Poster: P1597

Tenapanor Can Improve Abdominal Symptoms Independent of Changes in Bowel Movement Frequency in Adult Patients With IBS-C

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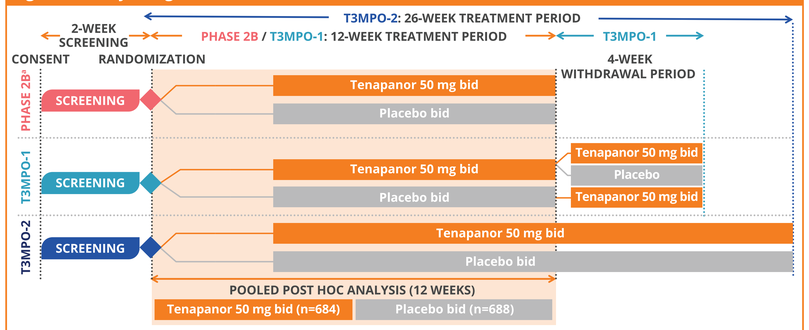
Introduction

- Irritable bowel syndrome with constipation (IBS-C) is a common disorder of gut-brain interaction characterized by abdominal pain, fewer bowel movements, and/or hard/lumpy stools.[1]
- Tenapanor is a first-in-class, minimally absorbed, small-molecule inhibitor of intestinal sodium/hydrogen exchanger isoform 3 (NHE3) approved by the FDA for adults with IBS-C.[2]
- Through NHE3 inhibition, tenapanor reduces the absorption of sodium and retains water content in the gut, leading to softer stool consistency and accelerated transit.
- In nonclinical studies, tenapanor was shown to decrease both intestinal permeability and visceral hypersensitivity.
  - Tenapanor increased transepithelial electrical resistance, decreased paracellular permeability, and normalized colonic sensory neuronal excitability and signaling through inhibition of the transient receptor potential cation channel subfamily V member 1 (TRPV1).[3-5]
- We conducted a post hoc analysis of pooled data from the phase 2b (NCT01923428)[6] and phase 3 T3MPO-1 (NCT02621892)[7] and T3MPO-2 (NCT02686138)[8] studies to examine the effects of tenapanor on abdominal pain and other abdominal symptoms independent of changes in bowel function in IBS-C.

Methods

- Study methods have been described previously for all individual studies.[6-8] Patients were randomized to tenapanor 50 mg or placebo twice a day for 12 (phase 2b and T3MPO-1) or 26 (T3MPO-2) weeks (**Figure 1**).
- Phone diaries were used to collect daily data on abdominal symptoms (including pain, bloating, and discomfort, each on a scale of 0 to 10; see **Box**).
- The 3-item abdominal symptom score (AS3) was derived from the mean of average weekly abdominal pain, bloating, and discomfort scores at their worst (0=none, 10=worst possible).[9]
- Patients with 0 complete spontaneous bowel movements (CSBMs) for ≥6 out of the first 12 weeks of treatment were grouped as the "low-CSBM subgroup."

Figure 1. Study Design



[a]The phase 2b study was a multiple-dose study (5 mg, 20 mg and 50 mg) with a placebo arm. Only patients randomized to tenapanor 50 mg bid or placebo bid were included in the analysis population.
bid, twice a day.

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.

Results

Patients

- The pooled population included 1372 intent-to-treat patients (688 placebo, 684 tenapanor; **Table 1**).
  - Patient demographics were generally similar across the studies.

Table 1. Patient Demographics and Baseline Characteristics (Integrated Safety Analysis Set)

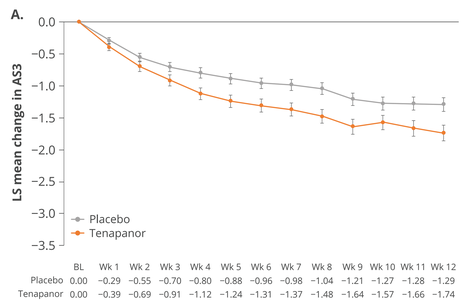
	Low-CSBM subgroup		Overall	
	Tenapanor 50 mg bid N=275	Placebo bid N=366	Tenapanor 50 mg bid N=684	Placebo bid N=688
Age, mean (SD), years	46.6 (12.5)	46.0 (13.3)	45.7 (13.1)	45.0 (13.5)
BMI, mean (SD), kg/m²	29.6 (6.6)	30.0 (6.8)	30.0 (7.0)	29.9 (6.8)
Duration of IBS-C before randomization, mean (SD), years[a]	10.9 (11.9)	11.9 (12.0)	11.2 (11.6)	11.6 (11.9)
Female, n (%)	226 (82.2)	301 (82.2)	559 (81.7)	572 (83.1)
Race, n (%)				
Black	89 (32.4)	114 (31.1)	195 (28.5)	214 (31.1)
White	165 (60.0)	235 (64.2)	452 (66.1)	442 (64.2)
Other[b]	21 (7.6)	17 (4.6)	37 (5.4)	32 (4.7)
Baseline weekly efficacy values, mean (SD)				
AS3	6.93 (1.56)	6.61 (1.64)	6.43 (1.64)	6.43 (1.65)
Abdominal pain score	6.73 (1.66)	6.46 (1.62)	6.24 (1.67)	6.27 (1.65)
CSBM frequency	0.06 (0.24)	0.08 (0.26)	0.16 (0.42)	0.16 (0.40)

[a]Six patients in the T3MPO-1 study did not report the start date of their IBS symptoms. Thus, the mean (SD) duration of IBS symptoms before randomization of the pooled population is reported for the following numbers of patients: placebo (n=684), tenapanor (n=682), and overall (n=1366). [b]Includes Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, multiple, and unknown.
AS3, 3-item abdominal symptom score; bid, twice a day; BMI, body mass index; CSBM, complete spontaneous bowel movement; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation.

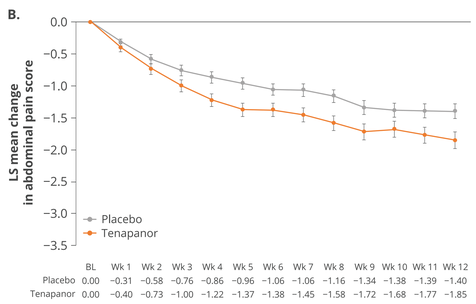
Change in Abdominal Symptom Scores in the Low-CSBM Subgroup

- The low-CSBM subgroup in the tenapanor arm had a greater decrease from baseline than patients in the placebo arm in both AS3 (**Figure 2A**) and average weekly abdominal pain score (**Figure 2B**).

Figure 2. LS Mean Change (±SE) in (A) AS3 and (B) Average Weekly Abdominal Pain Score in the Low-CSBM Subgroup



	BL	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12
Placebo	0.00	−0.29	−0.55	−0.70	−0.80	−0.88	−0.96	−0.98	−1.04	−1.21	−1.27	−1.28	−1.29
Tenapanor	0.00	−0.39	−0.69	−0.91	−1.12	−1.24	−1.31	−1.37	−1.48	−1.64	−1.57	−1.66	−1.74



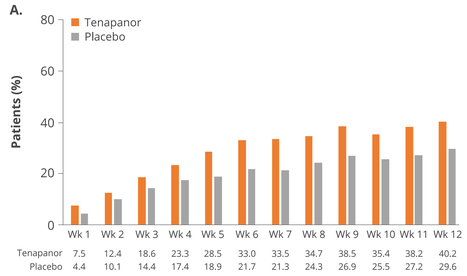
	BL	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12
Placebo	0.00	−0.31	−0.58	−0.76	−0.86	−0.96	−1.06	−1.06	−1.16	−1.34	−1.38	−1.39	−1.40
Tenapanor	0.00	−0.40	−0.73	−1.00	−1.22	−1.37	−1.38	−1.45	−1.58	−1.72	−1.68	−1.77	−1.85

AS3, 3-item abdominal symptom score; BL, baseline; CSBM, complete spontaneous bowel movement; LS, least-squares; wk, week.

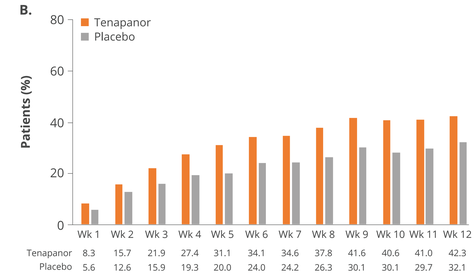
Abdominal Symptom Response Rate in the Low-CSBM Subgroup

- Compared with patients in the placebo arm, a greater proportion of the low-CSBM subgroup in the tenapanor arm had a ≥2-point reduction in AS3 (**Figure 3A**) and average weekly abdominal pain score (**Figure 3B**).

Figure 3. Percentage of Patients With ≥2-Point Reduction in (A) AS3 and (B) Average Weekly Abdominal Pain Score in the Low-CSBM Subgroup



	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12
Tenapanor	7.5	12.4	18.6	23.3	28.5	33.0	33.5	34.7	38.5	35.4	38.2	40.2
Placebo	4.4	10.1	14.4	17.4	18.9	21.7	21.3	24.3	26.9	25.5	27.2	29.6



	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12
Tenapanor	8.3	15.7	21.9	27.4	31.1	34.1	34.6	37.8	41.6	40.6	41.0	42.3
Placebo	5.6	12.6	15.9	19.3	20.0	24.0	24.2	26.3	30.1	30.1	29.7	32.1

AS3, 3-item abdominal symptom score; CSBM, complete spontaneous bowel movement; wk, week.

Safety

- Safety outcomes in NCT01923428,[1] T3MPO-1,[2] and T3MPO-2[3] have been previously reported. Tenapanor was generally well tolerated with an acceptable safety profile.
- The most common treatment-emergent adverse event (TEAE) during the randomized treatment period for both the entire integrated safety analysis set and the low-CSBM subgroup subset was diarrhea.
- In patients treated with tenapanor, the incidence of diarrhea was predictably lower in the low-CSBM subgroup subset (6.9%) than in the entire integrated safety analysis set (14.8%) (**Table 2**).

Table 2. Treatment-Emergent Adverse Events During the Randomized Treatment Period (Integrated Safety Analysis Set)

	Low-CSBM subgroup		Overall	
	Tenapanor 50 mg bid N=275	Placebo bid N=366	Tenapanor 50 mg bid N=691	Placebo bid N=691
Patients with any TEAE	103 (37.5)	125 (34.2)	298 (43.1)	236 (34.2)
TEAE by preferred term reported by >2% of patients				
Diarrhea	19 (6.9)	4 (1.1)	102 (14.8)	16 (2.3)
Nasopharyngitis	11 (4.0)	11 (3.0)	21 (3.0)	20 (2.9)
Urinary tract infection	7 (2.5)	8 (2.2)	14 (2.0)	23 (3.3)
Nausea	4 (1.5)	10 (2.7)	19 (2.7)	17 (2.5)
Headache	6 (2.2)	8 (2.2)	11 (1.6)	17 (2.5)
Flatulence	6 (2.2)	7 (1.9)	17 (2.5)	12 (1.7)
Vomiting	4 (1.5)	9 (2.5)	10 (1.4)	13 (1.9)
Sinusitis	1 (0.4)	10 (2.7)	8 (1.2)	12 (1.7)

Data are n (%). bid, twice a day; CSBM, complete spontaneous bowel movement; TEAE, treatment-emergent adverse event.

Conclusions

Tenapanor improved abdominal symptoms regardless of improvement in CSBMs in adult patients with IBS-C.

Improvement in abdominal symptoms without improvement in CSBMs may be a result of tenapanor's novel mechanism of action that has been shown to reduce both intestinal permeability and visceral hypersensitivity in nonclinical studies.

Overall, tenapanor demonstrated an acceptable safety and tolerability profile.

Disclosures

Darren M. Brenner is a consultant, advisor, and/or speaker for AbbVie (Allergan), Alnylam, Anji, Arena Pharmaceuticals, Ardelyx, Bayer, Entrinsic Bioscience, Gemelli, GI Health Foundation, Ironwood, Laborie, Mahana, Owlstone, RedHill, the Rome Foundation, Salix, Takeda, and Vibrant. He is a member of the board of directors for the International Foundation for GI Disorders (IFFGD). Anthony J. Lembo is a consultant for AEON, Alkermes, Allakos, Allergan, Ardelyx, Arena, Atmo, BioAmerica, Evoke Pharma, Gemelli, Ironwood Pharmaceuticals, OrthoMed, Pfizer, Takeda, and Vibrant, and has stock with Allurion, Bristol Myer Squibb, and Johnson & Johnson. Yang Yang and David Rosembaum are employees of Ardelyx, Inc.

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