Efficacy and safety of tenapanor in patients with constipation-predominant irritable bowel syndrome: a 12-week, double-blind, placebo-controlled, randomized phase 2b trial

William D Chey,1 Anthony J Lembo,2 James A Phillips,3 David P Rosenbaum4

1Division of Gastroenterology, Department of Medicine, University of Michigan Health System, Ann Arbor, MI, USA; 2Division of Gastroenterology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; 3Sage Statistical Solutions, Inc., Efland, NC, USA; 4Ardelyx, Inc., Fremont, CA, USA
Disclosures

- William D Chey
  - Consultancy: Ardelyx, Asubio Pharmaceuticals, AstraZeneca, Forest Laboratories (Actavis), Ironwood Pharmaceuticals, Nestlé Health Science, Prometheus Laboratories, QOL Medical, Salix Pharmaceuticals, SK Biopharmaceuticals, Sucampo and Takeda
  - Research funding: Ironwood Pharmaceuticals, Nestlé Health Science, Perrigo Company, Prometheus Laboratories, Synthetic Biologics and Vibrant Pharma

- Anthony J Lembo
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- James A Phillips
  - Consultancy: Ardelyx

- David P Rosenbaum
  - Employment and ownership interests: Ardelyx

- This study was funded by AstraZeneca and Ardelyx
Tenapanor (AZD1722) acts locally in the gut to reduce sodium absorption

● Sodium/hydrogen exchanger isoform 3 (NHE3) plays an important role in intestinal sodium/fluid homeostasis

● Tenapanor is a small-molecule inhibitor of NHE3

● Preclinical and phase 1 studies show that tenapanor reduces sodium absorption and has minimal systemic availability

● In a preclinical model, tenapanor showed antinociceptive effects on stress-induced mechanical colorectal hypersensitivity

*< 0.05 versus placebo; †< 0.05 versus tenapanor 30 mg q.d. b.i.d., twice daily; q.d., once daily; t.i.d., three times daily

Tenapanor is a potential treatment for constipation-predominant irritable bowel syndrome (IBS-C)

- IBS is a common, symptom-based condition defined by the presence of abdominal pain and altered bowel habits
  - In IBS-C, stools are hard/lumpy in ≥ 25% of bowel movements and loose/watery in < 25% of bowel movements
- Phase 2a data suggest that tenapanor improves IBS-C symptoms

Patients with a ≥ 30% decrease in abdominal pain and an increase of ≥ 1 in complete spontaneous bowel movements (CSBM) per week

IBS-C, constipation-predominant irritable bowel syndrome; CSBM, complete spontaneous bowel movement; q.d., once daily
Study aim
• To evaluate the efficacy and safety of tenapanor for the treatment of IBS-C

Key inclusion criteria
• Age 18–75 years
• IBS-C as defined by Rome III criteria
• Active disease during the screening period
  – < 3 CSBMs/week
  – < 5 SBMs/week
  – abdominal pain ≥ 3 (0–10 rating scale)

Key exclusion criteria
• IBS with diarrhea (IBS-D), mixed IBS (IBS-M) or unsubtyped IBS as defined by Rome III criteria
• Diagnosis or treatment of any clinically symptomatic biochemical or structural abnormality of the gastrointestinal tract in the 6 months before screening
• Use of medication known to affect stool consistency

SBM, spontaneous bowel movement
12-week dose-ranging study evaluating tenapanor 5 mg, 20 mg or 50 mg b.i.d. vs placebo (2/2)

Randomization (N = 356)

- Placebo
- Tenapanor 5 mg b.i.d.
- Tenapanor 20 mg b.i.d.
- Tenapanor 50 mg b.i.d.

Primary endpoint

- Proportion of patients with a ≥ 30% decrease in abdominal pain and an increase of ≥ 1 CSBM per week versus baseline for ≥ 6/12 treatment weeks

Key secondary endpoints

- Overall responder rate$^a$
- Abdominal pain responder rate$^b$

Exploratory endpoints

- Abdominal bloating, straining, IBS severity, constipation severity

Safety assessments

- Adverse event reporting throughout the trial
- Clinical laboratory tests (serum chemistry, hematology and urinalysis)
- Vital signs
- 12-lead ECG
- Physical examinations

$^a$Proportion of patients with a ≥ 30% decrease in abdominal pain and an increase of ≥ 1 CSBM per week versus baseline for ≥ 6/12 treatment weeks

$^b$Proportion of patients with a ≥ 30% decrease in abdominal pain from baseline for ≥ 6/12 treatment weeks
Patient demographics and baseline disease characteristics

356 patients with IBS-C were randomized
  - The majority of patients were women (87%), < 65 years old (93%; mean age 45.7 years) and white (76%)

<table>
<thead>
<tr>
<th>Baseline disease parameter</th>
<th>Placebo (n = 89)</th>
<th>Tenapanor 5 mg b.i.d. (n = 87)</th>
<th>Tenapanor 20 mg b.i.d. (n = 87)</th>
<th>Tenapanor 50 mg b.i.d. (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSBMs per week</td>
<td>0.2 (0.4)</td>
<td>0.2 (0.4)</td>
<td>0.2 (0.4)</td>
<td>0.2 (0.4)</td>
</tr>
<tr>
<td>SBMs per week</td>
<td>2.0 (1.2)</td>
<td>1.9 (1.3)</td>
<td>1.9 (1.1)</td>
<td>2.0 (1.3)</td>
</tr>
<tr>
<td>Stool consistency&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.8 (1.0)</td>
<td>1.8 (1.0)</td>
<td>1.6 (0.8)</td>
<td>1.8 (0.9)</td>
</tr>
<tr>
<td>Straining&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.1 (1.2)</td>
<td>3.1 (1.1)</td>
<td>3.1 (1.3)</td>
<td>3.2 (1.3)</td>
</tr>
<tr>
<td>Constipation severity&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.1 (0.7)</td>
<td>4.2 (0.6)</td>
<td>4.0 (0.7)</td>
<td>4.0 (0.8)</td>
</tr>
<tr>
<td>IBS severity&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.8 (0.7)</td>
<td>3.9 (0.7)</td>
<td>3.9 (0.8)</td>
<td>3.8 (0.7)</td>
</tr>
<tr>
<td>Abdominal pain&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6.1 (1.5)</td>
<td>6.1 (1.6)</td>
<td>6.3 (1.5)</td>
<td>6.0 (1.5)</td>
</tr>
</tbody>
</table>

ITT, intention-to-treat; SD, standard deviation. Data are mean (SD) for the ITT population. Baseline was defined as the mean of weeks -1 and -2.

<sup>a</sup>Assessed using the 7-point Bristol Stool Form Scale; weekly mean calculated from scores for all SBMs during the week.

<sup>b</sup>Assessed for each SBM using a 5-point scale: 1 = not at all, 2 = a little bit, 3 = a moderate amount, 4 = a great deal, 5 = an extreme amount; mean weekly score calculated from scores for all SBMs during the week.

<sup>c</sup>Assessed weekly using a 5-point scale: 1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe.

<sup>d</sup>Assessed daily using a 10-point scale: 0 = none to 10 = very severe; mean weekly score was calculated from scores for all days during a valid week.
Tenapanor 50 mg b.i.d. resulted in a significantly higher CSBM responder rate than placebo

- Primary endpoint (CSBM responder rate): proportion of patients with an increase of ≥ 1 CSBM per week from baseline for ≥ 6/12 treatment weeks (ITT analysis)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CSBM Responder Rate (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 89)</td>
<td>33.7</td>
<td></td>
</tr>
<tr>
<td>5 mg (n = 87)</td>
<td>40.2</td>
<td>0.345</td>
</tr>
<tr>
<td>20 mg (n = 87)</td>
<td>43.7</td>
<td>0.186</td>
</tr>
<tr>
<td>50 mg (n = 84)</td>
<td>60.7</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

CSBM, complete spontaneous bowel movement
CSBM improvements were maintained over the 12 weeks in a dose-dependent manner.

CSBM, complete spontaneous bowel movement
*p < 0.05, tenapanor 50 mg b.i.d. versus placebo
†p < 0.05, tenapanor 20 mg b.i.d. and 50 mg b.i.d. versus placebo
Tenapanor 50 mg b.i.d. resulted in a significantly higher overall responder rate than placebo

- Overall responder rate: proportion of patients with a ≥ 30% decrease in abdominal pain and an increase of ≥ 1 CSBM per week versus baseline for ≥ 6/12 treatment weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>Overall Responder Rate (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>23.6</td>
<td>0.815</td>
</tr>
<tr>
<td>5 mg</td>
<td>25.3</td>
<td></td>
</tr>
<tr>
<td>20 mg</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>50 mg</td>
<td>50.0</td>
<td></td>
</tr>
</tbody>
</table>

CSBM, complete spontaneous bowel movement
Improvements in other key secondary endpoints with tenapanor

**Abdominal pain responder rate**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Abdominal pain responder rate (%)</th>
<th>Risk Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 89)</td>
<td>48.3</td>
<td>17.2; p = 0.026</td>
<td></td>
</tr>
<tr>
<td>5 mg (n = 87)</td>
<td>44.8</td>
<td>4.6; p = 0.552</td>
<td></td>
</tr>
<tr>
<td>20 mg (n = 87)</td>
<td>52.9</td>
<td>-3.5; p = 0.684</td>
<td></td>
</tr>
<tr>
<td>50 mg (n = 84)</td>
<td>65.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Stool consistency**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LS mean change in BSFS from baseline to week 12</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 89)</td>
<td>1.0</td>
<td>1.2; p &lt; 0.001</td>
</tr>
<tr>
<td>5 mg (n = 87)</td>
<td>1.6</td>
<td>0.9; p &lt; 0.001</td>
</tr>
<tr>
<td>20 mg (n = 87)</td>
<td>1.9</td>
<td>0.6; p = 0.027</td>
</tr>
<tr>
<td>50 mg (n = 84)</td>
<td>2.2</td>
<td></td>
</tr>
</tbody>
</table>

BSFS, Bristol Stool Form Scale; LS, least-squares

*a* Proportion of patients with ≥ 30% decrease in abdominal pain from baseline for ≥ 6/12 treatment weeks; treatment comparisons versus placebo represent the risk difference

*b* Error bars represent upper limit of 95% confidence interval
Improvements in exploratory endpoints with tenapanor 50 mg b.i.d.

Abdominal bloating\(^a\)

- Placebo (n = 89): -1.6
- Tenapanor 50 mg b.i.d. (n = 84): -2.6

\(p = 0.023\)

Straining\(^b\)

- Placebo (n = 89): -0.7
- Tenapanor 50 mg b.i.d. (n = 84): -1.2

\(-0.5; p = 0.006\)

IBS severity\(^c\)

- Placebo (n = 89): -1.1
- Tenapanor 50 mg b.i.d. (n = 84): -1.4

\(-0.3; p = 0.024\)

Constipation severity\(^c\)

- Placebo (n = 89): -1.1
- Tenapanor 50 mg b.i.d. (n = 84): -1.7

\(-0.5; p < 0.001\)

\(^a\)Assessed daily using a 10-point scale: 0 = none to 10 = very severe; average weekly score was calculated from scores for all days during a week.

\(^b\)Assessed for each SBM using a 5-point scale: 1 = not at all to 5 = an extreme amount; average weekly straining score calculated from scores for all SBMs during the week.

\(^c\)Assessed weekly using a 5-point scale: 1 = none to 5 = very severe.
Tenapanor was generally well tolerated and had minimal systemic availability

- Most AEs were mild to moderate in severity and none of the three serious AEs in patients receiving tenapanor were judged to be treatment-related
- No clinically meaningful changes from baseline were reported for clinical laboratory parameters, vital signs, electrocardiographic parameters or physical examination findings
- Tenapanor had minimal to no systemic availability
  - Tenapanor concentrations were below the lower limit of quantification (0.5 ng/mL) in > 97% (283/291) samples (highest concentration measured: 1.03 ng/mL)

### AE summary, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 90)</th>
<th>Tenapanor 5 mg b.i.d. (n = 88)</th>
<th>Tenapanor 20 mg b.i.d. (n = 89)</th>
<th>Tenapanor 50 mg b.i.d. (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>38 (42.2)</td>
<td>43 (48.9)</td>
<td>32 (36.0)</td>
<td>45 (50.6)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>13 (14.4)</td>
<td>22 (25.0)</td>
<td>15 (16.9)</td>
<td>17 (19.1)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>1 (1.1)</td>
<td>2 (2.3)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>AEs leading to discontinuation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (3.3)</td>
<td>9 (10.2)</td>
<td>6 (6.7)</td>
<td>4 (4.5)</td>
</tr>
</tbody>
</table>

AE, adverse event

<sup>a</sup>Most common AEs leading to discontinuation: diarrhea (3 [3.4%] patients each in 5 mg, 20 mg and 50 mg b.i.d. groups), abdominal distension (3 [3.4%] patients in 5 mg b.i.d. group); no other specific AE led to discontinuation in > 2 patients in any treatment group
### AEs occurring in ≥ 3% of patients in any tenapanor group and more frequently than in the placebo group

<table>
<thead>
<tr>
<th>Individual event, n (%)</th>
<th>Placebo (n = 90)</th>
<th>Tenapanor 5 mg b.i.d. (n = 88)</th>
<th>Tenapanor 20 mg b.i.d. (n = 89)</th>
<th>Tenapanor 50 mg b.i.d. (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>0 (0.0)</td>
<td>7 (8.0)</td>
<td>11 (12.4)</td>
<td>10 (11.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1.1)</td>
<td>6 (6.8)</td>
<td>4 (4.5)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (2.2)</td>
<td>7 (8.0)</td>
<td>0 (0.0)</td>
<td>4 (4.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0)</td>
<td>4 (4.5)</td>
<td>1 (1.1)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>GERD</td>
<td>1 (1.1)</td>
<td>3 (3.4)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>0 (0.0)</td>
<td>3 (3.4)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (4.4)</td>
<td>3 (3.4)</td>
<td>2 (2.2)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Influenza</td>
<td>0 (0.0)</td>
<td>2 (2.3)</td>
<td>1 (1.1)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (5.6)</td>
<td>6 (6.8)</td>
<td>1 (1.1)</td>
<td>3 (3.4)</td>
</tr>
</tbody>
</table>

GERD, gastroesophageal reflux disease
Conclusions

- Tenapanor 50 mg b.i.d. significantly improved CSBM responder rate (primary endpoint) compared with placebo in patients with IBS-C
- Tenapanor 50 mg b.i.d. also improved key secondary endpoints compared with placebo, including overall responder rate, abdominal pain responder rate and stool frequency
- In addition, improvements were observed in several exploratory endpoints addressing a range of symptoms in patients with IBS-C
- Tenapanor was generally well tolerated and had minimal systemic availability
- Tenapanor shows promise as a future treatment option for patients with IBS-C
Acknowledgments

● The investigators acknowledge and thank the study participants, the study centres and the clinical teams

● The clinical operations were managed by Susan Edelstein, Lori Marshall and Jocelyn Tabora from Ardelyx

● Medical writing support was provided by Steven Inglis and Carolyn Brechin of Oxford PharmaGenesis, UK and was funded by Ardelyx
Back-up slides
Statistical analysis methods (1/2)

- CSBM responder rate (primary endpoint), overall responder rate and abdominal pain responder rate (key secondary endpoints)
  - Treatment comparisons versus placebo are presented as risk differences (slides 8, 10, 11)
  - A screening test was performed based on a 2-degree of freedom Cochran–Mantel–Haenszel test for an association between treatment (placebo, tenapanor 20 mg b.i.d. and tenapanor 50 mg b.i.d.) and responder rate, stratified by pooled investigator sites
  - If this test was significant, a Cochran–Mantel–Haenszel test was used to calculate $p$ values based on 1 degree of freedom for the association between treatment (placebo paired with each dose group separately) and responder rate, stratified by pooled investigator sites
Statistical analysis methods (2/2)

- Stool consistency (secondary endpoint), abdominal bloating, straining, IBS severity and constipation severity (exploratory endpoints)
  - Treatment comparisons versus placebo are presented as differences in LS mean changes from baseline (slide 11, 12)
  - A screening test was performed based on a 2-degree of freedom F-test from a full ANCOVA model to test for differences in mean changes from baseline among the placebo, tenapanor 20 mg b.i.d. and tenapanor 50 mg b.i.d. groups
  - LS means, 95% confidence intervals and $p$ values were calculated using an ANCOVA model, with treatment and pooled investigator site as factors and baseline value as a covariate