Poster: 1590

Improvement in Bloating and Overall Complete Spontaneous Bowel Movement Response With Tenapanor Treatment: A Post Hoc Analysis of the IBS-C Clinical Studies

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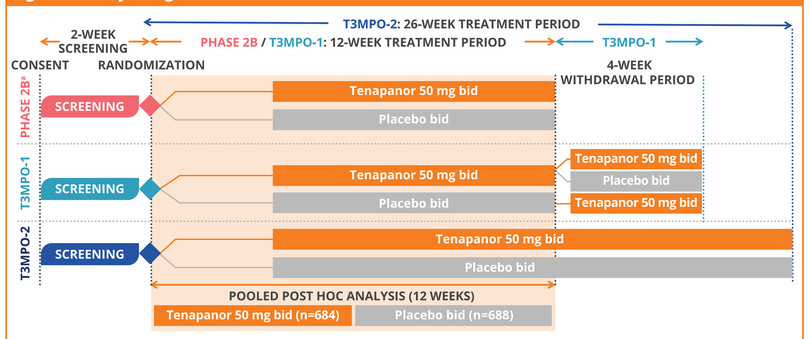
Introduction

- Irritable bowel syndrome with constipation (IBS-C) is a common disorder of gut-brain interaction characterized by abdominal pain, infrequent bowel movements, and/or hard/lumpy stools.[1]
- Bloating is also a common, bothersome abdominal symptom in IBS-C and a frequent reason to seek treatment.[2]
- Tenapanor is a first-in-class, minimally absorbed, small-molecule inhibitor of intestinal sodium-hydrogen exchanger isoform 3 (NHE3) approved by the Food and Drug Administration for adults with IBS-C.[3,4]
- Through NHE3 inhibition, tenapanor reduces the absorption of sodium and retains water content in the gut, leading to softer stool consistency and faster transit.[5,6]
  - In nonclinical studies, tenapanor was shown to decrease both intestinal permeability and visceral hypersensitivity.[7,8]
  - The phase 2b (NCT01923428) and phase 3 T3MPO-1 (NCT02621892) and T3MPO-2 (NCT02686138) studies showed that patients treated with tenapanor 50 mg twice a day experienced both significant increase in complete spontaneous bowel movements (CSBMs) and decrease in abdominal pain compared with those receiving placebo.[9-11] The most common adverse event seen across tenapanor studies was diarrhea.
  - We previously demonstrated that tenapanor improved bloating along with other abdominal symptoms in IBS-C in the phase 3 studies.[10,11]
- We conducted a post hoc analysis of pooled data from the phase 2b and 3 studies to assess the relationship between improvement in bloating and overall CSBM response with tenapanor treatment.

Methods

- Study methods have been described previously.[9-11] To summarize, the clinical trials enrolled adults with IBS-C who met the Rome III criteria. 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**). A phone diary was used to collect data on daily abdominal bloating on an 11-point scale.
- For this analysis, patients treated with tenapanor were categorized as those who met and those who did not meet the overall CSBM response, defined as achieving an increase of ≥1 weekly CSBM from baseline for ≥6 out of the first 12 weeks of treatment (ie, 6 of 12-week CSBM responses).
- For T3MPO-2 specifically, tenapanor-treated patients were also categorized as those who met and those who did not meet the overall CSBM response, defined as achieving an increase of ≥1 weekly CSBM from baseline for ≥13 out of 26 weeks (ie, 13 of 26-week CSBM responses).
- Patients who met these criteria were grouped as "responders," and those who did not meet these criteria were grouped as "the low-CSBM subgroup."
- We assessed mean change from baseline in average weekly bloating score stratified by overall CSBM responder status.

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.

Results

Patients

- The pooled population of the phase 2b and phase 3 studies included 684 intent-to-treat patients who received tenapanor (**Table 1**).
  - Patient demographics were generally similar between 6 of 12-week CSBM responders and the low-CSBM subgroup.

Table 1. Patient Demographics and Baseline Characteristics by 6 of 12-Week CSBM Response Status (Pooled Population)

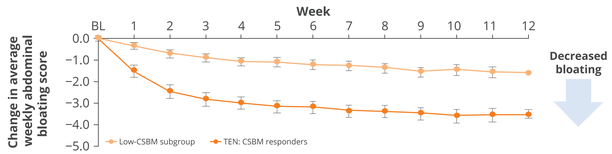
	6 of 12-week CSBM responders	Low-CSBM subgroup	Overall
	Tenapanor 50 mg N=294	Tenapanor 50 mg N=390	Tenapanor 50 mg N=684
Age, mean (SD), years	46.4 (12.9)	45.1 (13.2)	45.7 (13.1)
Sex, n (%)			
Female	249 (84.7)	310 (79.5)	559 (81.7)
Race, n (%)			
Black	85 (28.9)	110 (28.2)	195 (28.5)
White	197 (67.0)	255 (65.4)	452 (66.1)
Other[a]	12 (4.1)	25 (6.4)	37 (5.4)
Body mass index, mean (SD), kg/m²	30.0 (7.2)	30.0 (6.8)	30.0 (7.0)
Duration of IBS symptoms before randomization, mean (SD), years	11.3 (10.6)	11.2 (12.3)	11.2 (11.6)
Baseline average weekly score of efficacy measure, mean (SD)			
Bloating	6.20 (1.84)	6.92 (1.64)	6.61 (1.80)
CSBM frequency	0.17 (0.39)	0.15 (0.44)	0.16 (0.42)

Unless otherwise indicated, data are mean (SD).
[a]Includes Asian, Multiple, American Indian/Alaska Native, and Unknown.
CSBM, complete spontaneous bowel movement; IBS, irritable bowel syndrome.

Abdominal Bloating Scores

- In the pooled population, both 6 of 12-week CSBM responders and the low-CSBM subgroup showed improvements in abdominal bloating throughout the first 12 weeks of treatment, with mean reductions of 3.53 and 1.60, respectively, in weekly abdominal bloating score during week 12 (**Figure 2**).

Figure 2. Mean (±Standard Error) Change From Baseline in Average Weekly Bloating Score by 6 of 12-Week CSBM Response Status (Pooled Population)



	BL	1	2	3	4	5	6	7	8	9	10	11	12
TEN: Incompleters (n)	390	349	334	329	315	293	286	274	280	269	269	260	253
TEN: Responders (n)	294	289	288	289	287	290	290	288	286	280	276	271	260

BL, baseline; CSBM, complete spontaneous bowel movement; TEN, tenapanor.

- Similarly, in the individual studies, both 6 of 12-week CSBM responders and the low-CSBM subgroup had improvements in abdominal bloating, with mean reductions of 3.62 and 1.54 in the phase 2b study, 3.28 and 1.78 in T3MPO-1, and 3.69 and 1.37 in T3MPO-2, respectively, in weekly abdominal bloating score during week 12 (**Figure 3A-C**).
- In the T3MPO-2 study, both 13 of 26-week CSBM responders and the low-CSBM subgroup had improvements in abdominal bloating with mean reductions of 4.16 and 1.97, respectively, in weekly abdominal bloating score during week 26 (**Figure 3D**).

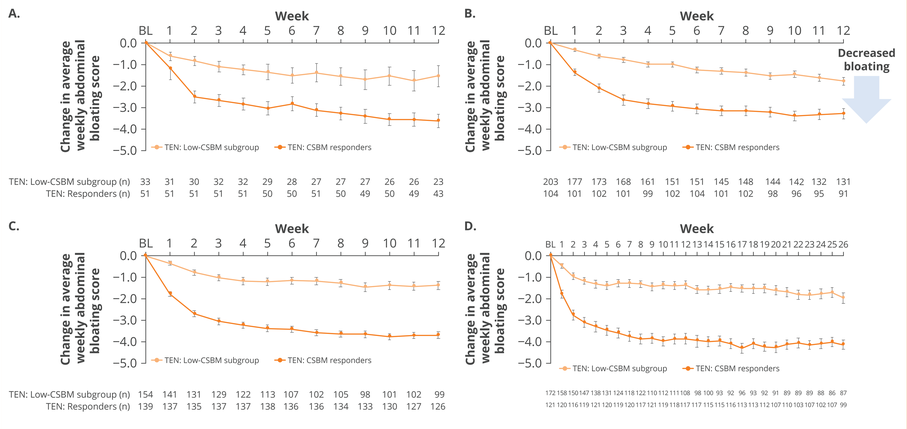
Correlation of Abdominal Bloating With Abdominal Pain

- There was a high correlation between improvement in abdominal bloating and abdominal pain.
- **Figure 4** demonstrates the high correlation between the average weekly scores of abdominal bloating and abdominal pain in the placebo group and tenapanor group at baseline and during week 12.

Safety

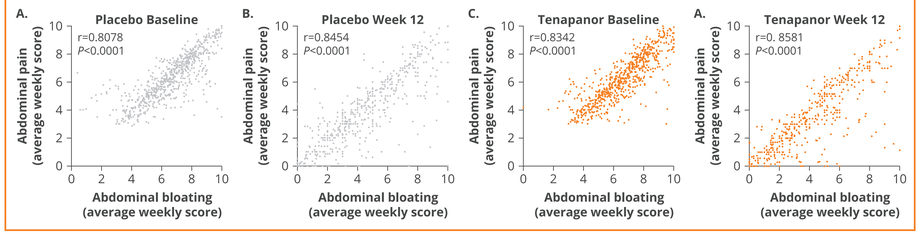
- Safety outcomes for the phase 2b study (NCT01923428),[9] T3MPO-1 (NCT02621892),[10] and T3MPO-2 (NCT02686138)[11] have been previously reported. The integrated safety analysis set included 1382 patients, with 691 in the tenapanor group and 691 in the placebo group.
- Tenapanor was generally well tolerated with an acceptable safety profile.
- The most common treatment-emergent adverse event was diarrhea, which was reported in 14.8% of tenapanor-treated patients from the integrated safety analysis set.
- Diarrhea was mostly mild to moderate in severity.

Figure 3. Mean (±Standard Error) Change From Baseline in Average Weekly Bloating Score by (A-C) 6 of 12-Week CSBM Response Status in the (A) Phase 2b Study, (B) T3MPO-1, and (C) T3MPO-2, and (D) 13 of 26-Week CSBM Response Status in T3MPO-2



BL, baseline; CSBM, complete spontaneous bowel movement; TEN, tenapanor.

Figure 4. Correlation Between the Average Weekly Scores of Abdominal Bloating and Abdominal Pain in the Placebo Group (A, B) and Tenapanor Group (C, D) at Baseline and During Week 12



Conclusions

- Patients with IBS-C treated with tenapanor demonstrated marked improvement in average weekly bloating score, with a greater improvement in bloating among patients who achieved an overall CSBM response.
- A high correlation was observed between the average weekly scores of abdominal bloating and abdominal pain, signifying a relationship between abdominal pain and bloating.
- Tenapanor treatment improved both abdominal bloating and abdominal pain.
- Tenapanor was generally well tolerated, with mild to moderate diarrhea as the most common adverse effect.

Disclosures

Eric Shah has served as a consultant for Salix Pharmaceuticals. Carol Antequera has no commercial interests or conflicts of interest to declare. Dheepika Weerasinghe, Yang Yang, and Susan Edelstein are employees of Ardelyx, Inc.

Dr. Shah can be contacted for further information on this study at ERShah@umich.edu.

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