Entereg® (alvimopan) Capsules for the Management of Postoperative Ileus

Safety

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Adolor Corporation
POI Safety Presentation Outline

- Safety analysis population
- Treatment-emergent and serious AEs
- Evaluation of CV, fracture, and neoplasia AEs
- Follow-up in POI studies
Safety Presentation Analysis Populations

Clinical pharmacology studies (23)

Controlled studies

Phase II (3) 206, 213, 214

Phase III (6) 302, 306, 308, 313, 314, 001

- Patients who underwent BR or TAH
- Patients who received placebo or alvimopan 1 - 3 mg, a 6 mg, or 12 mg

a Disposition only.
# Patient Disposition

**Worldwide POI Safety Population**

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Placebo n = 1365</th>
<th>1 - 3 mg n = 62</th>
<th>6 mg n = 898</th>
<th>12 mg n = 1650</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed treatment</td>
<td>76.5</td>
<td>79.0</td>
<td>80.8</td>
<td>82.7</td>
</tr>
<tr>
<td>Discontinued from treatment</td>
<td>23.5</td>
<td>21.0</td>
<td>19.2</td>
<td>17.3</td>
</tr>
<tr>
<td>Adverse event</td>
<td>11.1</td>
<td>11.3</td>
<td>7.7</td>
<td>7.6</td>
</tr>
<tr>
<td>Other</td>
<td>12.4</td>
<td>9.7</td>
<td>11.5</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Source: ISS T A.2.1
## Treatment-emergent AEs ≥ 10% in Any Group

**Worldwide POI Safety Population**

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Patients, %</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>6 mg</td>
<td>12 mg</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>51.2</td>
<td>40.9</td>
<td>52.0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>21.9</td>
<td>16.9</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>13.0</td>
<td>8.8</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13.8</td>
<td>9.4</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10.5</td>
<td>11.1</td>
<td>10.4</td>
<td></td>
</tr>
</tbody>
</table>

* Patients with > 1 AE in same category counted only once.
<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Patients, %</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Alvimopan</td>
<td>6 mg n = 898</td>
<td>12 mg n = 1650</td>
</tr>
<tr>
<td></td>
<td>Placebo n = 1365</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative ileus</td>
<td>4.4</td>
<td>1.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Small intestinal obstruction</td>
<td>1.9</td>
<td>0.8</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Postoperative infection</td>
<td>1.4</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Postoperative abscess</td>
<td>1.1</td>
<td>1.3</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>SAEs resulting in death</td>
<td>0.7</td>
<td>0.6</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

* Patients with > 1 AE in same category counted only once.
Cardiovascular Safety of Alvimopan—POI Program

Based on numerical imbalance of MIs in the alvimopan treatment group (0.5 mg BID) in a long-term OBD Study, GSK014

- FDA requested collection of additional source documentation (eg, ECG tracings, cardiac biomarkers) for POI patients with CV events of interest (as defined by FDA)
- Objective: evaluate balance of CV AEs across treatment groups by case adjudication
CV Adverse Events of Interest Categories

- Death (all cause)
- Death from CV events
- Myocardial infarction\(^a\) (MI)
- Unstable angina
- Cerebrovascular accident\(^a\) (CVA)
- Congestive heart failure\(^a\) (CHF)
- Serious arrhythmia\(^a\)
- Cardiac arrest\(^a\)

\(^a\) Includes fatal and nonfatal events.
Incidence of CV Events of Interest
Worldwide POI Safety Population

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo n = 1365</th>
<th>Alvimopan n = 2610</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>9 (0.66)</td>
<td>13 (0.50)</td>
<td></td>
</tr>
<tr>
<td>All CV AEs of interest</td>
<td>39 (2.86)</td>
<td>50 (1.92)</td>
<td></td>
</tr>
<tr>
<td>Death from CV events</td>
<td>2 (0.15)</td>
<td>4 (0.15)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>7 (0.51)</td>
<td>13 (0.50)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>4 (0.29)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CVA</td>
<td>4 (0.29)</td>
<td>4 (0.15)</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>12 (0.88)</td>
<td>17 (0.65)</td>
<td></td>
</tr>
<tr>
<td>Serious arrhythmia</td>
<td>11 (0.81)</td>
<td>16 (0.61)</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>6 (0.44)</td>
<td>5 (0.19)</td>
<td></td>
</tr>
</tbody>
</table>

Deaths of unknown cause included in CV death category.

Favors alvimopan  Favors placebo

(04151) Source: poi-cv-safety-summary.pdf T 1.1.1; CSR T 36
Duke Clinical Research Institute
Clinical Events Committee (CEC)

- Independent, blinded adjudication of all POI CV AE cases
  - Patient-level source documentation
- CEC charter and specific event definitions
  - AHA/ACC guidelines
  - Clinical judgment
- CEC team consisted of practicing physicians specializing in cardiology or neurology
Deaths of unknown cause included in CV death category.

Patients may appear in ≥1 category.
### Estimate of MI Following Bowel Resection Using NSQIP Database

- 19,895 colectomy patients identified by CPT codes<sup>a</sup>
- 1991 - 1999
- 30-day morbidity/mortality

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>POI safety population, BR</th>
<th>DCRI adjudication results, BR</th>
<th>VA NSQIP database</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Alvimopan</td>
<td>Placebo</td>
</tr>
<tr>
<td>Patients, n</td>
<td>986</td>
<td>1681</td>
<td>986</td>
</tr>
<tr>
<td>Patients with MI, %</td>
<td>0.71</td>
<td>0.71</td>
<td>0.71</td>
</tr>
</tbody>
</table>

NSQIP = National Surgical Quality Improvement Program.

## Fracture Treatment-emergent AEs
### Worldwide POI Safety Population

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Placebo n = 1365</th>
<th>Alvimopan 6 mg n = 898</th>
<th>Alvimopan 12 mg n = 1650</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rib fracture</td>
<td>0</td>
<td>0</td>
<td>1 (&lt; 0.1)</td>
</tr>
</tbody>
</table>

This 84 year-old female patient (14CL314.39.00178) experienced a fracture of the left 4th, 5th, and 6th ribs associated with syncope and a fall on postoperative day 9 following bowel resection surgery.
# Neoplasm Treatment-emergent AEs

## Worldwide POI Safety Population

**SOC neoplasms benign, malignant, and unspecified (including cysts and polyps)**

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Preferred term</th>
<th>Placebo n = 1365</th>
<th>6 mg n = 898</th>
<th>12 mg n = 1650</th>
<th>Total n = 2610&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasm SOC TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder neoplasm</td>
<td>1 (&lt; 0.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Burkitt's lymphoma</td>
<td>1 (&lt; 0.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>1 (&lt; 0.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>0</td>
<td>1 (&lt; 0.1)</td>
<td>0</td>
<td>1 (&lt; 0.1)</td>
<td></td>
</tr>
<tr>
<td>Colon cancer metastatic</td>
<td>0</td>
<td>1 (&lt; 0.1)</td>
<td>0</td>
<td>1 (&lt; 0.1)</td>
<td></td>
</tr>
<tr>
<td>Hepatic neoplasm</td>
<td>0</td>
<td>0</td>
<td>1 (&lt; 0.1)</td>
<td>1 (&lt; 0.1)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0</td>
<td>1 (&lt; 0.1)</td>
<td>0</td>
<td>1 (&lt; 0.1)</td>
<td></td>
</tr>
<tr>
<td>Thyroid neoplasm</td>
<td>0</td>
<td>0</td>
<td>1 (&lt; 0.1)</td>
<td>1 (&lt; 0.1)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Patients with > 1 AE in same category counted only once.

<sup>b</sup> The 62 patients in the alvimopan 1 mg to 3 mg group are included in the alvimopan total.

Source: ISS T A.2.11.23
Patient Follow-up in POI Studies
Worldwide POI Safety Population (N = 3975)

- 88% had follow-up
  - 75% contacted by telephone after last dose
    - Most at 1 to 2 weeks
  - 13% had a follow-up visit (Study 306)

Study 001\textsuperscript{a}
- Visit 6 weeks following surgery (health outcomes assessment)
- 76% completed

\textsuperscript{a} In addition to telephone contact at 5 to 7 days after last dose.
Patient Follow-up in POI Studies

Worldwide POI Safety Population

- Monitoring visits through 30 days after last dose or until resolution for all patients in NA studies
  - BR patients evaluated within 2 to 4 weeks for initial postoperative visit
- Metabolite concentrations negligible or BLQ at 6 to 11 days post discharge
- Monitoring period corresponds to time of initial postoperative evaluation

BLQ = Below level of quantification.
Summary—Safety of Alvimopan for Management of POI in BR Patients

- Well tolerated
- No evidence of increased CV risk
  - Clinical safety database
  - Blinded adjudication of patient-level data
- No evidence of reversal of opioid analgesia
- Results support a favorable risk profile
Entereg® (alvimopan)
Proposed Risk Management Plan
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan—
FDA Requests

Approvable letter 3 November 2006
- “Develop a risk management plan that includes elements to
  a) communicate the possible cardiovascular risk of longer-term alvimopan exposure and
  b) minimize off-label use
- This plan could include appropriate labeling for prescribers and patients, and restriction of alvimopan use to hospital settings.”
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan

Primary goal

- Entereg will be indicated for short-term use in inpatient settings
- Entereg will not be used
  - Outside the controlled setting of a hospital
  - Beyond 7 days or 15 doses
  - In opioid-tolerant patients
  - In patients not undergoing bowel resection
POI remains a serious condition with an unmet medical need

No drugs currently approved for the management of POI

Demonstrated clinical benefit in patients undergoing BR
  - Earlier resolution of POI and shortened hospital stay (~ 1 day)
  - Reduced incidence of NG tube insertion

No preclinical or clinical evidence of risk associated with acute (≤ 7 days) use in POI
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan—Considerations for Plan Development

- Single doses of $\geq 3.0$ mg in opioid-tolerant patients provoke moderate to severe GI distress
  - Nausea/vomiting
  - Abdominal cramping
  - Diarrhea

- Physical/Chemical properties of the hot-melt gelatin capsules

- Successful experience with limited distribution agreements

- Limit distribution without creating a burdensome process on hospitals and HCPs

- Entereg should be easily available to
  - Institutions where BRs are performed
  - HCPs that manage BR patients
  - BR patients as per label
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan—Components

- Limited distribution
- Professional labeling
- Targeted education
- Focused promotion
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan—
Distribution

- Limited distribution
  - NO samples
  - Wholesalers will limit sales to acute-care hospitals
  - Wholesalers will place NDC block on retail sales (ie, Entereg will not be a listed ordering option)
  - Major pharmacy data systems alert retail pharmacists that Entereg is for hospital use only and contraindicated in opioid-tolerant patients

NDC = National Drug Code.
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan—Assessment of Limited Distribution

- Monitor and detect inappropriate distribution
  - Daily reports from wholesales tracking distribution of product to end-users
  - Tracking sales of Entereg to end-users
- Immediate corrective action, as needed
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan—Experience With Limited Distribution

- Limited distribution agreements are relatively common with specialty products
- Wholesalers will be contractually required to limit distribution to hospitals only
- Frequent review of reports
  - Unauthorized shipments identified and corrective action taken immediately with wholesalers
- Has been successfully used to ensure 99% of sales are made to intended accounts
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan—Professional Labeling

- Myocardial infarctions in OBD Study GSK014 in draft label
- Use in BR patients only
- Contraindicated in opioid-tolerant patients

ENTEREG is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking ENTEREG. Use of Entereg 12 mg in opioid-tolerant patients results in significant GI adverse effects
  - Nausea/vomiting, abdominal cramping, diarrhea
  - Information included in Warnings and Precautions
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan—Professional Labeling

- Limited to 7 days or 15 doses
- In-hospital use only
  - Reinforced by
    - Highlighting on packaging (box and each individual capsule blister)
    - Highlighted in multiple sections of label
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan—Targeted Education

All HCPs involved in care of BR patients
- Key issues
  - BR patients only
  - **Contraindicated** in opioid-tolerant patients
  - Hospital use only
    - **Not** to be taken home by patient under any circumstance
  - Limited to 7 days or 15 doses

Continuing training for HCP
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan—Focused Promotion

- Directed only to surgeons and hospital-based personnel
  - NO samples
  - Sales force visits to hospital-based outpatient pharmacy reinforcing restriction to inpatient use

- Advertisements limited to journals associated with HCPs who manage BR patients
Entereg® (alvimopan) Capsules
Proposed Risk Management Plan—Conclusion

- Limited distribution with corrective actions in the event of inappropriate distribution will restrict Entereg to acute-care hospitals
- Professional labeling and targeted education to HCPs will reinforce the appropriate use of Entereg
  - Inpatient use
  - Limited to 7 days
  - No more than 15 doses
- Result
  - Access to treatment for an unmet medical need
  - Use only in the hospital setting
Entereg® (alvimopan)
Summary
Patients Achieving GI-2 Recovery by Postsurgical Day (PSD) 5
Studies 314, 313, 308, 302—BR Only

PSD = Defined in 24-hour intervals from the end of surgery.
Fewer Patients With Prolonged Hospital Stay—DOW ≥ 7 PODs
Pooled Studies 314, 313, 308, 302—BR Only

- Overall:
  - Placebo: 34.4%
  - Alvimopan 12 mg: 18.8%

- Age < 65 yr:
  - Placebo: 30%
  - Alvimopan 12 mg: 15.3%

- Age ≥ 65 yr:
  - Placebo: 40.5%
  - Alvimopan 12 mg: 23.4%

- Age ≥ 75 yr:
  - Placebo: 52.9%
  - Alvimopan 12 mg: 29.2%

Source: ISE T 8.1, 8.6, 8.7
Reduced Need for Intervention or Change in Hospital Management
Pooled Studies 314, 313, 308, 302—BR Only

Adapted from Wolff BG, et al. JACS. 2007;204:609-616.
*p < 0.001
Hospital Readmission
Pooled Studies 314, 313, 308, 302—BR only

* $p < 0.05$

(1620) Source: ISE T 9; ISE2 T 12.1
Entereg®
Overall Summary

- No safety issues identified in POI population
- Numerical imbalances in SAEs in OBD were unprecedented and principally isolated to GSK014
- Proposed Risk Management Plan will limit the drug to the hospital setting only
- Alvimopan represents a favorable and compelling benefit/risk profile in POI
Proposed Indication

ENTEREG® (alvimopan) is indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.