Evaluation of Tenapanor Efficacy in Clinical and Demographic Subgroups of Patients With Irritable Bowel Syndrome With Constipation

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Background

- Irritable bowel syndrome with constipation (IBS-C) is characterized by abdominal pain associated with changes in bowel movements that include infrequent bowel movements and hard or lumpy stools.[1]
- Tenapanor is a first-in-class, minimally absorbed, small molecule inhibitor of sodium/hydrogen exchanger isoform 3 (NHE3), which is expressed on the luminal surface of the gastrointestinal tract.[2-5]
- Tenapanor is approved for the treatment of adults with IBS-C based on two phase 3, randomized, placebo-controlled trials, T3MPO-1 (NCT02621892) and T3MPO-2 (NCT02686138), which demonstrated that tenapanor significantly improved both complete spontaneous bowel movements (CSBMs) and abdominal pain compared with placebo.[2,6,7]
- To further evaluate the efficacy of tenapanor in patients with IBS-C, we investigated patient subgroups based on clinical and demographic characteristics, specifically baseline abdominal pain severity, age, sex, and race.

Methods

- The phase 3 T3MPO-1 and T3MPO-2 trials enrolled adults with IBS-C (Rome III) who had <3 weekly CSBMs, ≤5 weekly spontaneous bowel movements (SBMs), and an average weekly worst abdominal pain score of ≥3 (0- to 10-point scale).[6,7]
- Patients were randomized (1:1) to tenapanor 50 mg twice a day (bid) or placebo for 12 weeks in T3MPO-1 and for 26 weeks in T3MPO-2.
- This post hoc analysis was conducted on the pooled intent-to-treat (ITT) populations from T3MPO-1 and T3MPO-2 over the first 12 weeks of treatment, with subgroups based on:
  - Abdominal pain severity score at baseline (<6.2 vs ≥6.2 [scale 0-10])
  - Age (<50 years vs 50-65 years vs ≥65 years)
  - Sex (female vs male)
  - Race (White vs Black vs Other)
    - The "Other" race subgroup included patients who were Asian, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander, multiple, and unknown.
- Durable overall CSBM response was defined as achieving an increase of ≥1 CSBM per week from baseline and having ≥3 CSBMs per week in the same week for ≥9 of 12 weeks, including ≥3 of the last 4 weeks of treatment.
- Early CSBM response was defined as having the first post-treatment CSBM by the end of day 2.

Results

Patients

- Baseline demographics and disease characteristics of the ITT populations of T3MPO-1 and T3MPO-2, which have been previously published,[4,5] are summarized in **Table 1** and **Table 2**.

Table 1. Baseline Demographics and Disease Characteristics of Patients in the ITT Populations of T3MPO-1 and T3MPO-2

	T3MPO-1		T3MPO-2		Pooled	
	Tenapanor 50 mg bid (n=307)	Placebo bid (n=299)	Tenapanor 50 mg bid (n=293)	Placebo bid (n=300)	Tenapanor 50 mg bid (n=600)	Placebo bid (n=599)
Mean age, years (SD)	45.0 (13.4)	44.9 (13.0)	46.1 (13.1)	44.8 (13.8)	45.5 (13.2)	44.9 (13.4)
Female, n (%)	244 (79.5)	249 (83.3)	240 (81.9)	247 (82.3)	484 (80.7)	496 (82.8)
Race, n (%)						
White	201 (65.5)	186 (62.2)	185 (63.1)	192 (64.0)	386 (64.3)	378 (63.1)
Black/African American	88 (28.7)	100 (33.4)	92 (31.4)	92 (30.7)	180 (30.0)	192 (32.1)
Other[a]	18 (5.8)	13 (4.4)	16 (5.5)	16 (5.3)	34 (5.7)	29 (4.8)
Mean BMI, kg/m² (SD)	29.9 (7.2)	29.3 (6.4)	30.5 (7.2)	30.9 (7.3)	30.2 (7.2)	30.1 (6.9)
Mean duration of IBS symptoms before randomization, years (SD)	n=305 10.7 (11.7)	n=295 11.2 (11.4)	n=293 11.1 (11.1)	n=300 11.1 (11.6)	n=598 10.9 (11.4)	n=595 11.2 (11.5)
Disease characteristic[b]						
Abdominal pain[c]	6.3 (1.6)	6.3 (1.6)	6.3 (1.7)	6.3 (1.7)	6.3 (1.7)	6.3 (1.7)
CSBMs per week	0.2 (0.5)	0.2 (0.5)	0.1 (0.3)	0.1 (0.3)	0.2 (0.4)	0.2 (0.4)
SBMs per week	1.8 (1.3)	1.7 (1.2)	1.6 (1.0)	1.7 (1.1)	1.7 (1.2)	1.7 (1.2)
Stool consistency[d]	0.5 (0.5)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)
Straining[e]	0.9 (0.6)	0.9 (0.6)	0.9 (0.6)	0.9 (0.6)	0.9 (0.6)	0.9 (0.6)
IBS severity[f]	3.9 (0.7)	3.9 (0.7)	3.9 (0.7)	3.9 (0.7)	3.9 (0.7)	3.9 (0.7)
Constipation severity[f]	4.1 (0.7)	4.0 (0.7)	4.1 (0.7)	4.0 (0.7)	4.1 (0.7)	4.0 (0.7)

[a]Includes American Indian or Alaskan Native, Asian, multiple (ie, self-reported >1 race), Native Hawaiian or other Pacific Islander, other, and unknown. [b]Data are mean (SD) of the average of the weekly scores during the 2-week screening period for individual patients. [c]Assessed daily using a scale of 0-10, where 0 = none and 10 = very severe. Average weekly score was calculated from scores for all days during a valid week. [d]Assessed using the 7-point BSFS. Average weekly score was calculated from scores for all valid SBMs during the week. Days with no stools were scored as 0, resulting in a mean baseline value of <1. [e]Assessed for each SBM using a scale of 1-5, where 1 = not at all and 5 = an extreme amount. Average weekly score was calculated from scores for all valid SBMs during the week. Days with no stools were scored as 0, resulting in a mean baseline value of <1. [f]Assessed weekly using a scale of 1-5, where 1 = none and 5 = very severe.
bid, twice a day; BMI, body mass index; BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; IBS, irritable bowel syndrome; ITT, intent-to-treat; SBM, spontaneous bowel movement.

Table 2. Sample Size of Each Subgroup in the T3MPO-1 and T3MPO-2 Pooled ITT Population

	Number of patients
Age, years	
<50	743
50-65	357
≥65	99
Sex, n	
Female	980
Male	219
Race, n (%)	
White	764
Black/African American	372
Other[a]	63
Baseline abdominal pain severity score[b]	
<6.2	598
≥6.2	601

[a]Includes American Indian or Alaskan Native, Asian, multiple (ie, self-reported >1 race), Native Hawaiian or other Pacific Islander, other, and unknown. [b]Assessed daily using a scale of 0-10, where 0 = none and 10 = very severe. Average weekly score was calculated from scores for all days during a valid week.
ITT, intent-to-treat.

Durable Overall CSBM Response

- A significantly higher proportion of patients randomized to tenapanor vs placebo had a durable CSBM response in most subgroups (**Figure 1**).

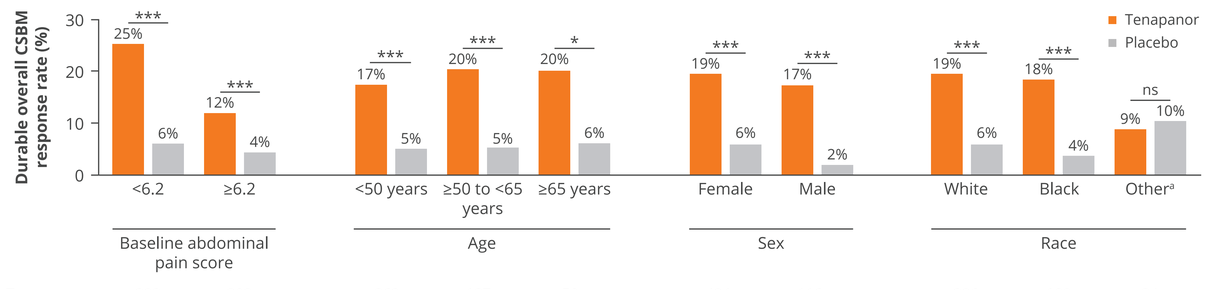
Early Response

- For most subgroups, a significantly higher proportion of patients randomized to tenapanor vs placebo had an early response (ie, first post-treatment CSBM prior to the end of day 2) (**Figure 2**).
- Similarly, for most subgroups, a significantly higher proportion of patients randomized to tenapanor vs placebo had an early response (ie, first post-treatment SBM prior to the end of day 2) (**Figure 3**).

Safety

- As reported previously, diarrhea was the most common adverse event in T3MPO-1 and T3MPO-2, with most cases being mild or moderate in severity.[6,7]
- Discontinuation rates due to diarrhea were low (<10%).

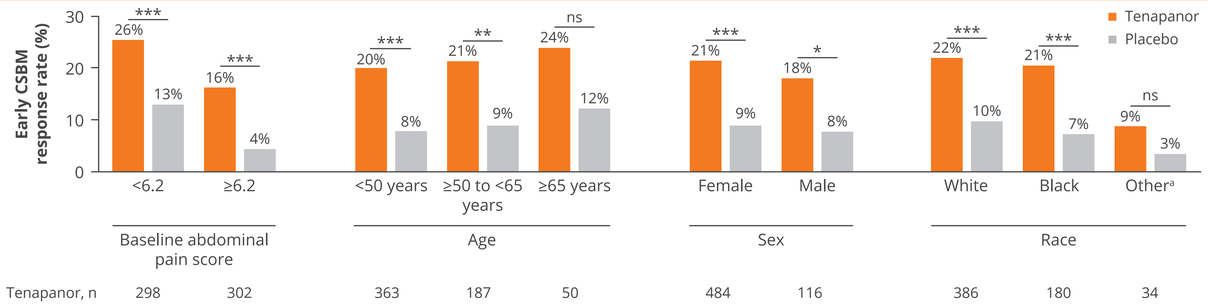
Figure 1. Subgroup Analyses of Durable Overall CSBM Response



Tenapanor, n	298	302	363	187	50	484	116	386	180	34
Placebo, n	300	299	380	170	49	496	103	378	192	29

Durable overall CSBM response defined as an increase of ≥1 CSBM per week from baseline and having ≥3 CSBMs per week in the same week for ≥9 of 12 weeks, including ≥3 of the last 4 weeks of treatment.
[a]Other includes American Indian or Alaskan Native, Asian, multiple (ie, self-reported >1 race), Native Hawaiian or other Pacific Islander, other, and unknown.
*P<0.05. **P<0.01. ***P<0.001.
P-values from Cochran–Mantel–Haenszel tests with pooled investigational site as a stratification factor.
CSBM, complete spontaneous bowel movement; NS, not significant.

Figure 2. Subgroup Analyses of Early CSBM Response (First Post-Treatment CSBM by End of Day 2)



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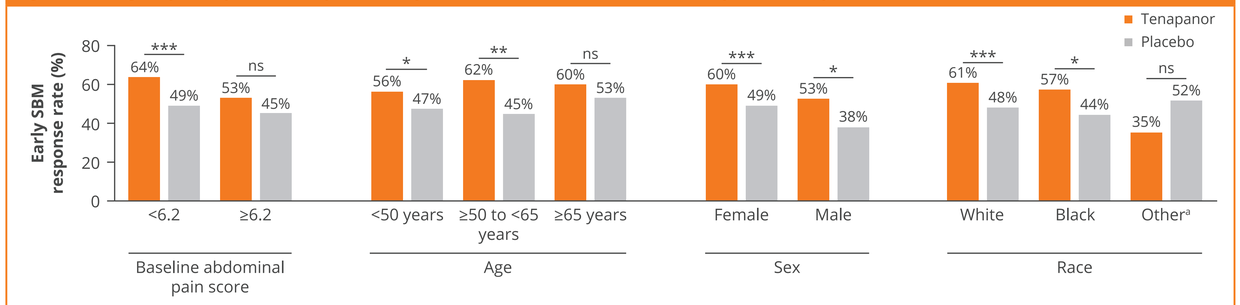
P-values from Cochran–Mantel–Haenszel tests with pooled investigational site as a stratification factor.
CSBM, complete spontaneous bowel movement; NS, not significant.

Figure 3. Subgroup Analyses of Early SBM Response (First Post-Treatment SBM by End of Day 2)



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*P<0.05. **P<0.01. ***P<0.001.
P-values from Cochran–Mantel–Haenszel tests with pooled investigational site as a stratification factor.
NS, not significant; SBM, spontaneous bowel movement.

Conclusions

Tenapanor, a novel drug for IBS-C, is effective in improving bowel symptoms and abdominal pain across a diverse population of patients including those with differing baseline abdominal pain severity scores, younger and older adults, Black and White race, and men and women.

References

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Disclosures

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Dr. Rao can be contacted for further information on this study at SRAO@augusta.edu.

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