Histologic and Symptomatic Improvement Across Multiple Forms of Eosinophilic Gastrointestinal Diseases in ENIGMA, a Randomized, Double-Blind, Placebo-Controlled Trial of Antolimab (AK002) (ENIGMA; NCT03496571)

Evan S. Dellon MD MPH\(^1\), Kathryn A. Peterson MD\(^2\), Joseph A. Murray MD\(^3\), Gary W. Falk MD\(^4\), Nirmala Gonsalves MD\(^5\), Mirna Chehade MD MPH\(^6\), John Leung MD\(^7\), Robert M. Genta MD\(^8\), Marc E. Rothenberg MD PhD\(^9\), Paneez Khoury MD MHS\(^c\)\(^10\), Adam C. Bledsoe MD\(^3\), Sandy R. Durrani MD\(^8\), Camilla Shaw NP\(^11\), Bhupinder Singh MD\(^11\), Alan T. Chang\(^11\), Amol P. Kamboj MD\(^11\), Henrik S. Rasmussen MD PhD\(^11\), Ikuo Hirano MD\(^5\)

\(^1\)University of North Carolina, Chapel Hill, NC; \(^2\)University of Utah, Salt Lake City, UT; \(^3\)Mayo Clinic Rochester, Rochester, MN; \(^4\)University of Pennsylvania, Philadelphia, PA; \(^5\)Northwestern University, Chicago, IL; \(^6\)Icahn School of Medicine at Mount Sinai, New York, NY; \(^7\)Tufts University, Boston, MA; \(^8\)Baylor College of Medicine, Houston, TX; \(^9\)Cincinnati Children’s Hospital, Cincinnati, OH; \(^10\)NIH/NIH, Bethesda, MD; \(^11\)Allakos, Inc., Redwood City, CA.

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Disclosures

• Dr. Evan Dellon is a principal investigator in the ENIGMA study

• Antolimab (AK002) is an investigational drug candidate and is not FDA/EMA approved
Eosinophilic Gastrointestinal Diseases (EGIDs)

- **Eosinophilic Gastritis (EG)**
- **Eosinophilic Esophagitis (EoE)**
- **Eosinophilic Duodenitis (EoD)**

**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:
Antolimab (AK002) Targets Siglec-8 on Eosinophils and Mast Cells

**Activation**
- Mast cell
- Eosinophil

**Inflammatory response**

**Inhibition**
- Mast cell
- Eosinophil
- ADCC/Apoptosis

**Antolimab**
- Targets Siglec-8 on Eosinophils and Mast Cells
- Activation
- Inhibition
- ADCC/Apoptosis
ENIGMA Phase 2 Study Aim and Inclusion

Study Aim
• Determine safety and efficacy of antolimab (AK002) for treatment of EG and/or EoD

Key Inclusion Criteria
• Active moderate to severe symptoms\(^1\) using the daily 8 symptom EG/EoD Questionnaire\(^2\)
• Biopsy confirmed
  - Stomach: ≥30 eos/hpf in 5 hpfs, and/or
  - Duodenum: ≥30 eos/hpf in 3 hpfs

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\(^1\) PRO entry criteria: average weekly score of ≥3 for either abdominal pain, diarrhea and/or nausea over ≥2 weeks

\(^2\) Questionnaire copyright unknown, please cite the source.
ENIGMA Phase 2 Study Design

Screening
2-4 Weeks

EGD w/ Biopsy (Baseline)

TSS Baseline

Treatment
12 Weeks

Dose Day 1
Dose Day 29
Dose Day 57
Dose Day 85
EGD w/ Biopsy Day 99

TSS End of Treatment 2 Weeks Post-Last Dose

Follow-Up
8 Weeks

Last ENIGMA Visit if Entering OLE Day 113
Last ENIGMA Visit if No OLE Day 141

EG/EoD

Antolimab High Dose (N=21)
0.3 → 1.0 → 3.0 → 3.0 mg/kg

Antolimab Low Dose (N=22)
0.3 → 1.0 → 1.0 → 1.0 mg/kg

Placebo (N=22)
Symptoms Assessed Using a PRO Questionnaire

**EG/EoD Questionnaire®**

- Developed in accordance with FDA guidance on PRO development
- 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
- Patients with concomitant eosinophilic esophagitis received a daily question to report severity of dysphagia on a scale of 0-10
Endpoints

Primary Endpoint
• Mean percent change in gastrointestinal eosinophil counts from baseline

Responder Secondary Endpoint
• Proportion of patients who have >75% decrease in tissue eosinophils
  AND >30% benefit in Total Symptom Score (TSS)

Symptoms Secondary Endpoint
• Mean percent change in TSS from baseline

Post-hoc analysis: histologic and symptomatic (TSS) changes in EG/EoD subgroups
• Proportion of patients with tissue eosinophils below threshold;
  ≤4 (stomach) and/or ≤15 (duodenum)
• Mean percent change in TSS from baseline
## Baseline Characteristics of EG/EoD Patients

<table>
<thead>
<tr>
<th>antolimab (AK002) Dose Groups</th>
<th>Placebo (n=20)</th>
<th>Total (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong> 0.3-3.0 mg/kg (n=20)</td>
<td>40 (18-67)</td>
<td>41 (18-74)</td>
</tr>
<tr>
<td><strong>Low</strong> 0.3-1.0 mg/kg (n=19)</td>
<td>42 (18-74)</td>
<td>42 (18-74)</td>
</tr>
<tr>
<td><strong>Combined</strong> High/Low (n=39)</td>
<td>42 (18-74)</td>
<td>42 (18-74)</td>
</tr>
</tbody>
</table>

### Age, Mean (Range)

<table>
<thead>
<tr>
<th></th>
<th>antolimab (AK002)</th>
<th>Placebo (n=20)</th>
<th>Total (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean (Range)</td>
<td>42 (20-67)</td>
<td>43 (18-74)</td>
<td>41 (18-74)</td>
</tr>
</tbody>
</table>

### Female

<table>
<thead>
<tr>
<th></th>
<th>antolimab (AK002)</th>
<th>Placebo (n=20)</th>
<th>Total (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>60%</td>
<td>84%</td>
<td>64%</td>
</tr>
</tbody>
</table>

### White

<table>
<thead>
<tr>
<th></th>
<th>antolimab (AK002)</th>
<th>Placebo (n=20)</th>
<th>Total (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>85%</td>
<td>95%</td>
<td>93%</td>
</tr>
</tbody>
</table>

### Mean Gastrointestinal\(^1\) Eosinophils/hpf

<table>
<thead>
<tr>
<th></th>
<th>antolimab (AK002)</th>
<th>Placebo (n=20)</th>
<th>Total (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Gastrointestinal(^1) Eosinophils/hpf</td>
<td>76</td>
<td>80</td>
<td>77</td>
</tr>
</tbody>
</table>

### Mean Gastrointestinal\(^1\) Mast Cells/hpf

<table>
<thead>
<tr>
<th></th>
<th>antolimab (AK002)</th>
<th>Placebo (n=20)</th>
<th>Total (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Gastrointestinal(^1) Mast Cells/hpf</td>
<td>59</td>
<td>70</td>
<td>62</td>
</tr>
</tbody>
</table>

### Mean Total Symptom Score (TSS) [0-80]

<table>
<thead>
<tr>
<th></th>
<th>antolimab (AK002)</th>
<th>Placebo (n=20)</th>
<th>Total (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Total Symptom Score (TSS) [0-80]</td>
<td>34.1</td>
<td>34.7</td>
<td>32.9</td>
</tr>
</tbody>
</table>

### % of Patients (n) by AEC\(^2/\mu L\)

<table>
<thead>
<tr>
<th></th>
<th>antolimab (AK002)</th>
<th>Placebo (n=20)</th>
<th>Total (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;250</td>
<td>45% (9)</td>
<td>26% (5)</td>
<td>39% (23)</td>
</tr>
<tr>
<td>250 to &lt;500</td>
<td>35% (7)</td>
<td>42% (8)</td>
<td>31% (18)</td>
</tr>
<tr>
<td>500 to &lt;1500</td>
<td>20% (4)</td>
<td>21% (4)</td>
<td>25% (15)</td>
</tr>
<tr>
<td>≥1500</td>
<td>0%</td>
<td>11% (2)</td>
<td>5% (3)</td>
</tr>
</tbody>
</table>

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1. Efficacy population; one patient withdrew after the 1st OLE dose with no qualifying weeks with symptom scores
2. Gastrointestinal; Gastric or duodenum site with highest eosinophil or mast cell counts
3. AEC: Absolute Eosinophil Count
## Antolimab Met ENIGMA
### Primary and Secondary Endpoints

<table>
<thead>
<tr>
<th>Prespecified Endpoints</th>
<th>Antolimab Dose Groups</th>
<th>Placebo (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High (n=20)</td>
<td>Low (n=19)</td>
</tr>
<tr>
<td><strong>1° - Tissue Eosinophils</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Baseline</td>
<td>76</td>
</tr>
<tr>
<td>% Δ</td>
<td>-97%</td>
<td>-92%</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>2° - Treatment Responders</strong>&lt;sup&gt;2&lt;/sup&gt; (Eos Δ &gt;-75% &amp; TSS Δ &gt;-30%)</td>
<td>%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.0009</td>
</tr>
<tr>
<td><strong>2° - Total Symptom Score</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Baseline</td>
<td>34</td>
</tr>
<tr>
<td>% Δ</td>
<td>-58%</td>
<td>-49%</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0012</td>
<td>0.0150</td>
</tr>
</tbody>
</table>

<sup>1</sup> Average count of the highest readings from the Day 99/End of study biopsy that correspond in location to the location with the highest average count at baseline.
Improvement Across All Symptoms on Antolimab

EG/EoD-PRO Symptom Score
Antolimab (n=39)

- Abdominal Pain: -59%
- Nausea: -79%
- Vomiting: -65%
- Early Satiety: -61%
- Loss of Appetite: -57%
- Abdominal Cramping: -47%
- Bloating: -55%
- Diarrhea: -100%
ENIGMA Patient Distribution

- Entered Screening: N=113
  - Met Symptom Criteria: n=88
    - ≥30 Eos/hpf: n=65
      - Eosinophilic Gastritis: n=10 (15%)
      - Eosinophilic Duodenitis: n=25 (38%)
      - Eos. Gastritis & Duodenitis: n=30 (46%)

61% (40/65) of patients had gastric eosinophilia ( +/- duodenal eosinophilia)
85% (55/65) of patients had duodenal eosinophilia ( +/- gastric eosinophilia)
Response in Eosinophilic Gastritis (EG)¹

1 Patients with gastric eosinophilia at baseline: ≥30 eos/hpf in 5 hpfs in the stomach
Response in Eosinophilic Duodenitis (EoD)\(^1\)

### Duodenal Eos ≤ 15/hpf

- **Antolimab (n=35):** 94%\(^*\)
- **Placebo (n=15):** 7%\(^*\)

\(^*\) p <0.0001

### Severity of Symptoms (TSS)

<table>
<thead>
<tr>
<th></th>
<th>Antolimab (n=35)</th>
<th>Placebo (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean %∆ from BL</td>
<td>-54%†</td>
<td>-29%</td>
</tr>
</tbody>
</table>

\(^†\) p=0.0035

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1 Patients with duodenal eosinophilia at baseline: ≥30 eos/hpf in 3 hpf's in the stomach
1 25 patients with concomitant EoE (≥15 eos/hpf or history of EoE) and baseline dysphagia
2 Excludes patients with eos < 6/hpf at baseline. At end of treatment, 10/14 AK002 patients had 0 eos/hpf; 2/14 AK002 patients had 1 eos/hpf; 1/14 AK002 patients had 3 eos/hpf; 1/14 AK002 patients had 105 eos/hpf (biopsy occurred 6 weeks post last dose instead of 2 weeks per protocol); 1/9 placebo patients had 2 eos/hpf; 8/9 placebo patients had 19 – 200 eos/hpf
3 All EoE patients with end of treatment dysphagia scores
† p = 0.00015
Absolute Blood Eosinophil Counts

- Absolute blood eosinophil counts were collected just prior to each infusion and days 4 and 15.

**Diagram:**
- Y-axis: Eosinophils (Cells/µL) Median ± IQR
- X-axis: Time (Days) BL 4 15 29 43 57 71 85 99
- Dose: Placebo (n=22), High (n=21), Low (n=22)

**Legend:**
- Black: Placebo (n=22)
- Blue: High (n=21)
- Cyan: Low (n=22)

*Note: *Blood eosinophils collected just prior to each infusion and days 4 and 15.
Safety Summary

Treatment-Emergent AEs in ≥5% of Patients

<table>
<thead>
<tr>
<th>% of Patients, (n)</th>
<th>Antolimab (n=43)</th>
<th>Placebo (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion related reaction</td>
<td>60% (26)</td>
<td>23% (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>9% (4)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9% (4)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9% (4)</td>
<td>5% (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7% (3)</td>
<td>14% (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7% (3)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5% (2)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5% (2)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2% (1)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>2% (1)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td>2% (1)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2% (1)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2% (1)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Cough</td>
<td>0% (0)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>Influenza</td>
<td>0% (0)</td>
<td>9% (2)</td>
</tr>
<tr>
<td>White blood cell count increased</td>
<td>0% (0)</td>
<td>9% (2)</td>
</tr>
</tbody>
</table>

• Generally well tolerated
• Most common AE was mild to moderate infusion related reactions (IRR)
  – 93% mild to moderate (flushing, feeling of warmth, headache, nausea, dizziness)
  – Mostly on first infusion, greatly reduced or does not occur on subsequent infusions
  – 1 drug-related serious adverse event, an IRR which recovered within 24 hours with no further sequelae
• Treatment-emergent SAEs: 9% on AK002, 14% on Placebo
• No other significant AEs
• The ENIGMA study met all prespecified endpoints, demonstrating significant histologic and symptomatic improvement in EG and/or EoD

• Eosinophils were reduced in blood and throughout the upper gastrointestinal tract (esophagus, stomach, and duodenum)

• Generally well-tolerated

• These results build on clinical activity of antolimab (AK002) observed in chronic urticaria, severe allergic conjunctivitis, asthma, atopic dermatitis, and indolent systemic mastocytosis

• Additional antolimab studies in EGIDs:
  – Phase 3 randomized trial in EG/EoD (NCT04322604)
  – Phase 2/3 randomized trial in EoE (NCT04322708)
We thank the patients who participated in this study, investigators, and study staff