Poster Mo1396

Long Term Treatment With Tenapanor Improves Abdominal Pain and Other Abdominal Symptoms Associated With IBS-C

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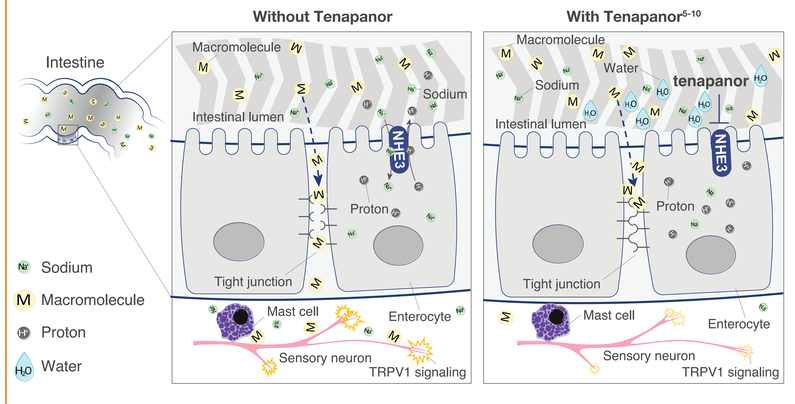
Background

- In patients with irritable bowel syndrome (IBS), abdominal pain may result from increased intestinal permeability and visceral hypersensitivity.[1,2]
  - Increased intestinal permeability has been linked to pain severity and is associated with upregulation of immune responses in the small and large intestine.[1,2]
  - Visceral hypersensitivity, or altered sensation in response to physiologic stimuli, may involve dysregulation in local, enteric neurons and/or gut-brain communication,[3] and has also been linked to neuroimmune interactions.[2]
- Tenapanor is a first-in-class, minimally systemic, small-molecule inhibitor of intestinal sodium-hydrogen exchanger isoform 3 (NHE3) that is approved by the FDA for the treatment of adults with IBS with constipation (IBS-C).[4-6]
- Inhibition of NHE3 with tenapanor reduces dietary sodium absorption (**Figure 1**), resulting in an increase in water volume into the intestinal lumen. The resulting increase in stool water content facilitates accelerated intestinal transit time and softer stool consistency, thereby improving gastrointestinal motility.[5-7]
- In vitro studies demonstrated that tenapanor also modulates tight junctions, which may potentially restore gut barrier function, although the relevance of experimental models to humans is not known.[8,9]
  - In human intestinal cell cultures, tenapanor treatment increased transepithelial electrical resistance and decreased paracellular permeability.[8]
  - Tenapanor significantly attenuated the increased permeability of inflammatory cytokine-treated human colon cell cultures to macromolecules.[9]
- Additionally, preclinical studies suggest that tenapanor may reduce abdominal pain and visceral hypersensitivity, although the relevance to humans is not known.[10]
  - In a rat model of IBS-like colonic hypersensitivity, treatment with tenapanor significantly reduced visceral motor responses to colorectal distension.[10]
  - In the same study, tenapanor normalized colonic sensory neuronal excitability and signaling through the transient receptor potential cation channel subfamily V member 1 (TRPV1),[10] which plays a role in the transduction of pain through primary sensory neurons in the gut.[11]
- In T3MPO-2, a phase 3 study of tenapanor in patients with IBS-C, both abdominal pain and complete spontaneous bowel movements were significantly improved with tenapanor compared with placebo.[12]
  - Safety and tolerability were acceptable, and diarrhea was the most common adverse event.[12]
- Here we perform a post-hoc analysis to further investigate abdominal symptoms reported during the T3MPO-2 (NCT02686138) phase 3 study of tenapanor.

Methods

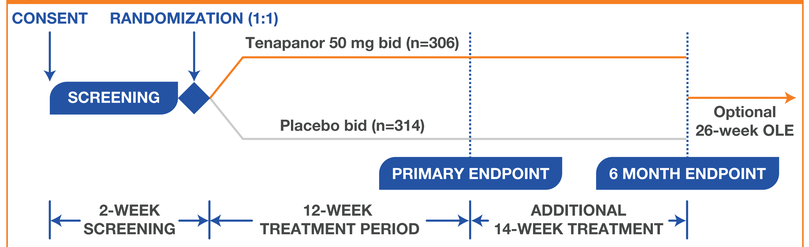
- In T3MPO-2, patients with IBS-C were randomized to tenapanor 50 mg twice a day (bid) or placebo bid for 26 weeks (**Figure 2**).
  - Full details of the study design were previously reported.[12]

Figure 1. Tenapanor Mechanism of Action



NHE3, sodium/hydrogen exchanger isoform 3; TRPV1, transient receptor potential cation channel subfamily V member 1.

Figure 2. T3MPO-2—Long-Term Safety and Efficacy of Tenapanor



bid, twice a day; OLE, open label extension.

- Abdominal symptoms (pain, bloating, discomfort, cramping, fullness) were assessed daily (scale of 0-10 points) using a telephone diary (**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:

0	**1**	2	**3**	4	**5**	6	**7**	8	**9**	10
None										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; IVRS, interactive voice response system.

Results

Patients

- The intent to treat (ITT) population included 293 patients with IBS-C who received tenapanor and 300 patients with IBS-C who received placebo.
  - Demographics and baseline characteristics were similar between the tenapanor and placebo groups. For the entire ITT population, most patients were women (82.1%); the mean age was 45.4 years; and the average weekly complete spontaneous bowel movements was 0.1 at baseline.[12]

Average Weekly Abdominal Symptoms

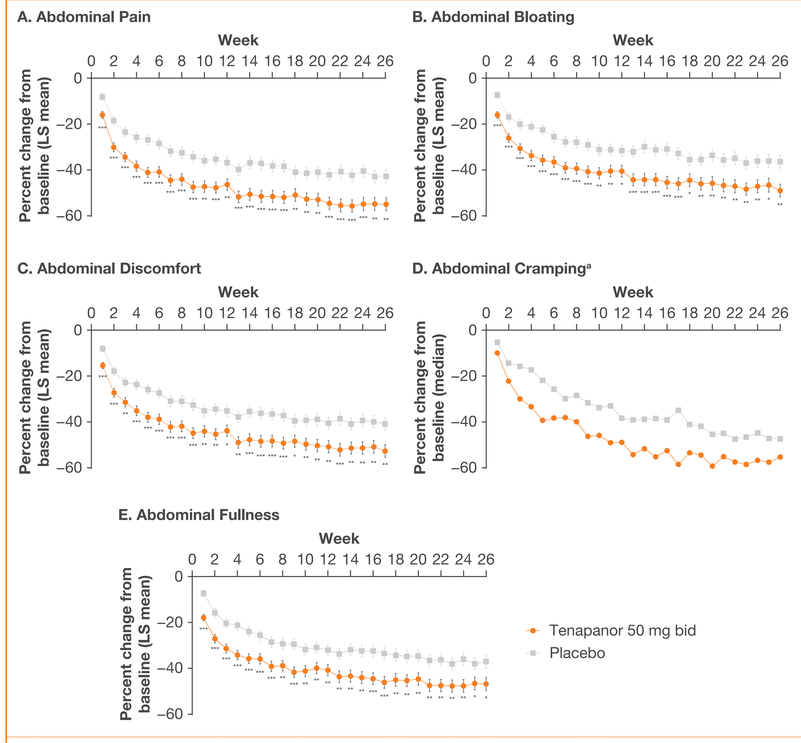
- The average weekly scores for abdominal pain, bloating, discomfort, cramping, and fullness significantly decreased from baseline to week 26 for patients with IBS-C who received tenapanor during T3MPO-2 (**Table 1; Figure 3**).
  - The least squares (LS) mean difference in percent change from baseline to week 26 for tenapanor vs placebo for the abdominal symptoms ranged from –9.8 (abdominal fullness) to –13.7 (abdominal cramping) (**Table 1**).
  - Improvement in abdominal pain, bloating, discomfort, cramping, and fullness was seen as early as the first week of treatment (**Figure 3**).

Table 1. Average Weekly Abdominal Symptom Scores

	Average weekly scores from the ITT population				Percent change from baseline to week 26[a]			
	Baseline		Week 26		LS mean (SE)			
	Tenapanor 50 mg bid n=293	Placebo n=300	Tenapanor 50 mg bid n=186	Placebo n=183	Tenapanor	Placebo	LS mean difference (SE) (vs placebo)	*P* value
Abdominal pain, mean (SD)	6.3 (1.7)	6.3 (1.7)	2.9 (2.4)	3.6 (2.6)	–55.0 (2.9)	–42.8 (2.9)	–12.2 (4.0)	0.002
Abdominal bloating, mean (SD)	6.7 (1.8)	6.6 (1.8)	3.4 (2.6)	4.1 (2.6)	–49.0 (2.8)	–36.4 (2.8)	–12.6 (3.9)	0.001
Abdominal discomfort, mean (SD)	6.4 (1.7)	6.5 (1.7)	3.1 (2.5)	3.8 (2.5)	–52.7 (2.8)	–40.8 (2.8)	–11.9 (3.9)	0.002
Abdominal cramping, mean (SD)	6.2 (1.9)	6.1 (1.8)	2.8 (2.4)	3.5 (2.6)	–56.2 (2.8)	–42.5 (2.8)	–13.7 (3.9)	<0.001
Abdominal fullness, mean (SD)	6.7 (1.8)	6.7 (1.8)	3.5 (2.7)	4.0 (2.5)	–46.8 (2.8)	–37.0 (2.8)	–9.8 (3.9)	0.014

[a]LS means, SE, and *P* values are from an analysis of covariance (ANCOVA) model with treatment and pooled investigator site as factors and baseline value as a covariate.
bid, twice a day; ITT, intent to treat; LS, least squares; SD, standard deviation; SE, standard error.

Figure 3. Percent Change From Baseline Abdominal Symptoms Scores Over Time (ITT Population)



Baseline is defined as the average value from the 2 screening weeks. Error bars represent SE. LS means, SEs, and *P* values are from an ANCOVA model with treatment and pooled investigator site as factors and baseline value as a covariate. *$P<0.05$; **$P<0.01$; ***$P<0.001$.
[a]Distributions were skewed in both arms for abdominal cramping, so median percent change from baseline is shown for this measure.
ANCOVA, analysis of covariance; bid, twice a day; ITT, intent to treat; LS, least squares; SE, standard error.

Conclusions

- In T3MPO-2, tenapanor treatment ameliorated a variety of abdominal symptoms associated with IBS-C, with improvements in abdominal pain, bloating, discomfort, cramping, and fullness that were observed as early as week 1 or 2 and sustained for the entire 26 weeks.
- Tenapanor has a novel mechanism of action and may provide sustained improvement in abdominal pain and other abdominal symptoms for some patients with IBS-C.

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Disclosures

Susan Edelstein, Yang Yang, and David P. Rosenbaum are employees of Ardelyx, Inc. Anthony Lembo is a consultant for Allergan, Ardelyx, Biomerica, Ironwood Pharmaceuticals, Aeon, Maunea Kea, Alkermes, Pfizer, Sebela, Orthomed, and Vibrant.