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Tenapanor Has Early Onset of Action in Treating Symptoms of Irritable Bowel Syndrome With Constipation (T3MPO-1 and T3MPO-2 Trials)

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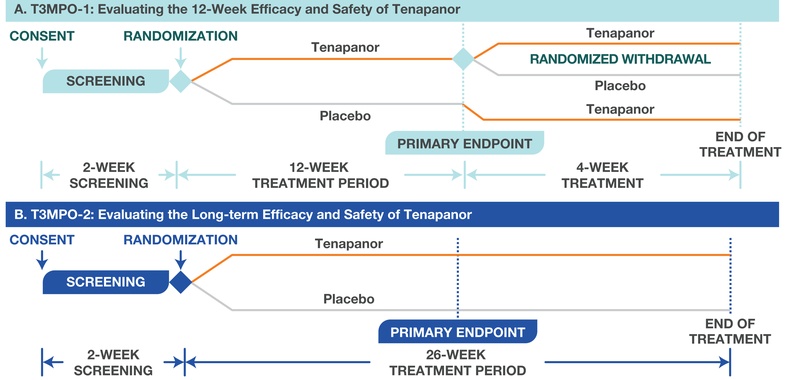
Background

- Tenapanor is a first-in-class, minimally systemic, small-molecule inhibitor of intestinal sodium-hydrogen exchanger isoform 3 (NHE3) that inhibits dietary sodium absorption, resulting in increased stool water content.[1,2]
- Tenapanor is approved for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) based on results from 2 phase 3 randomized clinical trials (T3MPO-1 [NCT02621892] and T3MPO-2 [NCT02686138]).[3-5]
- In the T3MPO-1 and T3MPO-2 clinical trials, tenapanor effectively improved IBS-C symptoms with acceptable safety and tolerability over 12 and 26 weeks, respectively.[3,4]
  - In the primary analyses, significantly more patients treated with tenapanor experienced a combined response rate, defined as a ≥30% reduction in average weekly worst abdominal pain and an increase of ≥1 average weekly complete spontaneous bowel movement (CSBM) from baseline for ≥6 of 12 weeks compared with placebo. Tenapanor-treated patients also experienced significant improvements in other abdominal symptoms, as well as global irritable bowel syndrome (IBS) symptoms.[3,4]
  - Diarrhea was the most commonly reported adverse event with tenapanor; in both studies, 6.5% of tenapanor-treated patients discontinued study drug due to diarrhea vs 0.7% with placebo.[3,4]
- To evaluate the onset of action for tenapanor, we investigated the efficacy of tenapanor within the first week of treatment in the T3MPO-1 and T3MPO-2 studies.

Methods

- T3MPO-1 and T3MPO-2 were phase 3, randomized, double-blind, placebo-controlled trials (**Figure 1**).
  - Full details of the study designs were previously reported.[3,4]
- After a 2-week screening period, patients were randomized to tenapanor 50 mg twice a day or placebo twice a day for 12- and 26-week treatment periods in T3MPO-1 and T3MPO-2, respectively.
- Patients self-reported information about the status of their IBS symptoms daily using an interactive voice response system (IVRS) diary accessed by a touch-tone telephone (**Box**).
- To evaluate the early response to treatment, we investigated the proportion of responders within the first week of treatment for overall response, CSBM response, and abdominal symptom (pain, discomfort, and bloating) responses.
  - An overall response consisted of both an abdominal pain and a CSBM response in the same week.
  - Abdominal pain response was defined as a reduction of ≥30% in average weekly worst abdominal pain score from baseline.
  - CSBM response was defined as an increase of ≥1 in the average weekly CSBM frequency from baseline.
  - Responses for abdominal discomfort and abdominal bloating were defined as a reduction of ≥30% from baseline in average weekly abdominal discomfort or abdominal bloating score, respectively.
- We examined the average weekly abdominal pain score, average weekly CSBM frequency, and average weekly spontaneous bowel movement (SBM) frequency as additional measures of efficacy in the first week of treatment.
- All analyses were performed on the intent-to-treat (ITT) population, which included all patients who met the study eligibility criteria, were randomized, and received ≥1 dose of study drug.

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



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:
  - Completing 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) 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 use in the preceding 24 hours). [b]CSBM was defined as a SBM accompanied by a 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]

- *How would you rate your worst abdominal pain over the past 24 hours? …your abdominal discomfort over the past 24 hours? …your abdominal bloating over the past 24 hours?* Each assessed on a scale of 1 (none) to 10 (very severe)
- *How many bowel movements have you had in the past 24 hours?* For each bowel movement:
  - *Please enter the time of the bowel movement using the 12 hours AM/PM format and indicate if it occurred today or yesterday.*
  - *Did you feel like you completely emptied your bowels?* Yes/No

[a]Entries into the IVRS diary must have been recorded between 6:00 PM and 11:59 PM (local time). [b]Sample 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.

Results

Patients

- Demographics and baseline characteristics were well balanced between the tenapanor and placebo groups in both T3MPO-1 and T3MPO-2.[3,4]

Week 1 response

- For week 1, the tenapanor group had a significantly higher overall responder rate than the placebo group. Significantly higher CSBM and abdominal symptom responder rates were also observed in the tenapanor arm (**Figure 2**).

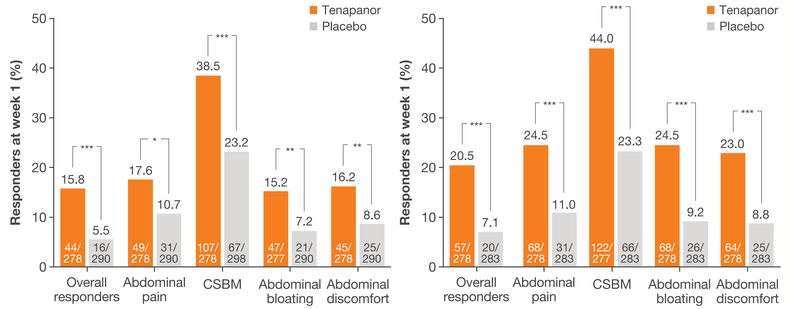
Week 1 change in abdominal pain score

- From baseline to week 1, the average weekly abdominal pain score decreased (**Figure 3**). The maximum mean percent decreases with tenapanor treatment were 44.3% and 54.1% over the 12 weeks of T3MPO-1 and 26 weeks of T3MPO-2, respectively (vs 31.0% and 42.0%, respectively, with placebo).

Week 1 change in bowel movement frequency

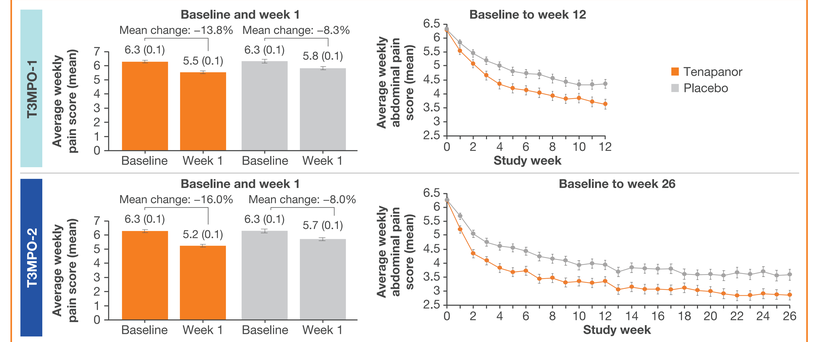
- The average weekly CSBM frequency increased from baseline to week 1 (**Figure 4**). Maximum mean increases in the average weekly CSBM frequency with tenapanor treatment were 2.3 and 3.5 over the 12-week T3MPO-1 and 26-week T3MPO-2 studies, respectively (vs 1.2 and 1.6, respectively, with placebo).
- The average weekly SBM frequency increased from baseline to week 1, with significant improvements with tenapanor compared with placebo in both studies (**Figure 5**).

Figure 2. Responder Rates for Week 1 in T3MPO-1 and T3MPO-2



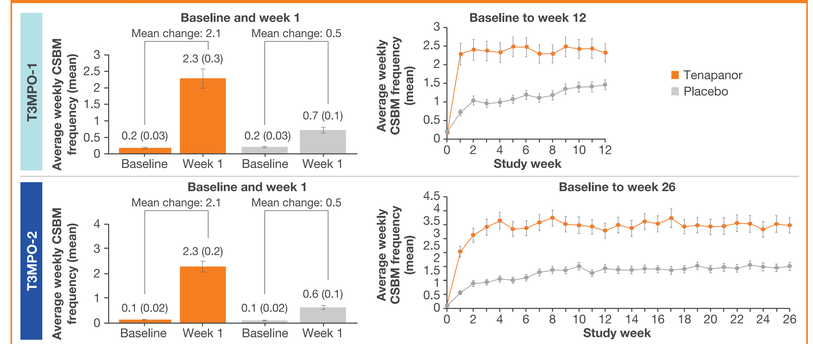
Response rate calculated as the proportion of patients meeting response criteria for week 1. *P* values based on the Cochran-Mantel-Haenszel test *P* value with 1 degree of freedom for the association between treatment (tenapanor and placebo), stratified by pooled investigator sites. Analyses are based on the ITT population.
*$P<0.05$; **$P<0.01$; ***$P<0.001$.
CBSM, complete spontaneous bowel movement; ITT, intent-to-treat.

Figure 3. Weekly Abdominal Pain Scores From T3MPO-1 and T3MPO-2



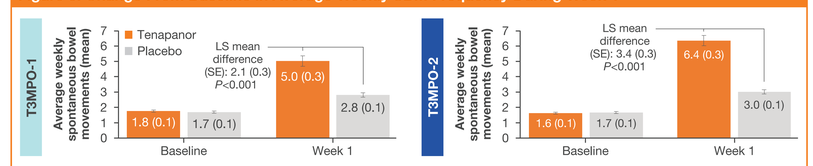
Error bars represent standard error. Abdominal pain was scored daily using a 0- to 10-point scale. The average weekly abdominal pain score was calculated as the average score for all days during a valid week. Baseline (shown as week 0) was calculated as the average of the 2-weeks during the screening period. Data are based on the intent-to-treat population.

Figure 4. Average Weekly CSBM Frequency in T3MPO-1 and T3MPO-2



Error bars represent standard error. A CSBM was defined as an SBM for which the subject responded "yes" to the following question: "Did you feel like you completely emptied your bowels?" Average weekly CSBM frequency was calculated as the sum of the number of CSBMs reported during each day of the defined weekly period divided by the number of days CSBMs were reported and multiplied by 7. Baseline (shown as week 0) was calculated as the average of the 2-weeks during the screening period. Data are based on the ITT population.
CSBM, complete spontaneous bowel movement; ITT, intent-to-treat; SBM, spontaneous bowel movement.

Figure 5. Change From Baseline in Average Weekly SBM Frequency During Week 1



Error bars represent SE. Average weekly SBM frequency was calculated as the average daily SBM frequency over days with SBM reporting within a week multiplied by 7. LS mean, SE, and *P* values are from an ANCOVA model with treatment and pooled investigator site as factors and baseline value as a covariate. Data are based on the ITT population.
ANCOVA, analysis of covariance; ITT, intent-to-treat; LS, least squares; SBM, spontaneous bowel movement; SD, standard deviation; SE, standard error.

Conclusions

- Tenapanor provided statistically significant and clinically meaningful improvements in gastrointestinal and pain symptoms compared with placebo in as early as the first week of treatment.
  - Within the first week of tenapanor treatment, approximately 40% of patients had a CSBM response (an increase of ≥1 in average weekly CSBM frequency), and approximately 20% of patients achieved a response to abdominal symptoms of pain, bloating, or discomfort (≥30% reduction in average weekly abdominal symptom score).
- Building on the overall findings from the T3MPO-1 and T3MPO-2 studies,[3,4] these data support tenapanor as a clinically meaningful treatment option for patients with IBS-C that provides symptom relief as soon as the first week of treatment in some patients.

Disclosures

Ron Fogel has no relationships to disclose. Susan Edelstein, Suling Zhao, Yang Yang, and David P. Rosenbaum are employees of Ardelyx, Inc.

Acknowledgments

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