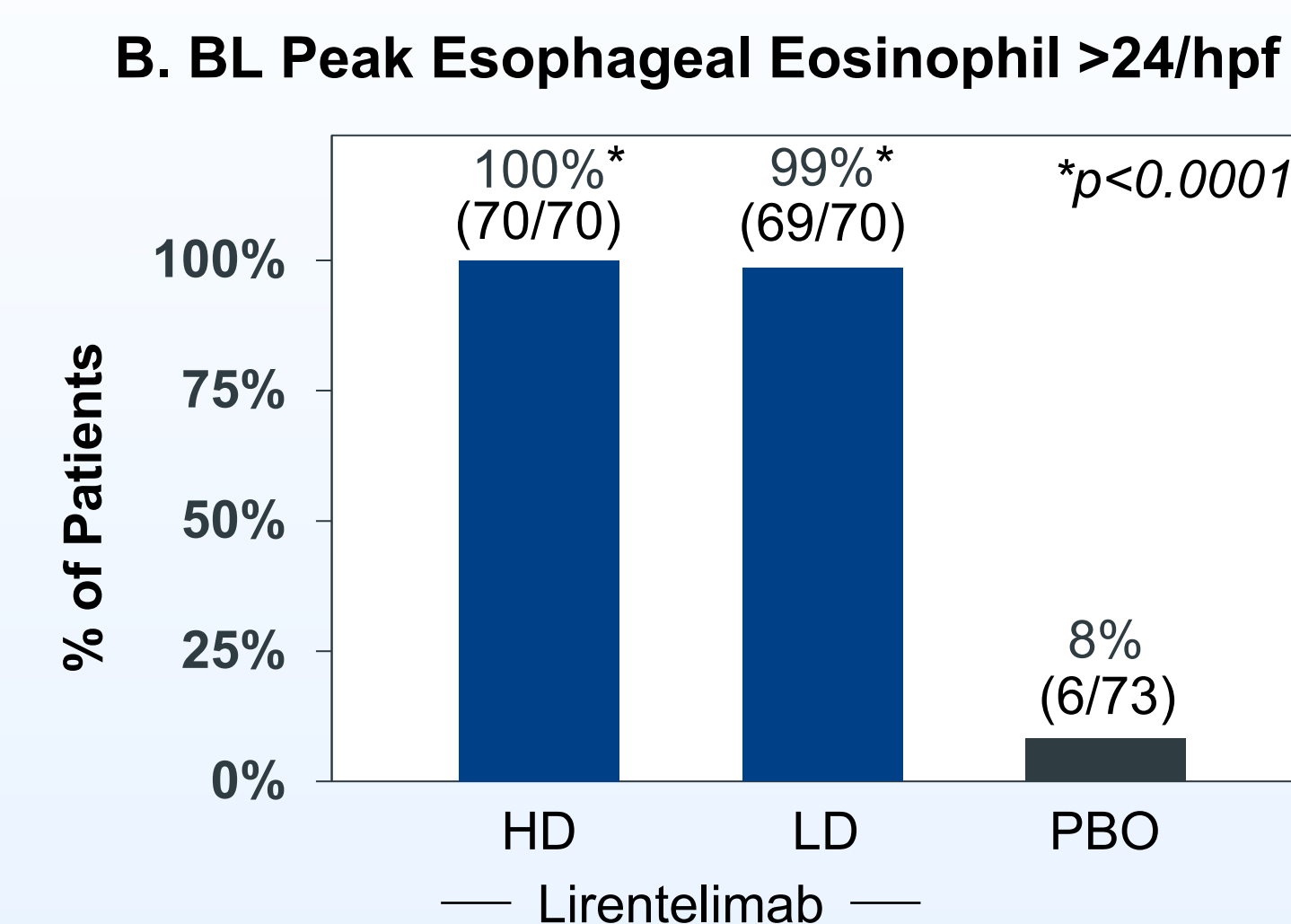
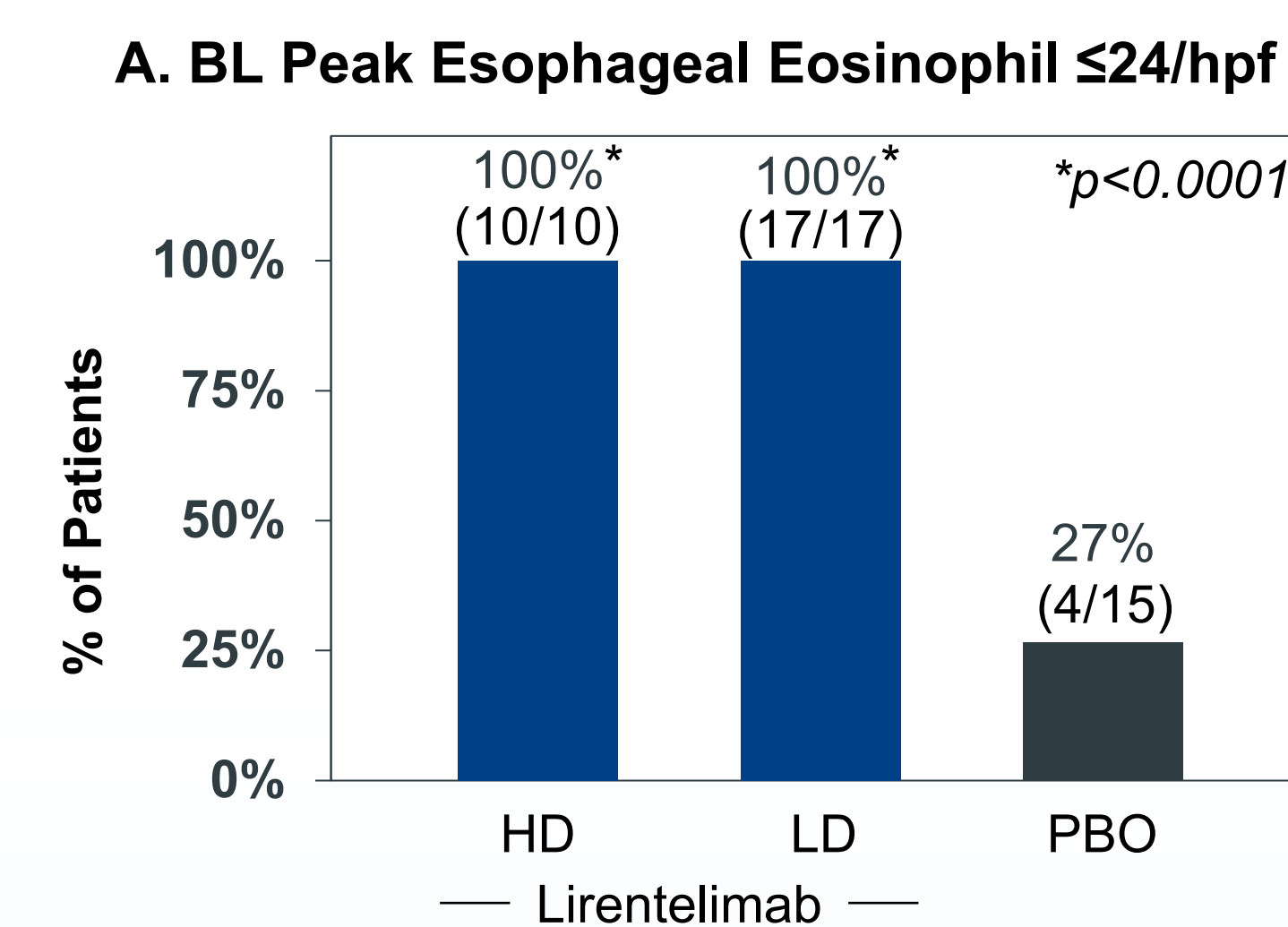
RESULTS

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	20 ± 3	19 ± 3	20 ± 3	66 ± 31	71 ± 32	67 ± 30
in distal location, mean ± SD	15 ± 7	17 ± 4	17 ± 7	54 ± 32	59 ± 31	55 ± 29
in proximal/mid location, mean ± SD	13 ± 9	7 ± 9	10 ± 9	48 ± 29	54 ± 37	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

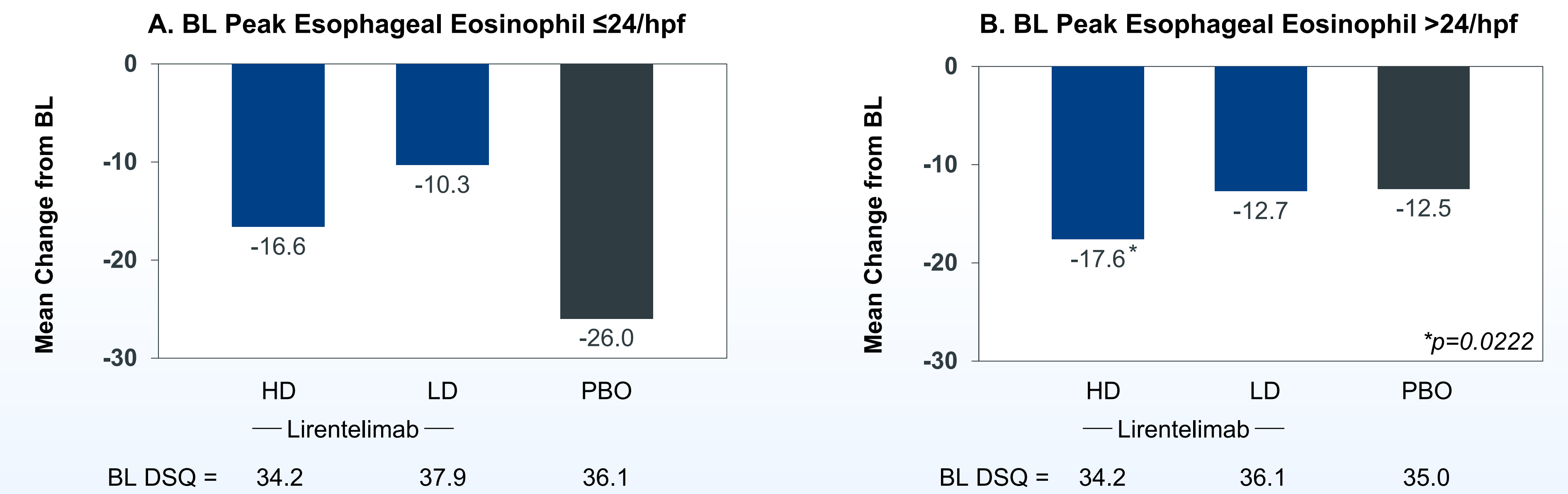
Figure 1. Proportion of Tissue Eosinophil Responders^a by Baseline Peak Eosinophil Count



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

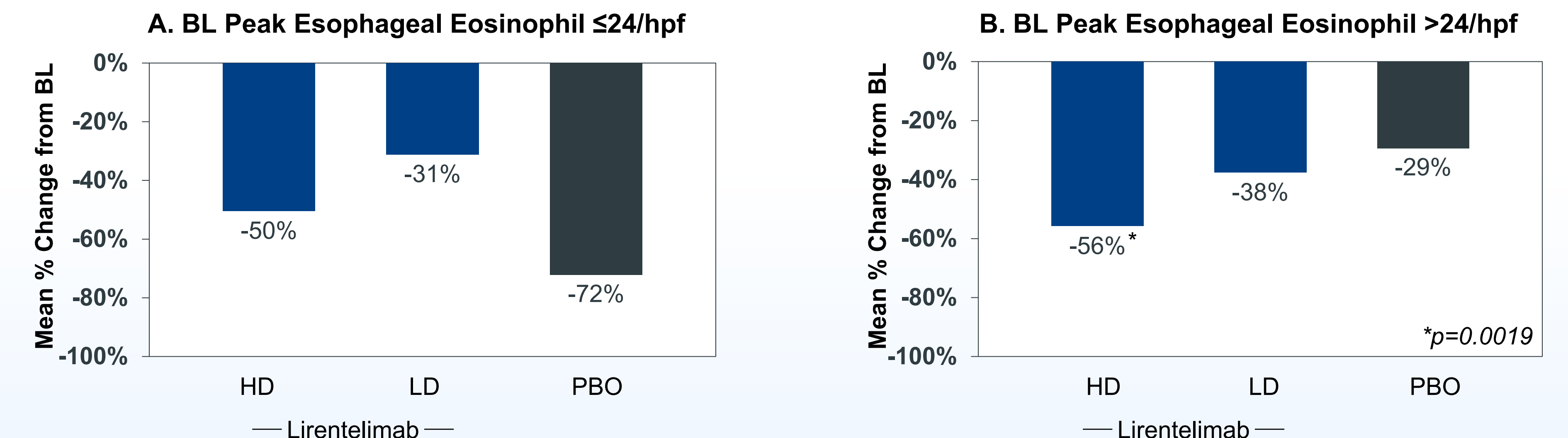
Figure 2. Change in DSQ at Weeks 23-24 by Baseline Eosinophil Counts



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



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

Table 3. KRYPTOS Safety Summary

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