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An open-label, long-term safety trial of tenapanor in patients with irritable bowel syndrome with constipation (IBS-C): T3MPO-3

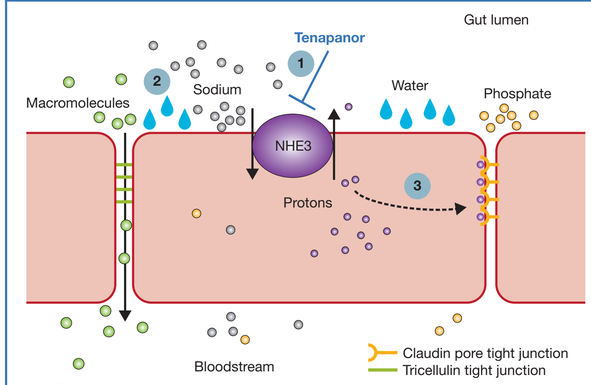
Anthony J Lembo,[1] William D Chey,[2] David P Rosenbaum[3]

[1]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA; [2]Michigan Medicine, Ann Arbor, MI, USA; [3]Ardelyx, Inc., Fremont, CA, USA

Background

- Tenapanor is a locally acting, minimally absorbed, selective small-molecule inhibitor of intestinal sodium/hydrogen exchanger 3 (NHE3) that increases luminal sodium, phosphate and water in a dose-dependent manner (Figure 1).[1]
- In preclinical models, tenapanor has been shown to reduce abdominal pain through inhibition of transient receptor potential cation channel subfamily V member 1 (TRPV1) signaling and by decreasing intestinal cell permeability.[2]
- In two previously completed phase 3 trials, T3MPO-1 and T3MPO-2 (ClinicalTrials.gov identifiers: NCT02621892 and NCT02686138, respectively), tenapanor 50 mg twice daily (b.i.d.) met the primary endpoint and significantly improved the key symptoms of irritable bowel syndrome with constipation (IBS-C) compared with placebo.[3,4]
- The aim of the T3MPO-3 study was to evaluate the long-term safety of tenapanor for the treatment of patients with IBS-C in extensions of the T3MPO-1 and T3MPO-2 studies up to approximately 1 year of total treatment time.

Figure 1. Mechanism of action of tenapanor.

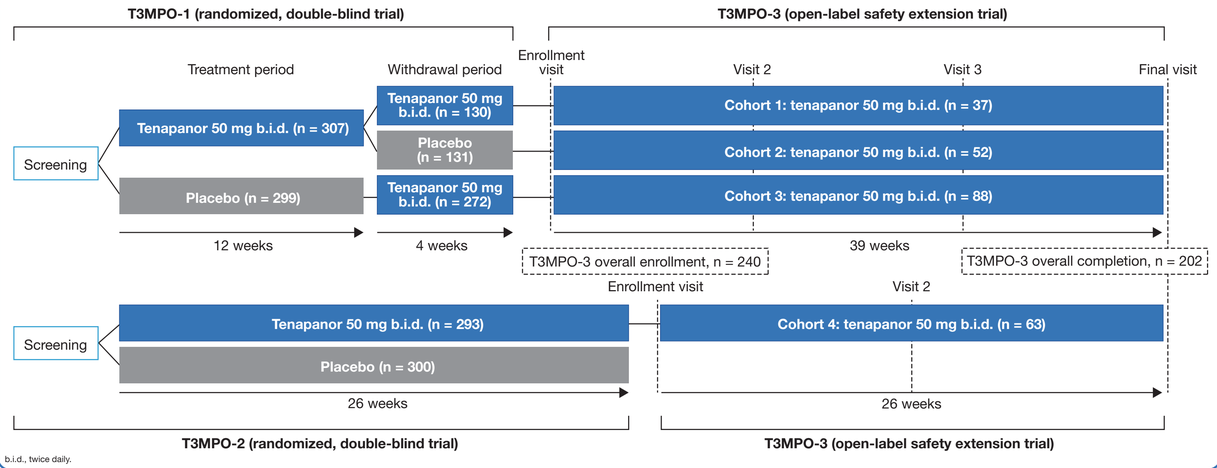


1. Tenapanor inhibits sodium/hydrogen exchanger 3 (NHE3), which transports luminal sodium in exchange for cellular protons.
2. Increased luminal sodium results in increased luminal water, loosening stool consistency.
3. Elevated proton levels within cells reduce tight junction permeability to phosphate, reducing paracellular absorption of luminal phosphate.

Methods

- The open-label safety study T3MPO-3 (NCT02727751) was conducted in accordance with the Declaration of Helsinki at 51 sites in the USA, with all patients providing written informed consent.
- Patients who completed either the T3MPO-1 study or the T3MPO-2 study were eligible for enrollment. In addition to an IBS-C diagnosis (modified Rome III criteria), the main eligibility criteria for these studies during the 2-week screening period were the following:
  - mean stool frequency of fewer than three complete spontaneous bowel movements and five or fewer spontaneous bowel movements per week
  - mean stool consistency of 3 or below using the 7-point Bristol Stool Form Scale[5]
  - mean weekly abdominal pain score of at least 3 (assessed daily using a 10-point Likert scale: from 0 = none to 10 = very severe; mean weekly score was calculated from scores for all days during a valid week).
- All participants received tenapanor 50 mg b.i.d., for either 39 weeks (T3MPO-1 cohorts) or 26 weeks (T3MPO-2 cohort) (Figure 2).
  - Patients enrolled from T3MPO-1 were divided into three cohorts for T3MPO-3 according to the treatments that they had received in the previous study.

Figure 2. Study design.



b.i.d., twice daily.

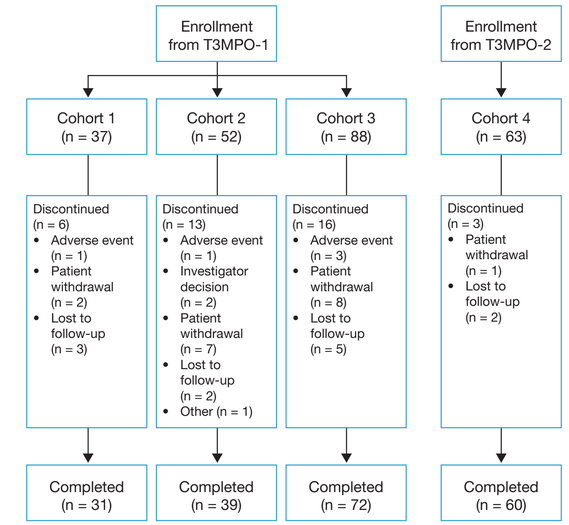
- Study center visits were scheduled approximately every 13 weeks; during these visits, patients underwent safety assessments including clinical laboratory measurements, a physical examination, and vital sign readings and electrocardiogram (ECG) readings. Adverse events (AEs) were recorded throughout the study.

Results

Study participants

- A total of 240 patients from T3MPO-1 and T3MPO-2 were enrolled in the extension study T3MPO-3 for a planned 43–55 weeks' total duration of tenapanor treatment; of these patients, 202 patients (84.2%) completed T3MPO-3 (Figure 3).

Figure 3. Patient flow diagram.



b.i.d., twice daily.

- Demographics and baseline characteristics were generally similar between the cohorts (Table 1).
  - The mean age of the participants was 49.6 years and 80.8% were women.
- Mean compliance with tenapanor treatment was 97.9%.
- Mean exposure to tenapanor during T3MPO-3 was 256, 234 and 251 days for the T3MPO-1 cohorts 1, 2 and 3, respectively, and 182 days for the T3MPO-2 cohort 4.

Adverse events

- Tenapanor was generally well tolerated, with diarrhea the most commonly reported AE (experienced by 9.2% of participants overall; Table 2).
- The overall rate of discontinuation due to AEs was 2.1%, with 1.7% of participants discontinuing owing to diarrhea.
  - There were no reported cases of severe diarrhea.
- Three serious AEs were reported: leukocytosis and status migrainosus in one participant in cohort 4 and endometriosis in one participant in cohort 2. None of these serious AEs was considered by the investigator to be related to tenapanor treatment.
  - There were no deaths during the study.

Other safety assessments

- Overall, no notable changes from baseline were observed in serum chemistry, hematology, urinalysis, vital signs or physical examination outcomes.
- There were no clinically significant abnormal ECG findings during the study, and no notable changes from baseline in QT interval, including when corrected using Bazett's or Fridericia's formulae, PR interval or QRS interval.

Table 1. Patient demographics and baseline characteristics.

	Cohort 1 (n = 37)	Cohort 2 (n = 52)	Cohort 3 (n = 88)	Cohort 4 (n = 63)	Overall (n = 240)
Age (years), mean (SD)	51.3 (12.3)	47.8 (13.8)	49.2 (12.2)	50.6 (13.9)	49.6 (13.0)
Women (%)	28 (75.7)	43 (82.7)	69 (78.4)	54 (85.7)	194 (80.8)
Caucasian (%)	29 (78.4)	40 (76.9)	59 (67.0)	41 (65.1)	169 (70.4)
Body mass index (kg/m^2), mean (SD)	29.87 (8.21)	28.18 (5.59)	29.64 (5.93)	31.45 (7.20)	29.83 (6.54)

SD, standard deviation.

Table 2. Adverse events summary.

	Cohort 1 (n = 37)	Cohort 2 (n = 52)	Cohort 3 (n = 88)	Cohort 4 (n = 63)	Overall (n = 240)
Any AE	15 (40.5)	19 (36.5)	34 (38.6)	20 (31.7)	88 (36.7)
Treatment-related AE	5 (13.5)	5 (9.6)	17 (19.3)	9 (14.3)	36 (15.0)
Serious AE	0	1 (1.9)	0	1 (1.6)	2 (0.8)
AE leading to discontinuation	1 (2.7)	1 (1.9)	3 (3.4)	0	5 (2.1)
AEs by preferred term[a]					
Diarrhea	2 (5.4)	3 (5.8)	8 (9.1)	9 (14.3)	22 (9.2)
Headache	0	2 (3.8)	6 (6.8)	1 (1.6)	9 (3.8)
Flatulence	1 (2.7)	1 (1.9)	2 (2.3)	2 (3.2)	6 (2.5)
Upper respiratory tract infection	1 (2.7)	0	2 (2.3)	2 (3.2)	5 (2.1)
Nasopharyngitis	2 (5.4)	2 (3.8)	0	0	4 (1.7)
Abdominal pain	2 (5.4)	0	1 (1.1)	0	3 (1.3)

Data are presented as n (%).
[a]Data shown for any AE experienced by ≥ 3% of participants in any cohort.
AE, adverse event.

Conclusions

- Overall, tenapanor 50 mg b.i.d. was generally well tolerated in patients with IBS-C when administered for up to 55 consecutive weeks.
- The combined results of the T3MPO studies indicate that tenapanor, with its unique mechanism of action, may offer a valuable new treatment option for patients with IBS-C.

References

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