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Assessment of Diarrhea in Patients With Irritable Bowel Syndrome With Constipation (IBS-C) Treated With Tenapanor: A Pooled Safety Analysis of the Phase 3 Studies

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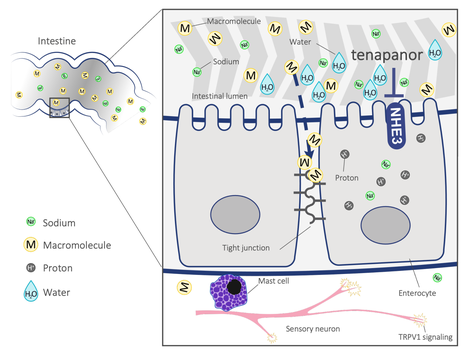
Background

- Irritable bowel syndrome with constipation (IBS-C) is a common disorder of the gut-brain interaction characterized by abdominal pain, fewer bowel movements, and hard/lumpy stools.[1]
- Tenapanor is a first-in-class, minimally absorbed, small molecule inhibitor of intestinal sodium/hydrogen exchanger isoform 3 (NHE3) that reduces dietary sodium absorption, leading to retention of luminal water. The resulting increase in stool water content facilitates accelerated intestinal transit time and softer stool consistency, thereby improving gastrointestinal motility (see **Figure 1**).[2-4]
- Tenapanor is approved for the treatment of adults with IBS-C based on the two pivotal phase 3, randomized, placebo-controlled trials, T3MPO-1 (NCT02621892) and T3MPO-2 (NCT02686138), that met the FDA-defined clinical endpoint.[5-7]
  - The primary endpoint in each pivotal trial was the 6/12 week overall response, defined as achieving a reduction of ≥30% from baseline in average weekly worst abdominal pain and an increase of ≥1 in average weekly complete spontaneous bowel movements (CSBMs) from baseline, both in the same week, for ≥6 of the first 12 treatment weeks.[5,6]
  - Patients who completed T3MPO-1 or T3MPO-2 could enroll in T3MPO-3 (NCT02727751), an open-label long-term safety extension trial.[8]
- Tenapanor was shown to have acceptable safety and was generally well tolerated across all 3 studies.[5,6,8]
- We report a pooled analysis of these phase 3 studies to further investigate diarrhea, the most common adverse event (AE) with tenapanor treatment.

Figure 1. Mechanism of Action of Tenapanor[2-4]



Tenapanor inhibits NHE3, leading to:

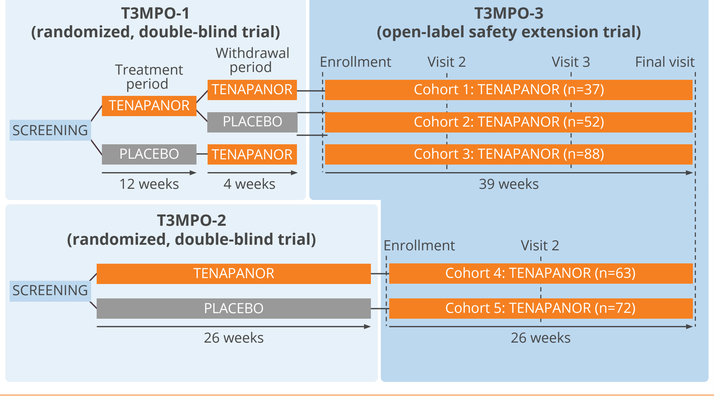
- Reduction of dietary sodium absorption, which in turn leads to retention of luminal water, resulting in a softer stool consistency and accelerated intestinal transit
- Decreased intestinal permeability to macromolecules in nonclinical studies
- Reduced visceral hypersensitivity and abdominal pain in nonclinical studies

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

Methods

- Methods for T3MPO-1 and T3MPO-2 have been previously described[5,6]; briefly:
  - The T3MPO-1 and T3MPO-2 studies enrolled adults with IBS-C (Rome III) who had <3 weekly CSBMs and average weekly worst abdominal pain score ≥3 (0- to 10-point scale).
  - The duration of the randomized treatment period (RTP) of the T3MPO-1 and T3MPO-2 studies was 12 and 26 weeks, respectively (**Figure 2**). Patients were randomized (1:1) to receive tenapanor (50 mg twice a day [bid]) or placebo (bid) during the RTP.
- Upon completion of T3MPO-1/T3MPO-2 (i.e., the parent study), patients could enter T3MPO-3, an open-label, long-term safety extension trial. Patients in T3MPO-3 received open-label tenapanor 50 mg bid for up to an additional 39 (for patients from T3MPO-1) or 26 (for patients from T3MPO-2) weeks (**Figure 2**).[7]
- In all 3 studies, information on each diarrhea event including start/end dates and degree of severity were recorded.

Figure 2. Study Design for T3MPO-1, T3MPO-2, and T3MPO-3



Tenapanor was administered as 50 mg bid in all 3 studies and study periods.

Results

Patients

- Demographics and baseline characteristics of the study-level safety population were previously published for the T3MPO-1,[5] T3MPO-2,[6] and T3MPO-3[8] studies.
- Three safety populations were studied:
  - The pooled T3MPO-1/T3MPO-2 population included 602 tenapanor-treated patients and 601 placebo-treated patients.
  - The T3MPO-3 population included 312 patients who entered the T3MPO-3 study after completion of the T3MPO-1 (n=177) and T3MPO-2 (n=135) studies.
  - The long-term subset of the T3MPO-3 population included 90 patients who received tenapanor for at least 52 weeks across the parent study (T3MPO-1/T3MPO-2) and the T3MPO-3 study.
- Demographics and baseline characteristics of the pooled T3MPO-1/T3MPO-2 population were similar between the tenapanor and placebo arms (**Table 1**).

Table 1. Demographics and Baseline Characteristics for the Pooled T3MPO-1/T3MPO-2 Population and T3MPO-3 Population (and Long-term Subset)

Characteristic	Pooled T3MPO-1/T3MPO-2 Population[a]			T3MPO-3 Population	
	Placebo (N=601)	Tenapanor (N=602)	Overall (N=1203)	Overall (N=312)	Long-term subset (N=90)[b]
Age at informed consent, years	44.9 (13.40)	45.5 (13.29)	45.2 (13.35)	49.1 (13.14)	50.9 (13.09)
Male, n (%)	103 (17.1)	117 (19.4)	220 (18.3)	57 (18.3)	17 (18.9)
Race, n (%)					
American Indian or Alaska Native	2 (0.3)	1 (0.2)	3 (0.3)	1 (0.3)	0
Asian	13 (2.2)	22 (3.7)	35 (2.9)	1 (0.3)	0
Black or African American	192 (32.0)	181 (30.1)	373 (31.0)	89 (28.5)	26 (28.9)
Multiple	8 (1.3)	7 (1.2)	15 (1.3)	2 (0.6)	0
Other/Unknown	6 (1.0)	4 (0.7)	10 (1.7)	2 (0.6)	1 (1.1)
White	380 (63.2)	387 (64.3)	767 (63.8)	217 (69.6)	63 (70.0)
Ethnicity, n (%)					
Not Hispanic or Latino	440 (73.2)	427 (70.9)	867 (72.1)	182 (58.3)	48 (53.3)
Hispanic or Latino	161 (26.8)	175 (29.1)	336 (27.9)	130 (41.7)	42 (46.7)
Baseline[c] weight, kg	82.4 (20.63)	82.7 (20.80)	82.6 (20.71)	80.9 (19.33)	81.8 (21.07)
Baseline[c] height, cm	165.3 (9.07)	165.5 (9.42)	165.4 (9.24)	164.7 (9.15)	164.1 (9.28)
Baseline[c] BMI, kg/m²	30.1 (6.90)	30.2 (7.19)	30.1 (7.04)	29.8 (6.60)	30.4 (7.38)

Unless otherwise indicated, data are mean (SD).
[a]Patients treated with placebo or tenapanor during the RTP of T3MPO-1 (12 weeks) and T3MPO-2 (26 weeks). [b]Subset of the T3MPO-3 population who received tenapanor for at least 52 weeks. [c]Baseline was defined as the measurement taken at T3MPO-1/T3MPO-2 day 1 pre-dose, or if missing the last measurement prior to the first dose of the study drug.
BMI, body mass index; RTP, randomized treatment period; SD, standard deviation.

Exposure to Tenapanor

- The mean exposure to study drug during the RTP (tenapanor or placebo) was 120.9 days in the placebo arm and 113.7 days in the tenapanor arm for the pooled T3MPO-1/T3MPO-2 population (**Table 2**).
- The mean exposure to tenapanor across the parent (T3MPO-1/T3MPO-2) and the T3MPO-3 studies was 286.9 days and the majority (253/312 [81.1%]) of patients received tenapanor for more than 26 weeks (**Table 2**).
  - 90 patients (28.8%) received tenapanor for more than 52 weeks (i.e., the long-term subset).

Table 2. Exposure to Study Drug During the RTP (Tenapanor or Placebo) for the Pooled T3MPO-1/T3MPO-2 Population and Exposure to Tenapanor Across the Parent Study (T3MPO-1/T3MPO-2) and T3MPO-3 for the T3MPO-3 Population

	Pooled T3MPO-1/T3MPO-2 Population[a]		T3MPO-3 Population[b]
	Placebo (N=601)	Tenapanor (N=602)	Overall (N=312)
Treatment duration, days			
mean (SD)	120.9 (53.29)	113.7 (57.57)	286.9 (94.39)
median (min, max)	87 (1, 211)	85 (1, 216)	306 (6, 445)
Exposure category, n (%)			
≤2 weeks	6 (1.0)	29 (4.8)	3 (1.0)
>2 to ≤4 weeks	10 (1.7)	16 (2.7)	1 (0.3)
>4 to ≤8 weeks	27 (4.5)	27 (4.5)	4 (1.3)
>8 to ≤12 weeks	192 (32.0)	190 (31.6)	3 (1.0)
>12 to ≤16 weeks	109 (18.1)	107 (17.8)	5 (1.6)
>16 to ≤20 weeks	12 (2.0)	7 (1.2)	6 (1.9)
>20 to ≤26 weeks	101 (16.8)	96 (16.0)	37 (11.9)
>26 to <52 weeks	144 (24.0)	130 (21.6)	163 (52.2)
≥52 weeks	NA	NA	90 (28.8)

[a]Exposure to study drug during the RTP was derived as defined as the date of the last dose of study drug during RTP (placebo or tenapanor) minus the date of the first dose of study drug plus 1, or if the date of the last dose of study drug was missing, the date of the last clinic visit minus the date of the first dose of study drug. [b]Exposure to tenapanor was derived as the date of the last dose of tenapanor (in T3MPO-3) minus the date of the first dose of tenapanor (in the parent study for cohorts 1-4 and in T3MPO-3 for cohort 5) plus 1.
NA, not applicable; RTP, randomized treatment period; SD, standard deviation.

Time to First Onset and Duration of Diarrhea

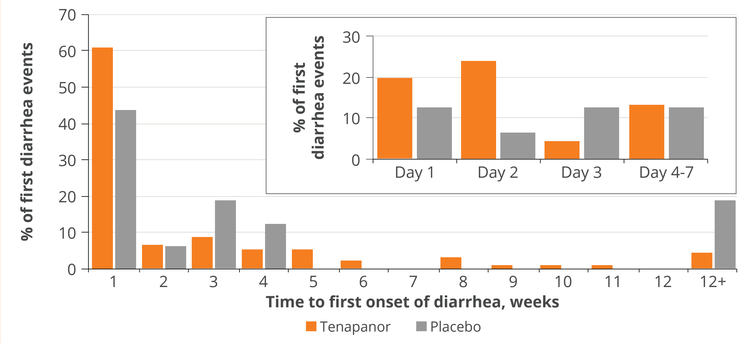
- For the pooled T3MPO-1/T3MPO-2 population, the median time to first onset of diarrhea during the RTP was 4 days in the tenapanor arm and 15.5 days in the placebo arm.
  - Among the 92/602 (15.3%) patients in the tenapanor arm who reported diarrhea during the RTP of T3MPO-1/T3MPO-2, 56/92 (60.9%) experienced their first diarrhea event within the first week of treatment (**Figure 3**) and 40/92 (43.5%) experienced their first diarrhea event within the first 2 days of treatment (**Figure 3**).
- Patients in cohort 5 of the T3MPO-3 population did not receive tenapanor in the parent study (T3MPO-2); 11/72 (15.3%) patients in cohort 5 reported diarrhea since their first exposure to tenapanor in T3MPO-3. Of these 11 patients, the median time to first onset of diarrhea was 2 days since the first dose of tenapanor and 7/11 (63.6%) experienced the first diarrhea event within the first week of tenapanor treatment in T3MPO-3.
- Patients in cohort 2 received placebo during the withdrawal period of T3MPO-1 and were reintroduced to tenapanor in T3MPO-3.
  - Since reintroduction to tenapanor, only 3 patients experienced diarrhea.
  - For these 3 patients, the first onset of diarrhea in T3MPO-3 occurred 2, 3, and 36 weeks since reintroducing tenapanor, respectively.
- Among resolved diarrhea events of the pooled T3MPO-1/T3MPO-2 population, the median duration of diarrhea during the RTP of patients in the placebo and tenapanor arms were 3 and 5.5 days, respectively (**Table 3**).
  - For the T3MPO-3 population, the median duration of diarrhea across the parent study and T3MPO-3 since the first dose of tenapanor was 4 days. The median duration observed in the long-term subset was also 4 days (**Table 3**).

Table 3. Incidence of Diarrhea and Duration of Resolved Diarrhea

	Pooled T3MPO-1/T3MPO-2 Population[a]		T3MPO-3 Population[b]	
	Placebo (N=601)	Tenapanor (N=602)	Overall (N=312)	Long-term subset (N=90)[c]
Incidence of diarrhea, n (%)				
Patients with diarrhea	16 (2.7)	92 (15.3)	44 (14.1)	10 (11.1)
Patients with diarrhea leading to study drug discontinuation	4 (0.7)	39 (6.5)	11 (3.5)	0
Diarrhea events, n	20	110	61	12
Resolved diarrhea events, n	18	94	55	12
Duration of resolved diarrhea, days, median (min, max)	3 (1, 84)	5.5 (1, 182)	4 (1, 287)	4 (1, 287)

[a]Patients treated with placebo or tenapanor during the RTP of T3MPO-1 (12 weeks) and T3MPO-2 (26 weeks). The summary was based on diarrhea events reported during the RTP of T3MPO-1/T3MPO-2. [b]The summary was based on diarrhea events reported since the first dose of tenapanor across the parent study and T3MPO-3. [c]Subset of the T3MPO-3 population who received tenapanor for at least 52 weeks. RTP, randomized treatment period; SD, standard deviation.

Figure 3. Distribution of Time to First Onset of Diarrhea During the RTP (Pooled T3MPO-1 and T3MPO-2 Population)[a]

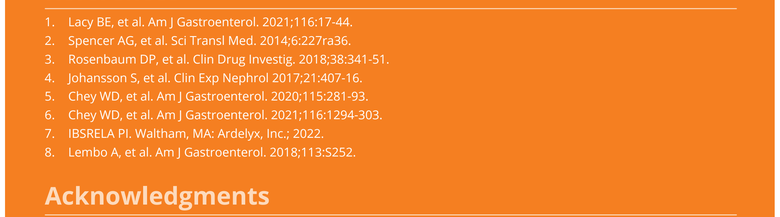


[a]Inset indicates the distribution of time to first onset of diarrhea within the first week of treatment in T3MPO-1/T3MPO-2.

Maximum Severity

- The maximum severity of diarrhea in the tenapanor arm (n=92) during the RTP of T3MPO-1/T3MPO-2 was mild in 34.8%, moderate in 48.9%, and severe in 16.3% of patients in the pooled T3MPO-1/T3MPO-2 population (**Figure 4A**).
- The maximum severity of diarrhea (n=44) since the first dose of tenapanor across the parent study (T3MPO-1/T3MPO-2) and T3MPO-3 was mild in 45.5%, moderate in 45.5%, and severe in 9.1% of patients in the T3MPO-3 population (**Figure 4B**).
- Overall, diarrhea was mild to moderate in the majority of cases, and hospitalization due to diarrhea was extremely rare; a single case was reported in the T3MPO-2 study.
  - Importantly, events of severe diarrhea were rare, and potentially more worrisome downstream consequences of diarrhea, such as dehydration, hypotension, syncope, falls and hospitalizations were uncommon.

Figure 4. Maximum Severity of Diarrhea During the RTP of T3MPO-1/T3MPO-2 and Since the First Dose of Tenapnaor Across the Parent Study and T3MPO-3 for the T3MPO-3 Population



n = the number of patients who reported diarrhea as an adverse event (A) during the RTP of T3MPO-1/T3MPO-2 for the pooled T3MPO-1/T3MPO-2 population or (B) across the parent study (T3MPO-1/T3MPO-2) and T3MPO-3 since the first dose of tenapanor for the T3MPO-3 population.

Long-Term Subset

- In the 90 patients who were treated with tenapanor for ≥52 weeks, 10 (11.1%) reported diarrhea as an AE since their first exposure to tenapanor.
  - Most diarrhea events were mild in intensity and there were fewer moderate cases than in the overall T3MPO-3 population (**Figure 4B**).
  - None of the patients in the long-term subset discontinued treatment due to diarrhea (**Table 3**).

Conclusions

Diarrhea was the most common AE in the tenapanor phase 3 studies for IBS-C. Time to first diarrhea onset typically occurred within the first week of treatment, and most cases were reported as mild to moderate in severity. Few patients experienced diarrhea when resuming tenapanor treatment after a 4-week placebo treatment.

Diarrhea is an expected AE in many prescribed treatments for IBS-C and is consistent with the mechanism of action of tenapanor given that NHE3 inhibition increases luminal water retention.

Patients treated with tenapanor long-term (≥52 weeks) did not have an increased incidence, duration, or severity of diarrhea compared to those treated for shorter durations.

These analyses support the safety and tolerability of tenapanor for long-term use in IBS-C.

Disclosures

Kyle Staller has consulted for Anji, Ardelyx, Arena, Gelesis, GI Supply, Restalsis, and Sanofi and has received research support from Ironwood and Urovant. Susan Wolgamott has consulted for AbbVie, Allergan, Ardelyx, Bristol Myers Squibb, Eli Lilly, Evoke Pharma, Ironwood, Janssen, Nestlé, Salix, and Synergy and has speaker's bureau contracts with AbbVie, Ardelyx, Eli Lilly, Evoke Pharma, Janssen and Salix. Suling Zhao, Yang Yang, Susan Edelstein, and David Rosembaum are employees of Ardelyx, Inc. Anthony J. Lembo is a consultant for Aeon, Allakos, Allergan, Alkermes, Ardelyx, Arena, Atmo, BioAmerica, Evoke Pharma, Gemelli, Ironwood, OrthoMed, Pfizer, Takeda, and Vibrant and has stock with Allurion, Bristol Myers Squibb, and Johnson & Johnson.

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