Eluxadoline for the Treatment of Diarrhea-Predominant Irritable Bowel Syndrome

Results of 2 Randomized, Double-blind, Placebo-Controlled Phase III Clinical Trials of Efficacy and Safety

From Digestive Disease Week 2014
Eluxadoline for IBS-D

- Mixed mu (μ) opioid receptor agonist / delta (δ) opioid receptor antagonist
- Low systemic absorption and bioavailability
  - Low potential for drug-drug interactions
- Animal studies suggest eluxadoline should improve the diarrheal symptoms of IBS-D with limited constipation and durable analgesia
- Phase II double blind PBO-controlled dose ranging trial\(^1\)
  - 807 patients (dosing 5, 25, 100, 200 mg BID)
  - Efficacy demonstrated at 100 and 200 mg BID

Eluxadoline Phase III Studies (3001 & 3002)

Goal: To assess the efficacy and safety of eluxadoline in men and women with IBS-D

- Two randomized, double-blind, double-dummy, PBO controlled trials (3001 & 3002)
  - 556 investigators (predominantly US)
- Each study had three treatment arms
  - 75 mg bid; 100 mg bid; PBO bid (1:1:1 randomization)
Study Outlines

Trial 3001

Prescreen (≤ 1 wk)  Screening (2-3 wks)  Double-blind Treatment (52 wks)  Post-Tx (2 wks)

- Randomization (Day 1)
- Efficacy 12 wks
- Efficacy 26 wks
- End of Treatment

Trial 3002

Prescreen (≤ 1 wk)  Screening (2-3 wks)  Double-blind Treatment (26 wks)  Blinded PBO Withdrawal (4 wks)

- Randomization (Day 1)
- Efficacy 12 wks
- Efficacy 26 wks
Inclusion and Exclusion Criteria

- IBS-D as defined by Rome III
- Two week baseline
  - Bristol stool score (BSS) ≥ 5.5 (scale 1-7)
  - Worst abdominal pain (WAP\textsuperscript{1}) > 3.0 (scale 0-10)
  - Global symptom score (GSS\textsuperscript{2}) ≥ 2.0 (scale 0-4)

Additional requirements:
- Diary compliance
- No rescue medications during baseline

Key Exclusions (medical history):
- Prior pancreatitis, alcohol abuse, cholecystitis past 6 mo, Sphincter of Oddi dysfunction, IBD, intestinal obstruction, GI infection or diverticulitis within 3 mo,
- Lipase >2x ULN; ALT or AST >3x ULN

\textsuperscript{1}WAP=Worst abdominal pain in past 24 hrs
\textsuperscript{2}GSS: 0 = no sx and 4 indicates very severe symptoms
Primary Composite Endpoints

- To be a responder a patient MUST meet BOTH responder criteria on ≥ 50% of days:
  - **Daily pain responder:** Worst abdominal pain (WAP) scores in the past 24 hours improved by ≥ 30% compared to average baseline pain
  - **Daily stool consistency responder:** Bristol Stool Score (BSS) score <5

- FDA 1° endpoint: weeks 1-12
- EMA 1° endpoint: weeks 1-26

1 In absence of a BM, if accompanied by ≥ 30% improvement in WAP compared to avg baseline pain
2 Subject must enter a minimum of 60 days of diary data to be a responder
3 Subject must enter a minimum of 110 days of diary data to be a responder
4 For primary endpoints, multiplicity adjustment for 2 doses (P < 0.025)
## Enrollment and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>3001 (mean (SD))</th>
<th>3002 (mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screened</strong></td>
<td>2832</td>
<td>2521</td>
</tr>
<tr>
<td><strong>Randomized</strong></td>
<td>1281</td>
<td>1146</td>
</tr>
<tr>
<td><strong>Mean Age</strong></td>
<td>44.9 (13.7)</td>
<td>45.9 (13.5)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>838 (65.4%)</td>
<td>768 (67.0%)</td>
</tr>
<tr>
<td><strong>&gt;65 years</strong></td>
<td>115 (9.0%)</td>
<td>126 (11.0%)</td>
</tr>
<tr>
<td><strong>Cholecystectomy</strong></td>
<td>272 (21.2%)</td>
<td>224 (19.5%)</td>
</tr>
<tr>
<td><strong>Used loperamide in prior yr</strong></td>
<td>466 (36.3%)</td>
<td>408 (35.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>3001 (mean (SD))</th>
<th>3002 (mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BSS</strong></td>
<td>6.3 (0.4)</td>
<td>6.2 (0.4)</td>
</tr>
<tr>
<td><strong>WAP</strong></td>
<td>6.2 (1.5)</td>
<td>6.0 (1.5)</td>
</tr>
<tr>
<td><strong># BMs/day</strong></td>
<td>4.9 (2.8)</td>
<td>4.8 (3.0)</td>
</tr>
<tr>
<td><strong>GSS</strong></td>
<td>2.9 (0.5)</td>
<td>2.8 (0.5)</td>
</tr>
</tbody>
</table>

BSS=Bristol Stool Score  
WAP=Worst Abdominal Pain in Past 24 hrs  
GSS=global symptom score
Primary Endpoint: FDA (Weeks 1-12)

3001

- Pbo: 17.1% (n=427)
- 75mg: 23.9% (n=426)
- 100mg: 25.1% (n=427)

3002

- Pbo: 16.2% (n=381)
- 75mg: 28.9% (n=382)
- 100mg: 29.6% (n=382)

Pooled

- Pbo: 16.7% (n=808)
- 75mg: 26.2% (n=806)
- 100mg: 27% (n=809)

Δ = 8.0
Δ = 6.8
Δ = 13.4
Δ = 12.7
Δ = 10.3
Δ = 9.5

P = .014
P = .004
P < .001
P < .001
P < .001
P < .001
Primary Endpoint: EMA (Weeks 1-26)

3001

- Pbo: 19% (n=427)
- 75mg: 23.4% (n=426)
- 100mg: 29.3% (n=427)

3002

- Pbo: 20.2% (n=381)
- 75mg: 30.4% (n=382)
- 100mg: 32.7% (n=382)

Pooled

- Pbo: 19.5% (n=808)
- 75mg: 26.7% (n=806)
- 100mg: 31% (n=809)

**∆ = 10.3**

100mg: 10.2% increase over Pbo (n=382, P < .001)

**∆ = 7.2**

75mg: 7.2% increase over Pbo (n=382, P < .001)

**∆ = 11.5**

Pooled: 11.5% increase over Pbo (n=809, P < .001)

**P = .112**

Pooled: 10.3% increase over 3001 and 3002 (P < .001)
Daily Composite Response
Weeks 0-26 (Pooled)

Percentage of Daily Composite Responders

0 7 14 21 28 35 42 49 56 63 70 77 84 91 98 105 112 119 126 133 140 147 154 161 168 175 182

Treatment
- Eluxadoline 75mg BID
- Eluxadoline 100mg BID
- Placebo BID
# Efficacy on Primary Composite Endpoint by Gender (pooled)

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg</td>
<td>Pbo</td>
</tr>
<tr>
<td></td>
<td>n=268</td>
<td>n=282</td>
</tr>
<tr>
<td>Weeks 1-12</td>
<td>26.10%</td>
<td>15.20%</td>
</tr>
<tr>
<td>Weeks 1-26</td>
<td>31.70%</td>
<td>19.10%</td>
</tr>
</tbody>
</table>
Pre-Specified Secondary Endpoints
# Individual Components of the Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Pain responder (30% improvement)</th>
<th>Stool Consistency responder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Responders</td>
<td>p value</td>
</tr>
<tr>
<td><strong>Weeks 1-12</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg PBO</td>
<td>46.8%</td>
<td>0.069</td>
</tr>
<tr>
<td>42.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weeks 1-26</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg PBO</td>
<td>48.3%</td>
<td>0.086</td>
</tr>
<tr>
<td>44.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Pooled Studies
Pain Responder (weeks 1-12)

Subject has 30%, 40% or 50% improvement of worst abd. pain vs. baseline avg) for 50% of days in study

<table>
<thead>
<tr>
<th>Pain Improvement(^1)</th>
<th>PBO</th>
<th>100 mg</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30% Daily Pain</td>
<td>44.0 %</td>
<td>48.3 %</td>
<td>0.086</td>
</tr>
<tr>
<td>≥ 40% Daily Pain</td>
<td>35.8 %</td>
<td>43.2 %</td>
<td>0.003</td>
</tr>
<tr>
<td>≥ 50% Daily Pain</td>
<td>30.0 %</td>
<td>36.0 %</td>
<td>0.011</td>
</tr>
</tbody>
</table>

\(^1\)Similar results for pain improvement ≥40% & ≥50% over weeks 1-26

\(^2\)Similar results for Cumulative Distribution over weeks 1-26
### Adequate Relief of IBS Symptoms: 50% Responder Analysis

<table>
<thead>
<tr>
<th></th>
<th>3001</th>
<th>3002</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% responders</td>
<td>p value</td>
</tr>
<tr>
<td><strong>Weeks 1-12</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg PBO</td>
<td>54.20%</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>43.8%</td>
<td></td>
</tr>
<tr>
<td><strong>Weeks 1-26</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg PBO</td>
<td>49.50%</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>40.00%</td>
<td></td>
</tr>
</tbody>
</table>

1. Pt. asked each week (1-26): “Have you had adequate relief of your IBS symptoms?”

2. Response=(Yes or No). Study responder = “Yes” for ≥6 of 12 weeks or “Yes” for ≥13 of 26 weeks.
# Efficacy Demonstrated with Additional Secondary Endpoints

| Secondary Endpoint (% responders)                          | 100 mg | PBO | p value  
|-----------------------------------------------------------|--------|-----|--------
| >50% Urgency Free Days (Wks 1-12)                         | 42%    | 29% | <0.001 |
| >75% Urgency Free Days (Wks 1-12)                         | 21%    | 12% | <0.001 |

| Secondary Endpoint (least square means) △ baseline        | 100 mg | PBO | p value  
|-----------------------------------------------------------|--------|-----|--------
| IBS-QOL Scores 1 : Wk 12                                  | 22.8   | 17.8| <0.001 |
| IBS-QOL Scores: Wk 26                                     | 25.0   | 20.4| <0.001 |
| Global Symptom Scores2 : Wk 12                            | -1.4   | -1.2| <0.001 |
| Global Symptom Scores :Wk 26                              | -1.5   | -1.3| <0.001 |
| BM frequency (avg/day @ wk 12) 3                          | -1.8   | -1.5| <0.001 |
| BM frequency (avg/day @ Wk 26)                             | -2.0   | -1.6| <0.001 |

1 IBS-QOL=Quality of Life (scale 0-100) were assessed on a single day at wk 12 & 26  
2 Global Symptoms Scores represent change from baseline of avg score at week 12 & 26  
3 Bowel Movement Frequency=change from baseline in avg # BMs/day during Wk 12 &26 compared to the Average # of BMs day in the wk before randomization.  
4 Logistic regression  
5 ANCOVA.
## Summary: Adverse Events (pooled)

<table>
<thead>
<tr>
<th></th>
<th>75 mg n=807</th>
<th>100 mg n=859</th>
<th>PBO n=808</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># Pts (%) with AE</strong></td>
<td>466 (57.7)</td>
<td>477 (55.5)</td>
<td>427 (52.8)</td>
</tr>
<tr>
<td><strong># Pts (%) with SAE</strong></td>
<td>28 (3.5)</td>
<td>38 (4.4)</td>
<td>22 (2.7)</td>
</tr>
</tbody>
</table>

**Most Common**

<table>
<thead>
<tr>
<th>Event</th>
<th>75 mg n=807</th>
<th>100 mg n=859</th>
<th>PBO n=808</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>60 (7.4)</td>
<td>71 (8.3)</td>
<td>19 (2.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>63 (7.8)</td>
<td>63 (7.3)</td>
<td>39 (4.8)</td>
</tr>
<tr>
<td>Abdominal Pain³</td>
<td>46 (5.7)</td>
<td>59 (6.9)</td>
<td>31 (3.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29 (3.6)</td>
<td>35 (4.1)</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>Abdominal Distention</td>
<td>21 (2.6)</td>
<td>22 (2.6)</td>
<td>13 (1.6)</td>
</tr>
<tr>
<td>Gastroenteritis⁴</td>
<td>33 (4.1)</td>
<td>17 (2.0)</td>
<td>26 (3.2)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>21 (2.6)</td>
<td>27 (3.1)</td>
<td>11 (1.4)</td>
</tr>
<tr>
<td>URI</td>
<td>23 (2.9)</td>
<td>45 (5.2)</td>
<td>30 (3.7)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>25 (3.1)</td>
<td>24 (2.8)</td>
<td>17 (2.1)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>26 (3.2)</td>
<td>23 (2.7)</td>
<td>23 (2.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>30 (3.7)</td>
<td>22 (2.6)</td>
<td>26 (3.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (2.6)</td>
<td>26 (3.0)</td>
<td>17 (2.1)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9 (1.1)</td>
<td>18 (2.1)</td>
<td>13 (1.6)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>15 (1.9)</td>
<td>24 (2.8)</td>
<td>12 (1.5)</td>
</tr>
</tbody>
</table>

1. Most common Adverse Events = Events in either treatment arm >2.0% and > PBO
2. All constipation events were non-serious. 1.3 % pts receiving active and 0.2% in PBO discontinued due to non serious constipation.
3. Abdominal Pain = Abdominal pain, abdominal pain upper, abdominal pain lower
4. Gastroenteritis= gastroenteritis and viral gastroenteritis
8 adjudicated cases of hepatobiliary sphincter of Oddi spasm (epigastric or biliary pain, transaminase ↑, often w/nausea). Bilirubin, alk phosph, lipase unremarkable

- 8/8 patients had prior cholecystectomy
- 6/8 noted symptoms during 1st week of treatment
- 7/8 managed as outpatients by stopping Rx; 1/8 briefly hospitalized for nausea/vomiting
  - Drug stopped in 7/8 patients w/ rapid resolution of transaminases and symptoms
  - 1 subject continued Rx for several more weeks with no further AEs

- 7/8 rec’d 100 mg, 1/8 rec’d 75 mg, 0 rec’d PBO
  - Favorable prognosis and rapid reversal on d/c drug
  - Ph III rate ~0.49% of all eluxadoline-treated patients
  - Ph III rate ~2.4% of eluxadoline treated-patients w/ prior cholecystectomy

- Opiate-induced sphincter of Oddi spasm has a known association w/ cholecystectomy

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1 Cholecystectomy status was collected prospectively in Ph III. (One of these subjects had agenesis of the gall bladder which is functionally similar to cholecystectomy). Overall cholecystectomy rate in Phase III was ~20%.

2 Not all patients sought medical attention during week 1
Pancreatitis

- 5 cases adjudicated as pancreatitis by external committee (Atlanta criteria definition\(^1\)).
- All cases adjudicated as **mild** (Atlanta Criteria\(^1\))
- Rate in Phase III is ~0.3% of eluxadoline treated patients
- All subjects w/ pancreatitis had risk factors which may have predisposed
  - Hx of cholecystectomy consistent w/ Sphincter of Oddi spasm (1 case)
  - Biliary sludge (1 case)
  - Chronic heavy EtOH use (3 cases)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time to Onset</th>
<th>Age/Gender</th>
<th>EtOH</th>
<th>Cholecystectomy</th>
<th>Initial Lipase XULN</th>
<th>F/U Lipase XULN @ time</th>
<th>Imaging</th>
<th>Clinical Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>mins</td>
<td>62 / f</td>
<td>No</td>
<td>Yes</td>
<td>8.4X</td>
<td>1.1X; 24 hr</td>
<td>negative</td>
<td>mild transient pancreatitis c/w SO spasm.</td>
</tr>
<tr>
<td>75 mg</td>
<td>26 wks</td>
<td>43 / f</td>
<td>No</td>
<td>No</td>
<td>10.2X</td>
<td>2.2X; 24 hr</td>
<td>negative</td>
<td>Obese; DM; <strong>biliary sludge.</strong></td>
</tr>
<tr>
<td>75 mg</td>
<td>4 wks</td>
<td>50 / f</td>
<td>Yes</td>
<td>No</td>
<td>13.3X</td>
<td>1.2X; 96 hr</td>
<td>acute pancreatitis</td>
<td>chronic vodka consumption; steatohepatitis; referred to alcoholics anonymous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>without complication</td>
<td></td>
</tr>
<tr>
<td>100 mg</td>
<td>1.5 days</td>
<td>63 / m</td>
<td>Yes</td>
<td>No</td>
<td>20.0X</td>
<td>2.3X; 24 hr</td>
<td>moderately severe peri-pancreatic inflammation.</td>
<td>longstanding alcoholism; severe gastritis; coagulopathy; prior alcoholic pancreatitis.</td>
</tr>
<tr>
<td>100 mg</td>
<td>10 wks</td>
<td>57 / m</td>
<td>Yes</td>
<td>Yes</td>
<td>2.1X</td>
<td>1.2X; 24 hr</td>
<td>peri-pancreatic fluid.</td>
<td>smoker; EtOH consumption increased weeks prior to event; hepatic steatosis.</td>
</tr>
</tbody>
</table>

\(^1\) Banks, PA et al. Gut: 62 (2013)
Rapid declines in lipase, brief hospitalizations
No sequelae
Pancreatitis likely due to increased contractility at sphincter of Oddi
  - Locally / topically mediated as eluxadoline transits the GI tract
  - Eluxadoline has low systemic availability
  - Duodenal concentrations in excess of EC$_{50}$ for smooth muscle contractility
Risks can be mitigated through education, appropriate patient selection
Conclusions

- Eluxadoline is a 1\textsuperscript{st} in class, oral, locally-acting drug candidate for IBS-D, with a novel mechanism.

- Efficacy demonstrated in two Phase III studies (for both FDA & EMA endpoints):
  - Significant improvements in 1\textsuperscript{st} composite endpoint (simultaneous improvement in both pain & diarrhea).
  - Effects seen within first few days of therapy and durable for 26 week study period.
  - Efficacy in both males and females.
  - Efficacy demonstrated for patients’ most bothersome IBS-D symptoms:
    - diarrhea, urgency/frequency, pain (2\textsuperscript{nd} endpoints)
  - Efficacy demonstrated for other global 2\textsuperscript{nd} endpoints:
    - IBS-quality of life, adequate relief, global symptoms.

- >2500 subjects exposed; well-tolerated, low constipation rates.

- Infrequent events of hepatobiliary sphincter of Oddi spasm, and MILD pancreatitis.
  - Improved rapidly, without sequelae.
  - Likely topically/locally mediated and consistent with opiate class-effects.
  - Clearly defined risk factors (prior cholecystectomy, alcohol abuse) enable straightforward patient selection and risk mitigation.
Acknowledgments

We thank the study investigators, their staff and the IBS-D patients participating in the eluxadoline Phase III studies.

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