

# 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

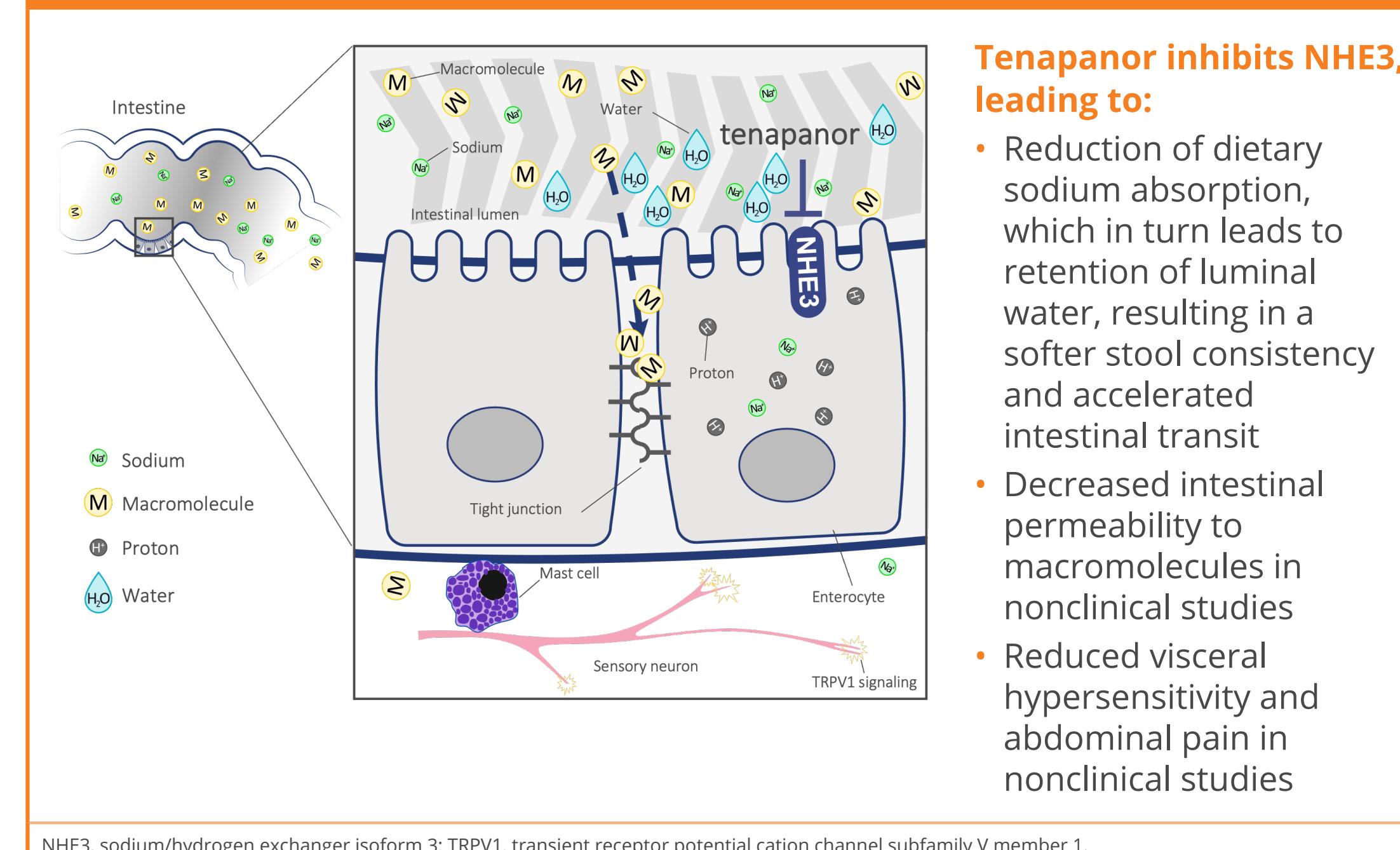
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## Background

- 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.<sup>1</sup>
- 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).<sup>2,4</sup>
- 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.<sup>5,7</sup>
  - The primary endpoint in each pivotal trial was the 6/12 week overall response, defined as achieving a reduction of  $\geq 30\%$  from baseline in average weekly worst abdominal pain and an increase of  $\geq 1$  in average weekly complete spontaneous bowel movements (CSBMs) from baseline, both in the same week, for  $\geq 6$  of the first 12 treatment weeks.<sup>5,6</sup>
  - Patients who completed T3MPO-1 or T3MPO-2 could enroll in T3MPO-3 (NCT02727751), an open-label long-term safety extension trial.<sup>8</sup>
- Tenapanor was shown to have acceptable safety and was generally well tolerated across all 3 studies.<sup>5,6,8</sup>
- We report a pooled analysis of these phase 3 studies to further investigate diarrhea, the most common adverse event (AE) with tenapanor treatment.

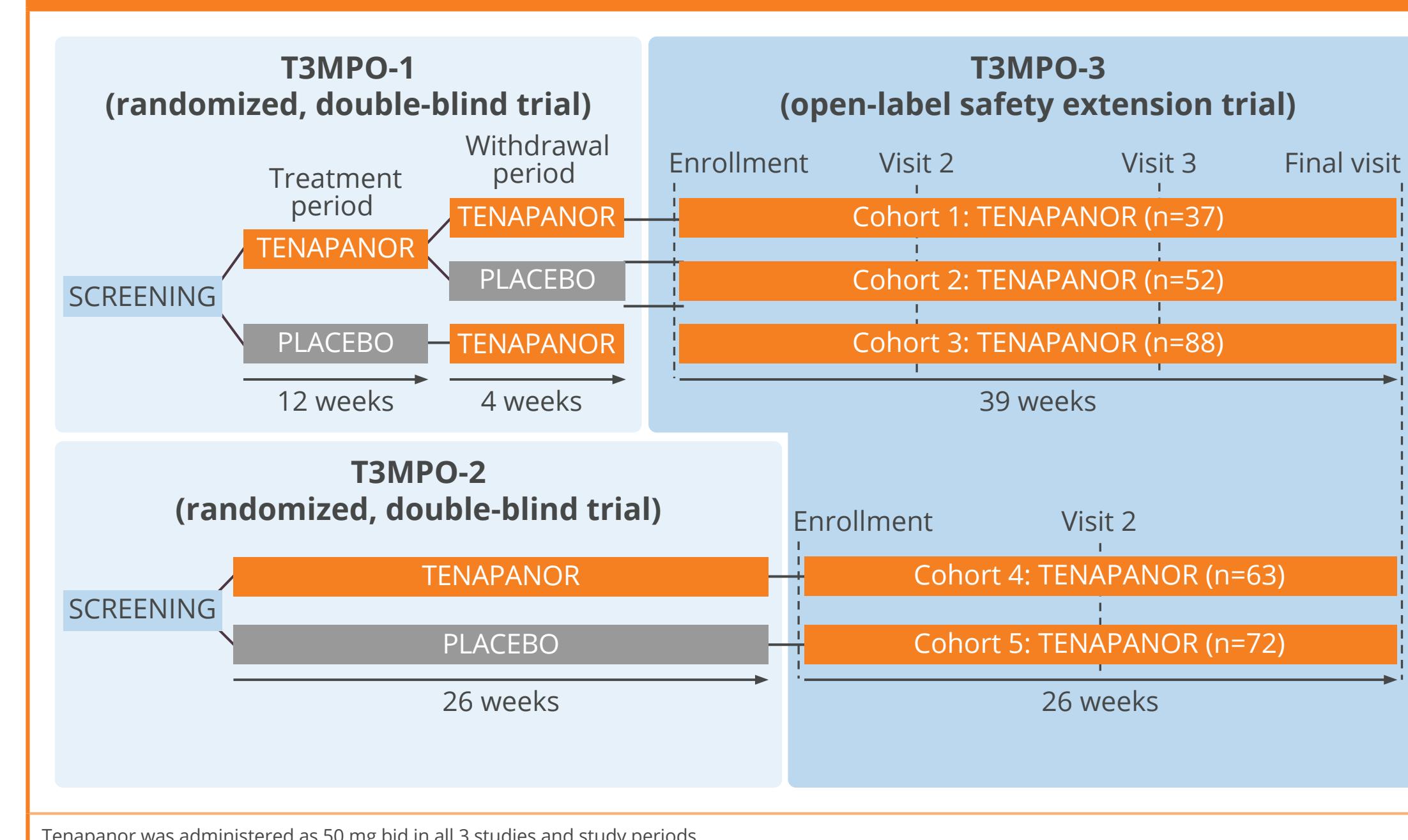
Figure 1. Mechanism of Action of Tenapanor<sup>2,4</sup>



## Methods

- Methods for T3MPO-1 and T3MPO-2 have been previously described<sup>5,6</sup>; 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  $\geq 3$  (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).<sup>7</sup>
- 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



## Results

### Patients

- Demographics and baseline characteristics of the study-level safety population were previously published for the T3MPO-1,<sup>5</sup> T3MPO-2,<sup>6</sup> and T3MPO-3<sup>8</sup> 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 <sup>a</sup>		T3MPO-3 Population		
	Placebo (N=601)	Tenapanor (N=602)	Overall (N=1203)	Overall (N=312)	Long-term subset (N=90) <sup>b</sup>
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)	23 (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 <sup>c</sup> weight, kg	82.4 (20.63)	82.7 (20.80)	82.6 (20.71)	80.9 (19.33)	81.8 (21.07)
Baseline <sup>c</sup> height, cm	165.3 (9.07)	165.5 (9.42)	165.4 (9.24)	164.7 (9.15)	164.1 (9.28)
Baseline <sup>c</sup> BMI, kg/m <sup>2</sup>	30.1 (6.90)	30.2 (7.19)	30.1 (7.04)	29.8 (6.60)	30.4 (7.38)

<sup>a</sup>Unless otherwise indicated, data are mean (SD).  
<sup>b</sup>Patients treated with placebo or tenapanor during the RTP of T3MPO-1 (12 weeks) and T3MPO-2 (26 weeks).  
<sup>c</sup>Subset of the T3MPO-3 population who received tenapanor for at least 52 weeks. 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

Treatment duration, days	Pooled T3MPO-1/T3MPO-2 Population <sup>a</sup>		T3MPO-3 Population <sup>b</sup>	
	Placebo (N=601)	Tenapanor (N=602)	Overall (N=312)	Long-term subset (N=90)
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 (%)				
$\leq 2$ weeks	6 (1.0)	29 (4.8)	3 (1.0)	
$>2$ to $\leq 4$ weeks	10 (1.7)	16 (2.7)	1 (0.3)	
$>4$ to $\leq 8$ weeks	27 (4.5)	27 (4.5)	4 (1.3)	
$>8$ to $\leq 12$ weeks	192 (32.0)	190 (31.6)	3 (1.0)	
$>12$ to $\leq 16$ weeks	109 (18.1)	107 (17.8)	5 (1.6)	
$>16$ to $\leq 20$ weeks	12 (2.0)	7 (1.2)	6 (1.9)	
$>20$ to $\leq 26$ weeks	101 (16.8)	96 (16.0)	37 (11.9)	
$>26$ to $\leq 52$ weeks	144 (24.0)	130 (21.6)	163 (52.2)	
$\geq 52$ weeks	NA	NA	90 (28.8)	

<sup>a</sup>Exposure to study drug during the RTP was derived 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. <sup>b</sup>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 2 days 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, only 3 patients experienced diarrhea.
  - 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

Incidence of diarrhea, n (%)	Pooled T3MPO-1/T3MPO-2 Population <sup>a</sup>		T3MPO-3 Population <sup>b</sup>	
	Placebo (N=601)	Tenapanor (N=602)	Overall (N=312)	Long-term subset (N=90)
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)

<sup>a</sup>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. <sup>b</sup>The summary was based on diarrhea events reported since the first dose of tenapanor across the parent study and T3MPO-3. 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)<sup>a</sup>

