Long-term Treatment of Patients with Eosinophilic Gastritis and/or Eosinophilic Duodenitis with Lirentelimab, a Monoclonal Antibody Against Siglec-8

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#539
Disclosures

- Dr. Kathryn Peterson is an investigator in the ENIGMA study

- Lirentelimab is an investigational drug candidate and is not FDA/EMA approved

- This study is in progress. Data presented are current as of 3/3/2021
Eosinophilic Gastrointestinal Diseases (EGIDs)

Eosinophilic Gastritis (EG)

Eosinophilic Esophagitis (EoE)

Eosinophilic Duodenitis (EoD)

ESOPHAGUS

STOMACH

DUODENUM

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

Lirentelimab (AK002) Targets Siglec-8 on Eosinophils and Mast Cells

Activating Receptors

Siglec-8

Inhibiting Siglec-8

Mast cell
Eosinophil

Lirentelimab (AK002)

Activation

Inflammation response

Inhibition

Mast cell
Eosinophil

ADCC/Apoptosis

ENIGMA Phase 2 Study Summary

INCLUSION CRITERIA

- Patient-reported active moderate-to-severe symptoms per the EG/EoD Questionnaire®
  - 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
  - Symptom criteria: weekly average ≥3 to 10 for abdominal pain, nausea, or diarrhea for at least 2 weeks
- Biopsy-confirmed EG and/or EoD
  - EG: ≥30 eos/hpf in 5 hpfs (stomach)
  - EoD: ≥30 eos/hpf in 3 hpfs (duodenum)

STUDY DESIGN

- Phase 2 multi-center, randomized, double-blind, placebo-controlled study
- 65 Patients – 3 arms, 4 monthly doses
  - 21 patients 0.3, 1.0, 3.0, 3.0 mg/kg lirentelimab
  - 22 patients 0.3, 1.0, 1.0, 1.0 mg/kg lirentelimab
  - 22 patients placebo
- Primary endpoint: Mean % reduction in tissue eosinophils from baseline to day 99
- Secondary endpoints
  - % Treatment responders (>75% reduction in tissue eosinophil counts AND >30% reduction in symptoms (TSS) from baseline to 2 weeks post-last dose)
  - Mean % reduction in TSS from baseline to 2 weeks post-last dose

RANDOMIZED STUDY RESULTS

<table>
<thead>
<tr>
<th>Prespecified Endpoints</th>
<th>lirentelimab (n=39)</th>
<th>Placebo (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° - Tissue Eosinophils</td>
<td>% Δ -95%</td>
<td>+10%</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>-</td>
</tr>
<tr>
<td>2° - Treatment Responders</td>
<td>% 69%</td>
<td>5%</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0008</td>
<td>-</td>
</tr>
<tr>
<td>2° - TSS</td>
<td>% Δ -53%</td>
<td>-24%</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0012</td>
<td>-</td>
</tr>
</tbody>
</table>

- All primary and secondary endpoints met in the first randomized trial in patients with EG and EoD
- Generally well tolerated

Open-Label Extension (OLE) Study Aim & Design

- **Study Aim**
  - Determine safety and efficacy of long-term use of lirentelimab for treatment of EG and/or EoD

- **Study Design**
  - Patients who completed ENIGMA had the option to receive lirentelimab in an OLE study
  - Patients enrolled in the OLE received up to 26 monthly lirentelimab infusions, administered intravenously every 28 days, titrated up to 3.0 mg/kg
  - Patients underwent an upper endoscopy with biopsy on Days 323 (week 46) and 659 (week 94) from entering ENIGMA
• **Patient Population**
  - 58 of 59 eligible patients entered the OLE study
  - As of 3/3/2021,
    - 34 patients ongoing
      - 26 patients have completed ≥94 weeks, average ~104 weeks
      - 8 patients with <94 weeks, average ~82 weeks
    - 24 patients no longer on treatment, average of ~49 weeks
## Baseline Characteristics

### Patient Characteristics

<table>
<thead>
<tr>
<th>Description</th>
<th>Enrolled in OLE (N=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years Mean (Range)</td>
<td>41 (18-74)</td>
</tr>
<tr>
<td>Female</td>
<td>60%</td>
</tr>
<tr>
<td>White</td>
<td>93%</td>
</tr>
<tr>
<td>GI(^{a}) Eosinophil/hpf, Mean (Range)</td>
<td>74 (33-201)</td>
</tr>
<tr>
<td>GI(^{a}) Mast Cells/hpf, Mean (Range)</td>
<td>60 (20-114)</td>
</tr>
<tr>
<td>Total Symptom Score [0-80], Mean (Range)</td>
<td>32 (6-61)</td>
</tr>
<tr>
<td>% of Patients (n) by AEC(^{b})/µL</td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>69% (40)</td>
</tr>
<tr>
<td>≥500</td>
<td>31% (18)</td>
</tr>
</tbody>
</table>

\(^{a}\) Gastrointestinal; Gastric (5 hpfs) or duodenum (3 hpfs) site with highest eosinophil or mast cell counts  
\(^{b}\) AEC: Absolute Eosinophil Count
Substantial Symptom Improvement Over Time

EG/EoD-PRO Total Symptom Score (n=55)

Time on lirentelimab (Weeks)\(^a\)

% Δ from ENIGMA BL

Dose

\(^a\) Total lirentelimab exposure, inclusive of lirentelimab exposure during the Phase 2 ENIGMA study
## Change in Symptoms Over Time

<table>
<thead>
<tr>
<th>Total lirenlimab Exposure (Weeks)$^a$</th>
<th>TSS Mean Change from ENIGMA BL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>13-14 (n=55)</td>
<td>32</td>
</tr>
<tr>
<td>51-52 (n=38)</td>
<td>34</td>
</tr>
<tr>
<td>93-94 (n=25)</td>
<td>35</td>
</tr>
</tbody>
</table>

*a Total lirenlimab exposure, inclusive of lirenlimab exposure during the Phase 2 ENIGMA study*
Change in Symptom Response Rate Over Time

<table>
<thead>
<tr>
<th>Total lirentelimab Exposure (Weeks)a</th>
<th>% of Patients (n) by TSS Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥50%</td>
</tr>
<tr>
<td>13-14 (n=55)</td>
<td>58% (32/55)</td>
</tr>
<tr>
<td>51-52 (n=38)</td>
<td>74% (28/38)</td>
</tr>
<tr>
<td>93-94 (n=25)</td>
<td>84% (21/25)</td>
</tr>
</tbody>
</table>

a Total lirentelimab exposure, inclusive of lirentelimab exposure during the Phase 2 ENIGMA study
## Symptom Response Rate in Patients with ≥94 Weeks of Lirentelimab Treatment

<table>
<thead>
<tr>
<th>Weeks&lt;sup&gt;a&lt;/sup&gt;</th>
<th>≥50% Response</th>
<th>≥70% Response</th>
<th>≥90% Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-14</td>
<td>64%</td>
<td>32%</td>
<td>20%</td>
</tr>
<tr>
<td>51-52</td>
<td>68%</td>
<td>56%</td>
<td>24%</td>
</tr>
<tr>
<td>93-94</td>
<td>84%</td>
<td>64%</td>
<td>40%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Total liurentelimab exposure, inclusive of liurentelimab exposure during the Phase 2 ENIGMA study.
Abdominal Pain
Nausea
Vomiting
Early Satiety
Loss of Appetite
Abdominal Cramping
Bloating
Diarrhea

EG/EoD-PRO Symptom Score
Lirentelimab Patients with ≥94 Weeks of Treatment (n=25)

-92%
-100%
-100%
-100%
-89%
-97%
-74%
-100%

Baseline
Wks 93-94a

Median Score

-92%
-100%
-100%
-100%
-89%
-97%
-74%
-100%

Abdominal Pain
Nausea
Vomiting
Early Satiety
Loss of Appetite
Abdominal Cramping
Bloating
Diarrhea

a Total lirentelimab exposure, inclusive of lirentelimab exposure during the Phase 2 ENIGMA study.
Sustained Histologic Remission on Lirentelimab

Proportion of Patients Meeting Histologic Remission Criteria
Eosinophils ≤4/hpf (Stomach) and/or ≤15/hpf (Duodenum)\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Day 99</th>
<th>Day 323</th>
<th>Day 659</th>
</tr>
</thead>
<tbody>
<tr>
<td>lirentelimab</td>
<td>97% (35/36)</td>
<td>94% (45/48)</td>
<td>100% (29/29)</td>
</tr>
<tr>
<td>placebo</td>
<td>0% (0/19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Only patients enrolled in OLE displayed at day 99. 37/39 (95%) lirentelimab patients and 3/20 (15%) placebo patients met histologic remission criteria (predefined as <30 eos/hpf.) at the end of ENGIMA; SOURCE: Dellon ES, et al. New England Journal of Medicine. 2020;383:1624-34.
Sustained Depletion of Blood Eosinophils

- Blood eosinophils collected just prior to each infusion
- Total lirentelimab exposure, inclusive of lirentelimab exposure during the Phase 2 ENIGMA study
Safety Summary

### Treatment-Emergent AEs in >5% of Patients

<table>
<thead>
<tr>
<th>% of Patients, (n)</th>
<th>Total (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion related reaction</td>
<td>33% (19)</td>
</tr>
<tr>
<td>Headache</td>
<td>16% (9)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>16% (9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12% (7)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>10% (6)</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
<td>10% (6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10% (6)</td>
</tr>
<tr>
<td>Influenza</td>
<td>10% (6)</td>
</tr>
<tr>
<td>Rash</td>
<td>9% (5)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>9% (5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9% (5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>7% (4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7% (4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7% (4)</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>7% (4)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>7% (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7% (4)</td>
</tr>
</tbody>
</table>

- Generally well-tolerated
- Most common AE was mild to moderate infusion related reactions (IRR)
  - All were mild to moderate (flushing, feeling of warmth, headache, nausea, dizziness)
  - Mostly on first two infusions, greatly reduced or does not occur on subsequent infusions (prior to prednisone pre-treatment protocol)
  - No IRRs in 20 patients who received single-dose oral prednisone night before first infusion
- No drug-related serious AEs in OLE
• Long-term treatment with lirentelimab results in sustained histologic & symptomatic improvements in patients with EG and/or EoD through week 94
  – Sustained response of blood and tissue eosinophil depletion
  – Symptomatic responses improved with increased duration of treatment

• Long-term treatment with lirentelimab was generally well-tolerated

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