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Efficacy of Tenapanor in Improving IBS-C Abdominal Symptoms: A Post Hoc Analysis of Multi-item Abdominal Score From the 26-Week Phase 3 T3MPO-2 Study

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Introduction

- Tenapanor is a minimally absorbed, small-molecule inhibitor of intestinal sodium/hydrogen exchanger 3 (NHE3)[1-3] approved for the treatment of adults with irritable bowel syndrome with constipation (IBS-C).[4]
- Preclinical studies demonstrated that tenapanor reduced intestinal permeability by increasing transepithelial resistance in the gut[5,6] and inhibited transient receptor potential cation channel subfamily V member 1 (TRPV1) signaling, leading to reduced visceral hypersensitivity and abdominal pain,[7] although the relevance of experimental models to humans is not known.
- In the phase 3 T3MPO-2 trial (NCT02686138), abdominal pain, complete spontaneous bowel movement (CSBM) frequency, and abdominal bloating were significantly improved with tenapanor vs placebo in patients with IBS-C.[8]
  - Overall safety and tolerability were acceptable, with diarrhea being the most common adverse event.[8]
- Here we use 2 multi-item abdominal scores to investigate the effects of tenapanor on abdominal symptoms in the T3MPO-2 trial.

Methods

- The study design and primary results of T3MPO-2 have been reported previously.[8] Briefly, patients with IBS-C with <3 weekly CSBMs and weekly abdominal pain score ≥3 (0-10 scale) during a 2-week screening period were eligible for study inclusion.[8]
  - Patients were randomized to tenapanor 50 mg or placebo twice a day in a 26-week randomized treatment period (RTP).
  - Patients rated 5 abdominal symptoms (pain, bloating, discomfort, cramping, and fullness) on an 11-point scale (**Box**).

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? …your abdominal cramping over the past 24 hours? …your abdominal fullness over the past 24 hours?*

Questions were assessed separately using the following scale for responses:

None 0 **1** 2 **3** 4 **5** 6 **7** 8 **9** 10 Very Severe

[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.

- Weekly scores for each abdominal symptom were calculated as the average score for all days, during a week with ≥4 days of reporting of the given abdominal symptom.
- In this post hoc analysis, multi-item abdominal scores were calculated using 2 approaches:
  - The abdominal score 3 (AS3) was the mean of weekly scores for abdominal pain, discomfort, and bloating, as described by Chang et al.[9]
  - The expanded abdominal score 5 (AS5) was calculated as the mean of weekly scores for abdominal pain, discomfort, bloating, fullness, and cramping.
- The AS3 and AS5 in the tenapanor and placebo arms were evaluated using the following endpoints:
  - Abdominal score overall change from baseline during the 26-week RTP (mixed-effects model with repeated measures [MMRM]).
    - The MMRM used fixed effect factors of treatment, week, and treatment-by-week; fixed effect covariates of baseline abdominal score and baseline-by-week; and patient as a random effect.
  - Abdominal score change from baseline for each week of the RTP (MMRM with the parameters described above).
  - Cumulative distribution of the change from baseline in AS3 or AS5 at week 26 (Wilcoxon rank sum test; *P* value estimated using a Monte Carlo approach).
  - A weekly response for AS3 and AS5 was defined as achieving a reduction of ≥2 points in AS3 or AS5 for a given week.
  - Weekly response rates were analyzed using Pearson's chi-square test, in which patients with a missing weekly abdominal score due to discontinuation or an "invalid week" (ie, <4 days of reporting of abdominal symptom[s]) were included in the calculation and assumed to have no response in that week (ie, a worst-imputation approach).
  - A 13/26-week AS3 or AS5 response was defined as achieving an AS3 or AS5 response for ≥13 weeks of the 26-week RTP. The 13/26-week response rates were also analyzed using Pearson's chi-square test, with the worst-imputation approach applied to determine a patient's response status for each week of the RTP.
- Analyses of the AS3 and AS5 were conducted in the intent-to-treat population of patients that included all patients who met the study eligibility criteria, were randomized, and received ≥1 dose of study drug.

Results

Patients

- In the T3MPO-2 trial, 620 patients were randomized to treatment in the RTP, and demographic and baseline characteristics were well balanced in the intent-to-treat analysis set (tenapanor, n=293; placebo, n=300).[8]

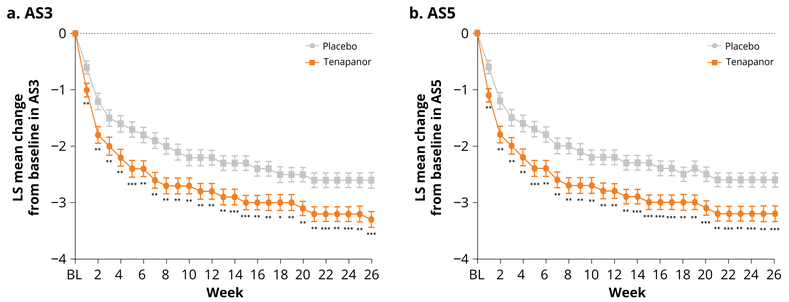
Change in abdominal scores over the 26-week RTP

- There was a greater mean change in abdominal scores with tenapanor compared with placebo over the 26-week RTP for both the AS3 (−3.27 vs −2.60, *P*=0.0007) and the AS5 (−3.23 vs −2.59, *P*=0.0009) (**Figure 1**).
- At week 26, cumulative distribution of change from baseline significantly favored tenapanor over placebo for both the AS3 (estimated *P*=0.0094; 99% CI: 0.0086, 0.0102) and the AS5 (estimated *P*=0.0121; 99% CI: 0.0112, 0.0130) (**Figure 2**).

Abdominal score response rate

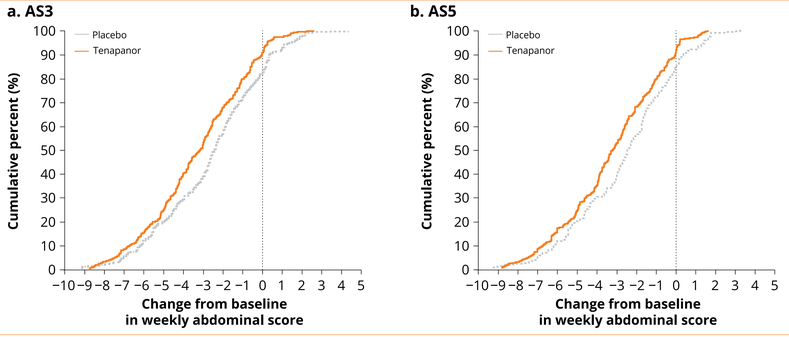
- Weekly AS3 and AS5 response rates were consistently higher with tenapanor compared with placebo over 26 weeks (**Figure 3**), and patients receiving tenapanor had a higher 13/26-week abdominal score response rate compared with patients receiving placebo for both the AS3 (46.4% vs 35.7%, *P*=0.0078) and the AS5 (46.1% vs 33.3%, *P*=0.0015) (**Figure 4**).

Figure 1. Weekly Treatment Effect on the AS3 and AS5



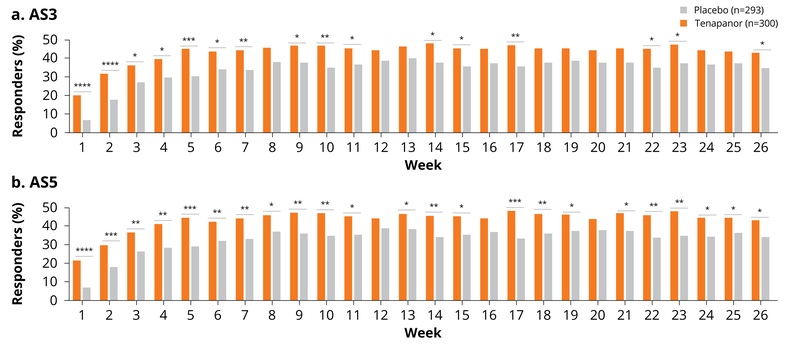
Error bars represent standard error. Data are shown for the intent-to-treat analysis set. *P* values were derived from a MMRM with fixed effect factors of treatment, week, and treatment-by-week; fixed effect covariates of baseline abdominal score and baseline-by-week; and patient as a random effect. *P<0.05; **P<0.01; ***P<0.001.
AS3, abdominal score 3 (mean of weekly scores for abdominal pain, discomfort, and bloating); AS5, abdominal score 5 (mean of weekly scores for abdominal pain, discomfort, bloating, fullness, and cramping); BL, baseline; LS, least squares; MMRM, mixed-effects model with repeated measures.

Figure 2. Cumulative Distribution Function of the Change From Baseline in Week 26 for the AS3 and AS5



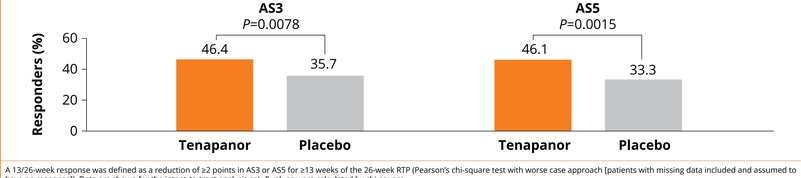
Data are shown for the intent-to-treat analysis set.
AS3, abdominal score 3 (mean of weekly scores for abdominal pain, discomfort, and bloating); AS5, abdominal score 5 (mean of weekly scores for abdominal pain, discomfort, bloating, fullness, and cramping).

Figure 3. Weekly Response Rate Over 26 Weeks



A weekly response was defined as a reduction of ≥2 points in the AS3 or AS5 for a given week (Pearson's chi-square test with worse case approach [patients with missing data included and assumed to have no response]). Data are shown for the intent-to-treat analysis set. *P* values were calculated by chi-square. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.
AS3, abdominal score 3 (mean of weekly scores for abdominal pain, discomfort, and bloating); AS5, abdominal score 5 (mean of weekly scores for abdominal pain, discomfort, bloating, fullness, and cramping).

Figure 4. 13/26-Week AS3 and AS5 Response Rate



A 13/26-week response was defined as a reduction of ≥2 points in AS3 or AS5 for ≥13 weeks of the 26-week RTP (Pearson's chi-square test with worse case approach [patients with missing data included and assumed to have no response]). Data are shown for the intent-to-treat analysis set. *P* values were calculated by chi-square.
AS3, abdominal score 3 (mean of weekly scores for abdominal pain, discomfort, and bloating); AS5, abdominal score 5 (mean of weekly scores for abdominal pain, discomfort, bloating, fullness, and cramping); RTP, randomized treatment period.

Conclusions

- Few treatments for IBS-C consistently improve the range of abdominal symptoms that patients may experience, which include abdominal pain, discomfort, bloating, cramping, and fullness.[10-14]
- In the T3MPO-2 study, treatment with tenapanor resulted in a greater and sustained change from baseline in combined abdominal scores over the 26-week treatment period compared with placebo, when assessed as abdominal pain, discomfort, and bloating (AS3) and when symptoms of fullness and cramping were also included (AS5).
- This post hoc analysis demonstrates that tenapanor significantly improves IBS-C–associated abdominal symptoms with an early onset of action that is sustained throughout the 6-month treatment period.

Disclosures

Anthony Lembo is a consultant for Allergan, Ardelyx, Biomerica, Ironwood Pharmaceuticals, Aeon, Maunea Kea, Alkermes, Pfizer, Sebela, Orthomed, and Vibrant. William D. Chey is a consultant for Abbvie, Ardelyx, Arena, Bausch, Biomerica, Gemelli, Ironwood, Isothrive, Nestle, Progenity, Salix, Takeda, Urovant, and Vibrant, and has stock options with GI on Demand/Gastro Girl, Isothrive, Modify Health. Susan Edelstein, Yang Yang, David M. Spiegel, and David P. Rosenbaum are employees of Ardelyx, Inc.

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IBSRELA® (tenapanor) is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults

Important Safety Information

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- **IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats, administration of tenapanor caused deaths presumed to be due to dehydration.** ***[see PI Contraindications (4), Use in Specific Populations (8.4)]*****.**
- **Avoid use of IBSRELA in patients 6 years to less than 12 years of age.** ***[see PI Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*****.**
- **The safety and effectiveness of IBSRELA have not been established in pediatric patients less than 18 years of age.** ***[see PI Use in Specific Populations (8.4)]*****.**

CONTRAINDICATIONS

IBSRELA is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.

IBSRELA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

WARNINGS AND PRECAUTIONS

Risk of Serious Dehydration in Pediatric Patients

IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).

Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age.

Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients. If severe diarrhea occurs, suspend dosing and rehydrate patient.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions in IBSRELA-treated patients (incidence ≥2% and greater than placebo) were: diarrhea (16% vs 4% placebo), abdominal distension (3% vs <1%), flatulence (3% vs 1%) and dizziness (2% vs <1%).

For additional safety information, including the Boxed Warning, please see full Prescribing Information: click here.

IBS-C, irritable bowel syndrome with constipation.

IBSRELA (tenapanor hydrochloride). Prescribing information. Ardelyx, Inc; 2025.
Available at: https://www.ibsrela-hcp.com/PI