Efficacy and Safety of Tenapanor in Patients with Constipation-Predominant Irritable Bowel Syndrome: A 12-Week, Double-Blind, Placebo-Controlled, Randomized Phase 3 Trial

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Tenapanor is a First-in-Class, Minimally Systemic, Small-Molecule Inhibitor of Gastrointestinal NHE3

- Na\(^+\)/H\(^+\) exchanger isoform 3 (NHE3) is the major absorptive Na\(^+\)/H\(^+\) exchanger in the gut\(^1\)
- Specific inhibitor of NHE3 that reduces absorption of dietary sodium and phosphate (via a downstream effect) in preclinical and clinical studies\(^2,3\)
- Undergoing evaluation in clinical trials as a potential treatment for IBS-C and for hyperphosphatemia in patients with end-stage renal disease on dialysis\(^4,5\)

Phase 2b Study Results: Rationale for Phase 3

- Randomized study in 356 patients with IBS-C (Rome III criteria)
- Results provided clinical rationale for a phase 3 study with similar design
  - Combined, CSBM and abdominal pain responder rates (6 of 12 and 9 of 12 weeks) significantly greater with tenapanor 50 mg bid vs placebo
  - Tenapanor was well tolerated; most frequent adverse event was diarrhea


CSBM, complete spontaneous bowel movement
T3MPO-1 Phase 3 Study: Aims, Participants and Design

Aim

• Efficacy and safety of tenapanor 50 mg bid for the treatment of patients with IBS-C

Main eligibility criteria

• IBS-C diagnosis (modified Rome III criteria)
• Two-week screening criteria:
  – Mean average: < 3 CSBMs and ≤ 5 SBMs per week
  – Mean weekly abdominal pain score\(^\text{a}\) ≥ 3

111 sites in the USA

Randomization to treatment
\(N = 606\)

Screening

Placebo (\(n = 299\))

Tenapanor 50 mg bid (\(n = 307\))

Randomized / assigned to withdrawal
\(N = 533\)

Placebo (\(n = 131\))

Tenapanor 50 mg bid (\(n = 130\))

End of withdrawal
\(N = 510\)

Tenapanor 50 mg bid (\(n = 272\))

2 weeks

12 weeks

4 weeks

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


SBM, spontaneous bowel movement
Main Study Endpoints

Primary endpoint
• Combined responder rate
  – Proportion reporting $\geq 30\%$ abdominal pain reduction and an increase of $\geq 1$ CSBM from baseline in the same week for $\geq 6$ of 12 treatment weeks

Key secondary endpoints
• CSBM responder rate
  – Proportion with an increase of $\geq 1$ CSBM per week from baseline ($\geq 6$ of 12 weeks, $\geq 9$ of 12 weeks, sustained response\(^a\))
• Abdominal pain responder rate
  – Proportion with a decrease in abdominal pain of $\geq 30\%$ from baseline ($\geq 6$ of 12 weeks, $\geq 9$ of 12 weeks, sustained response\(^a\))
• Combined responder rate ($\geq 9$ of 12 weeks, sustained response\(^a\))

\(^a\)Responder for $\geq 9$ of 12 weeks and $\geq 3$ of the last 4 weeks
Patient Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Tenapanor 50 mg bid (n = 307)</th>
<th>Placebo (n = 299)</th>
<th>Overall (n = 606)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean</td>
<td>45.0</td>
<td>44.9</td>
<td>45.0</td>
</tr>
<tr>
<td>Women (%)</td>
<td>79.5</td>
<td>83.3</td>
<td>81.4</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>65.5</td>
<td>62.2</td>
<td>63.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean</td>
<td>29.9</td>
<td>29.3</td>
<td>29.6</td>
</tr>
<tr>
<td>Number of CSBMs per week, mean</td>
<td>0.18</td>
<td>0.21</td>
<td>0.2</td>
</tr>
<tr>
<td>Number of SBMs per week, mean</td>
<td>1.76</td>
<td>1.69</td>
<td>1.7</td>
</tr>
<tr>
<td>Abdominal pain, weekly mean</td>
<td>6.29</td>
<td>6.32</td>
<td>6.3</td>
</tr>
</tbody>
</table>

*Assessed daily using a 10-point Likert scale: 0 = none to 10 = very severe; mean weekly score was calculated from scores for all days during a valid week.*
Primary and Key Secondary Endpoints
Responder Analysis ≥ 6 of 12 Weeks

- Tenapanor 50 mg bid (n = 306)
- Placebo (n = 299)

- Combined responder rate: Tenapanor 27.0% vs. Placebo 18.7% (p = 0.02)
- CSBM responder rate: Tenapanor 33.9% vs. Placebo 29.4% (p = 0.27)
- Abdominal pain responder rate: Tenapanor 44.0% vs. Placebo 33.1% (p = 0.008)

Cochran–Mantel–Haenszel test, stratified by pooled investigator site; intention-to-treat analysis
CSBM and SBM Frequency Over 16 Weeks

CSBMs per week

SBMs per week

Intention-to-treat population; data are mean ± standard error; * p < 0.001; # p = 0.001 vs placebo
PBO, placebo; TEN, tenapanor
### Key Secondary Endpoints

#### ≥ 9 of 12 Weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Combined Responder Rate (%)</th>
<th>CSBM Responder Rate (%)</th>
<th>Abdominal Pain Responder Rate (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenapanor 50 mg bid (n = 306)</td>
<td>13.7</td>
<td>16.9</td>
<td>30.3</td>
<td><em>p</em> &lt; 0.001</td>
</tr>
<tr>
<td>Placebo (n = 299)</td>
<td>3.3</td>
<td>5.0</td>
<td>19.4</td>
<td><em>p</em> = 0.003</td>
</tr>
</tbody>
</table>

#### Sustained Response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Combined Responder Rate (%)</th>
<th>CSBM Responder Rate (%)</th>
<th>Abdominal Pain Responder Rate (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenapanor 50 mg bid (n = 306)</td>
<td>13.0</td>
<td>16.0</td>
<td>29.3</td>
<td><em>p</em> &lt; 0.001</td>
</tr>
<tr>
<td>Placebo (n = 299)</td>
<td>3.3</td>
<td>4.7</td>
<td>19.4</td>
<td><em>p</em> = 0.006</td>
</tr>
</tbody>
</table>

*Respond for ≥ 9 of 12 weeks and ≥ 3 of the last 4 weeks*
### Summary of Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Tenapanor 50 mg bid (n = 309)</th>
<th>Placebo (n = 301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>110 (35.6)</td>
<td>74 (24.6)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>57 (18.4)</td>
<td>18 (6.0)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>4 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>23 (7.4)</td>
<td>2 (0.7)</td>
</tr>
</tbody>
</table>

**AEs occurring in ≥ 2% of patients in any treatment group and more frequently than in the placebo arm**

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<th>Tenapanor 50 mg bid (n = 309)</th>
<th>Placebo (n = 301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>45 (14.6)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (2.6)</td>
<td>5 (1.7)</td>
</tr>
</tbody>
</table>

- No drug-related serious AEs
- No clinically meaningful changes from baseline in clinical laboratory parameters, vital signs, electrocardiographic parameters, or physical examination findings
- The majority of AEs leading to discontinuation of tenapanor were diarrhea (6.5%)
Conclusions

- Tenapanor is a first-in-class, minimally systemic NHE3 inhibitor.
- In patients with IBS-C, treatment with tenapanor 50 mg bid produced a statistically significant improvement in the combined responder (≥ 6 of 12 weeks) primary endpoint, comprised of CSBM and abdominal pain responders.
  - Significant improvements were seen in CSBMs, abdominal pain and the combined response in the ≥ 9 of 12 weeks responder analysis, with similar, clinically relevant improvements in the sustained responder analysis.
- Tenapanor was generally well tolerated, with diarrhea the most common adverse event.
- Additional phase 3 trials in patients with IBS-C are ongoing.
  - T3MPO-2 efficacy and safety study (6 months)\(^1\)
  - T3MPO-3 long-term safety study (1 year)\(^2\)
- Tenapanor, with a novel mechanism of action, may offer a new treatment option for patients with IBS-C.

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