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Effect of Tenapanor on Treatment Satisfaction, Degree of Relief, and Quality of Life for Patients With Irritable Bowel Syndrome With Constipation

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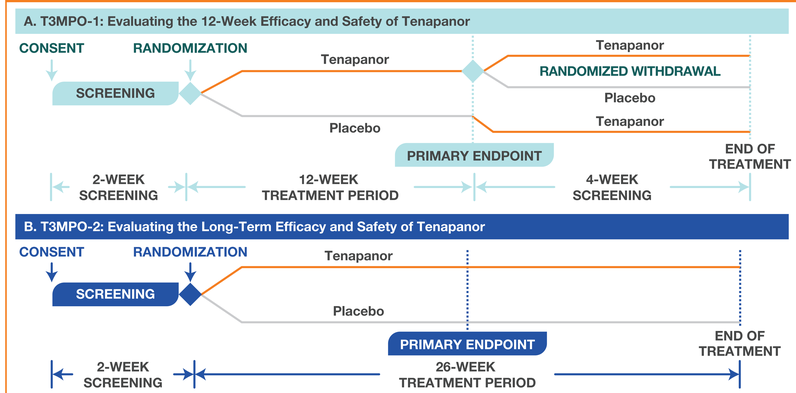
Background

- IBS-C is a chronic condition characterized by recurrent bouts of abdominal pain and constipation-related symptoms that significantly reduce patient quality of life.[1,2]
- In a 2015 survey of patients with IBS-C, 34% reported that IBS-C symptoms interfere with personal activities (eg, parties, sporting events, family activities) ≥10 days a month.[2]
  - The majority reported that IBS-C symptoms prevent them from enjoying daily activities and reaching their full potential, and cause them to not feel like themselves.[2]
- A survey conducted from 2016 to 2017 found that patients diagnosed with IBS-C felt frustrated by their IBS-C, and only 37% of patients who were taking prescription medication for IBS-C expressed satisfaction with their treatment.[3]
- Tenapanor is a first-in-class, minimally absorbed, small-molecule inhibitor of sodium-hydrogen exchanger isoform 3 (NHE3), approved for the treatment of adults with IBS-C in 2019.[4-6]
- In the T3MPO-1 (NCT02621892) and T3MPO-2 (NCT02686138) phase 3 clinical trials, tenapanor effectively improved IBS-C symptoms with acceptable safety and tolerability.[7,8]
  - Significantly more patients treated with tenapanor experienced a ≥30% reduction in average weekly worst abdominal pain and an increase of ≥1 average weekly complete spontaneous bowel movement (CSBM) from baseline compared with placebo.[7,8]
  - Diarrhea was the most commonly reported adverse event in both trials.[7,8]
- Here we describe patient-reported outcomes of symptom relief, treatment satisfaction, and quality of life measures captured during these studies.

Methods

- T3MPO-1 and T3MPO-2 consisted of 12- and 26-week randomized treatment periods, respectively, in which patients received tenapanor 50 mg twice a day (bid) or placebo bid (**Figure 1**).
  - In T3MPO-1, the 12-week treatment period was followed by a 4-week randomized withdrawal period.
  - Full details of the study designs were previously reported.[7,8]
- For both studies, adequate relief of IBS-C symptoms and degree of relief of IBS-C symptoms were reported by patients weekly by phone diary (**Box**).
- Patients rated treatment satisfaction monthly during the treatment period of both studies and at the end of the randomized withdrawal period in T3MPO-1.
  - Satisfaction was scored on a scale from 1 (not at all satisfied) to 5 (very satisfied).
- Scores from the validated IBS-QoL instrument at baseline were compared with those at week 12 and week 26/early termination visit (T3MPO-2 only).
  - The IBS-QoL instrument includes 34 individual questions that measure 8 subscales found to be relevant to IBS patients: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, relationship, and overall. Scores range from 0 to 100.[9]

Figure 1. Study Design for T3MPO-1 and T3MPO-2



ENROLLMENT CRITERIA FOR T3MPO-1 and T3MPO-2
- Age 18-75 years
- Met the Rome III criteria for IBS-C
- Colonoscopy if any history of unexplained warning signs/symptoms or within 10 years if ≥50 years
- Met additional entry criteria during the 2-week screening period, including:
  - Completed IVRS diary on ≥11 of 14 days
  - Average weekly stool frequency of ≤5 SBMs[a] with <3 CSBMs[b]
  - Average weekly stool consistency ≤3 on BSFS
  - Average weekly abdominal pain score ≥3

PRIMARY ENDPOINT FOR T3MPO-1 and T3MPO-2
Proportion of patients who had a 6/12 week combined response defined as an abdominal pain response (≥30% reduction in average weekly worst abdominal pain from baseline) and CSBM response (≥1 increase in weekly CSBM from baseline) both in the same week for ≥6 weeks of the first 12 weeks of treatment

[a]SBM was defined as any nonaided bowel movement (no rescue medication used in the preceding 24 hours). [b]CSBM was defined as an SBM accompanied by the sensation of complete evacuation.
BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; IBS-C, irritable bowel syndrome with constipation; IVRS, interactive voice response system; SBM, spontaneous bowel movement.

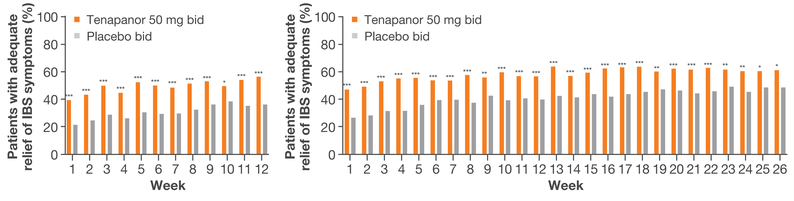
Box. Interactive Voice Response System (IVRS) Diary

The IVRS diary collected information on daily stool frequency, stool consistency, straining, abdominal pain, abdominal discomfort, abdominal bloating, abdominal fullness, abdominal cramping, and rescue medication usage. IBS severity and constipation severity were assessed weekly through the IVRS diary.[a]

Example questions:[b]
- *Have you had adequate relief of your IBS symptoms over the past week?* Yes/No
- *How would you rate the degree of relief of your IBS symptoms over the past week?* Assessed on a scale from 1 (completely relieved) to 7 (as bad as I can imagine)

[a]Entries into the IVRS diary must have been recorded between 6:00 PM and 11:59 PM (local time). [b]Example questions reflect questions relevant to the analysis presented. The full IVRS diary included 4 weekly questions and 7 daily questions (with sub-questions for each bowel movement and each use of rescue medication).
IBS, irritable bowel syndrome; IVRS, interactive voice response system.

Figure 2. Proportion of Patients with Adequate IBS Symptom Relief by Week (ITT Population)



Data are shown for the randomized treatment period of each trial. CMH test *P* value based on 1-degree of freedom test for association between treatment (tenapanor 50 mg bid and placebo), stratified by pooled investigator sites. *P<0.05; **P<0.01; ***P<0.001.
bid, twice a day; CHM, Cochran–Mantel–Haenszel; IBS, irritable bowel syndrome; ITT, intent to treat.

Results

Patients

- Demographics and disease characteristics were well balanced between the tenapanor and placebo groups in both T3MPO-1 and T3MPO-2.[7,8]
  - In the T3MPO-1 intent to treat (ITT) population (tenapanor n=307; placebo n=299), patients overall had a mean age of 45.0 years, 81.4% were female, and they had an average of 0.2 complete spontaneous bowel movements (CSBMs) per week at baseline.[7]
  - In the T3MPO-2 ITT population (tenapanor n=293; placebo n=300), patients overall had a mean age of 45.4 years, 82.1% were female, and they had an average of 0.1 CSBMs per week at baseline.[8]

IBS Symptom Relief

- A significantly higher proportion of tenapanor-treated patients reported adequate relief of IBS-C symptoms vs placebo each week during the randomized treatment period of each study (**Figure 2**; T3MPO-1, $P \leq 0.029$; T3MPO-2, $P \leq 0.021$).
- Similarly, the average weekly degree of IBS symptom relief reported was significantly greater for tenapanor-treated patients vs placebo at all weeks (**Figure 3**).

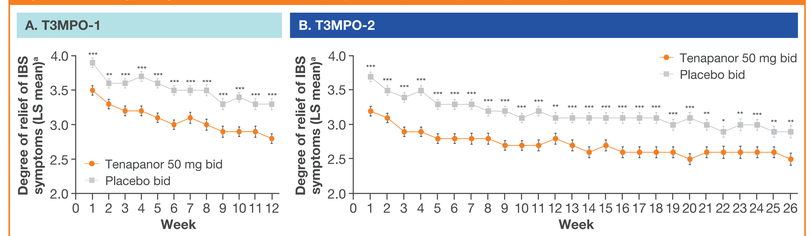
Treatment Satisfaction

- On average, patients treated with tenapanor from both studies were significantly more satisfied than patients treated with placebo ($P<0.001$ all months).
  - For both studies, a higher percentage of patients treated with tenapanor reported that they were "quite" or "very" satisfied with treatment vs patients treated with placebo (**Figure 4**).

Quality of Life

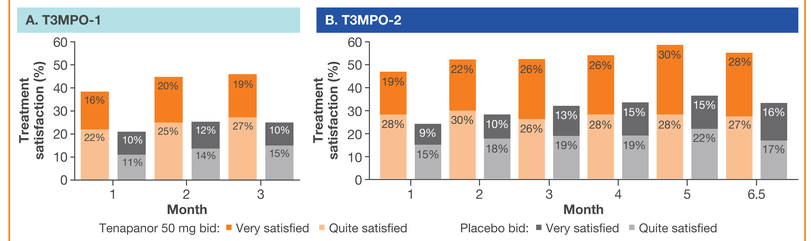
- During T3MPO-1, from baseline to week 12, tenapanor-treated patients had a mean (SD) change of 16.9 (21.2) in their overall IBS-QoL score vs 13.2 (17.4) with placebo ($P=0.089$).
  - From baseline to week 12, the proportion of patients with an IBS-QoL overall score >80 increased with a greater shift in the tenapanor group (14% to 42%) than the placebo group (17% to 36%) (**Figure 5A**).
- During T3MPO-2, from baseline to week 12, tenapanor-treated patients had a mean (SD) change of 19.8 (21.2) in their overall IBS-QoL score vs 16.7 (19.8) with placebo ($P=0.025$), and from baseline to week 26 or early termination visit, tenapanor-treated patients had a change of 21.0 (22.7) in their overall IBS-QoL score vs 17.1 (22.0) with placebo ($P=0.011$).
  - From baseline to week 26 or early termination visit, the proportion of patients with an IBS-QoL overall score >80 increased with a greater shift in the tenapanor group (16% to 49%) than the placebo group (13% to 39%) (**Figure 5B**).

Figure 3. Average Degree of Relief of IBS Symptoms by Week (ITT Population)



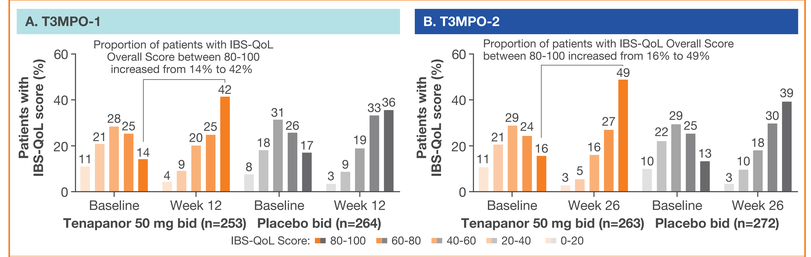
Data are shown for the randomized treatment period of each trial. Error bars represent SE.
LS means, SE, and *P* values are from an ANOVA model with treatment and pooled investigator site as factors (tenapanor 50 mg bid vs placebo). *P<0.05; **P<0.01; ***P<0.001.
[a]Degree of relief was measured on a 7-point scale, where 1=completely relieved and 7=as bad as I can imagine.
ANOVA, analysis of variance; bid, twice daily; IBS, irritable bowel syndrome; ITT, intent to treat; LS, least squares; SE, standard error.

Figure 4. Proportion of Patients Who Were Satisfied With Study Treatment by Month (ITT Population)



bid, twice a day; ITT, intent to treat.

Figure 5. Shifts in IBS-QoL Overall Score From Baseline to Week 12 in T3MPO-1 and Week 26/early termination visit in T3MPO-2 (ITT Population)



Greater IBS-QoL overall score indicates better quality of life.
bid, twice daily; IBS-QoL, irritable bowel syndrome quality of life.

Conclusions

- Patients treated with tenapanor experienced significantly greater relief of their IBS-C symptoms compared with patients who received placebo during the 12-week and 26-week treatment periods of T3MPO-1 and T3MPO-2.
- Greater treatment satisfaction was experienced by patients treated with tenapanor compared with placebo during both studies.
- Treatment with tenapanor led to greater improvements in IBS-related quality of life compared with placebo during the T3MPO-1 and T3MPO-2 treatment periods.
- Overall, tenapanor ameliorates the abdominal pain and constipation associated with IBS-C,[7,8] while improving quality of life for some patients.

Disclosures

Susan Edelstein, Suling Zhao, Yang Yang, and David P. Rosenbaum are employees of Ardelyx, Inc. William D. Chey is a consultant for Abbvie, Ardelyx, Arena, Baush, Biomerica, Gemelli, Ironwood, Isothrive, Nestle, Progenity, Salix, Takeda, Urovant, Vibrant and has stock options with GI on Demand/Gastro Girl, Isothrive, Modify Health.

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