Results from KRYPTOS, a Phase 2/3 Study of Lirentelimab (AK002) in Adults and Adolescents with EoE

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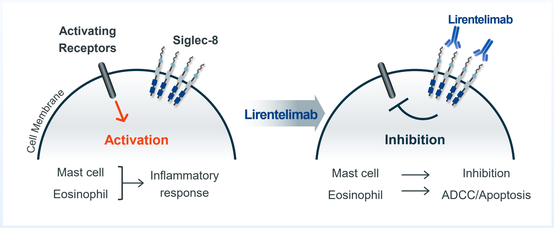
BACKGROUND

- Currently, EoE is managed with dietary elimination, proton pump inhibitors, topical or systemic steroids and/or a recently approved biologic, dupilumab®[1]
- Given the chronic, progressive nature of the disease, new and targeted treatment options are needed
- Lirentelimab (AK002) is a humanized IgG1 mAb directed against Siglec-8, which is expressed selectively on the surface of mature eosinophils and mast cells[2-3]

Figure 1. Mechanism of Action of Lirentelimab (AK002)



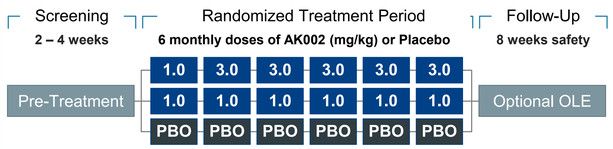
OBJECTIVE

- The aim of this randomized, double-blind, placebo-controlled phase 2/3 clinical trial was to evaluate the safety and efficacy of lirentelimab (AK002) in adults and adolescents with active EoE (NCT04322708, "KRYPTOS")

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) lirentelimab (n=91)
  - Low dose (LD) lirentelimab (n=93)
  - Placebo (n=92)
- 6 monthly IV doses and optional open-label extension (OLE)

Figure 2. KRYPTOS Study Design



Primary Objective:

- **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 eosinophil count ≤1 and <15 eos/hpf

RESULTS

Table 1. Baseline Characteristics

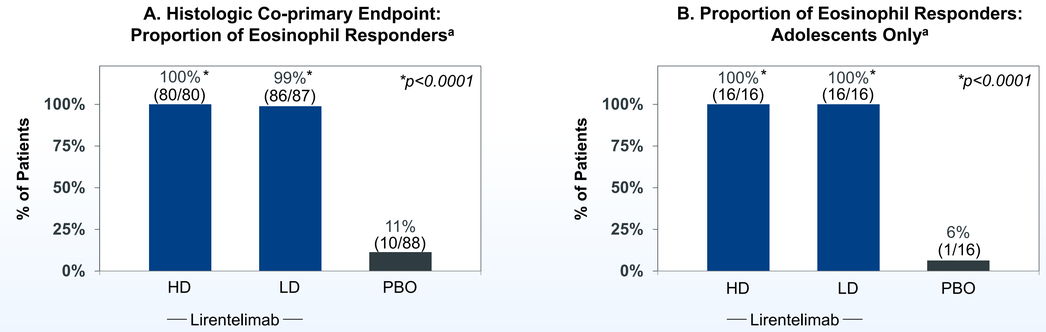
Patient Characteristics	HD Lirentelimab (n=91)	LD Lirentelimab (n=93)	PBO (n=92)
Age, median years (range)	29 (12 - 69)	34 (12 - 67)	32 (12 - 70)
Female sex, n (%)	26 (29%)	40 (43%)	37 (40%)
History of EoE, n (%)	81 (89%)	84 (90%)	86 (93%)
Duration of EoE, median years (range)	4 (0 - 38)	5 (0 - 56)	4 (0 - 18)
History of atopy[a], n (%)	69 (76%)	66 (71%)	73 (79%)
History of esophageal dilatations, n (%)	4 (4%)	6 (6%)	7 (8%)
Number of prior esophageal dilatations, mean ± SD	2.3 ± 1.3	2.3 ± 1.5	1.4 ± 0.5
Peak esophageal eosinophil counts/hpf, mean ± SD	59 ± 33	61 ± 35	59 ± 33
Peripheral blood eosinophils cells/μL, median (IQR)	300 (230 - 470)	270 (180 - 440)	350 (200 - 435)
Serum IgE, kU/L, median (IQR)	103 (53 - 349)	99 (39 - 283)	90 (29 - 241)
Baseline DSQ [0-84], mean ± SD	34 ± 12	36 ± 12	35 ± 12

Table 2. Baseline Characteristics by Age

Patient Characteristics	Overall (n=276)	Adults (n=225)	Adolescents (n=51)
Age, median years (range)	32 (12 - 70)	36 (18 - 70)	14 (12 - 17)
Female sex, n (%)	103 (37%)	92 (41%)	11 (22%)
History of EoE, n (%)	251 (91%)	202 (90%)	49 (96%)
History of atopy[a], n (%)	208 (75%)	163 (72%)	45 (88%)
History of esophageal dilatations, n (%)	17 (6%)	17 (8%)	0 (0%)
Food elimination diet at screening, n (%)	30 (11%)	18 (8%)	12 (24%)
Prior Treatments[b]			
PPI use, n (%)	191 (69%)	143 (64%)	48 (94%)
Swallowed topical corticosteroid use, n (%)	71 (26%)	45 (20%)	26 (51%)
Peak esophageal eosinophil counts/hpf, mean ± SD	60 ± 34	58 ± 34	68 ± 32
Peripheral blood eosinophils cells/μL, median (IQR)	300 (210 - 460)	290 (200 - 430)	395 (253 - 635)
Serum IgE, kU/L, median (IQR)	96 (39 - 275)	83 (32 - 241)	213 (98 - 535)
Baseline DSQ [0-84], mean ± SD	35 ± 12	35 ± 12	35 ± 13

a Asthma, allergic rhinitis, atopic dermatitis and/or food allergy
b Adolescent prior treatment data were collected from chart reviews

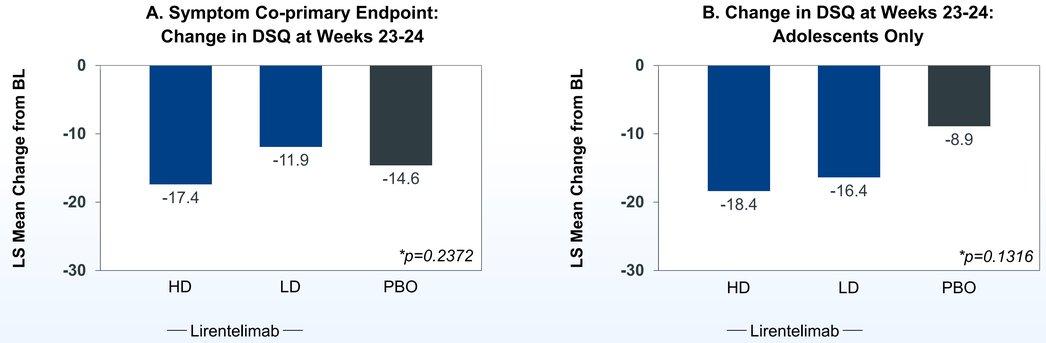
Figure 3. Proportion of Histologic Responders in Overall and Adolescents



Lirentelimab achieved histologic co-primary endpoint in all age groups

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

Figure 4. Change in DSQ at Weeks 23-24 in Overall and Adolescents



Lirentelimab did not meet the symptom co-primary endpoint, however among adolescents, patients on lirentelimab had greater symptom improvement compared to patients on placebo

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

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

- The KRYPTOS Phase 2/3 trial met the histologic co-primary endpoint, although it did not meet the DSQ patient-reported outcome symptom endpoint
- The study included a broad range of EoE patients where some patients may not have been ideal for biologic therapy
- In the adolescent sub-group, lirentelimab activity was observed by a decrease in symptoms compared to placebo
- The safety profile of lirentelimab was consistent with previous reports, with the majority of TEAEs being mild to moderate IRRs; Lirentelimab was well-tolerated in both adults and adolescents with EoE

Reference: (1) Regeneron press release May 20, 2022; (2) Youngblood, BA, et al. Int Arch Allergy Immunol 2019; (3) Youngblood BA, et al. Cells 2021.

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