E0264

Potential of Tenapanor as a Treatment for Chronic Idiopathic Constipation: A Post Hoc Analysis from the Phase 3 T3MPO-1 and T3MPO-2 Studies for Irritable Bowel Syndrome With Constipation in Adults

Lucinda A. Harris,[1] David P. Rosenbaum[2]

[1]Alix School of Medicine, Mayo Clinic, Scottsdale, AZ, USA; [2]Ardelyx, Inc., Waltham, MA, USA

Introduction

- Tenapanor is a first-in-class, minimally absorbed, small-molecule inhibitor of intestinal sodium/hydrogen exchanger isoform 3 (NHE3)[1,2] approved for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.[3]
- In the phase 3 T3MPO-1 (NCT02621892) and T3MPO-2 (NCT02686138) trials, both abdominal pain and complete spontaneous bowel movement (CSBM) frequency were significantly improved with tenapanor compared with placebo in patients with IBS-C.[4,5]
  - Tenapanor was generally well tolerated.[4,5] Diarrhea was the most common adverse event and was typically transient (≤1 week duration) and mild to moderate in intensity.[5]
- The most recent Rome diagnostic criteria (Rome IV) recognize that, rather than being distinct entities, functional constipation (FC), also known as chronic idiopathic constipation (CIC), and IBS-C represent a continuum of symptoms. Patients often alternate clinically between the 2 diagnoses and patients with FC can experience abdominal pain.[6]
- In a secondary analysis of a larger prospective study of 432 participants who met Rome III criteria for IBS-C or FC, 180 of 201 (89.5%) patients meeting Rome III criteria for IBS-C also met the criteria for FC.[7]
  - In addition, 180 of 411 (43.8%) of patients fulfilling criteria for FC also met criteria for IBS-C.[7]
- Recognizing that IBS-C and FC/CIC represent a continuum of symptoms, the T3MPO-1 and T3MPO-2 studies, which enrolled patients according to Rome III criteria, provide an opportunity to evaluate the potential effect of tenapanor among patients with symptoms consistent with FC/CIC.
- Therefore, we conducted a post hoc analysis using the CIC endpoint for clinical trials and other measures of functional constipation to determine the effect of tenapanor in patients from the T3MPO-1 and T3MPO-2 studies.

Methods

- The study designs and primary results of T3MPO-1 and T3MPO-2 have been reported previously.[4,5] Briefly, both studies enrolled adult patients with IBS-C according to Rome III criteria and with <3 weekly CSBMs, ≤5 weekly spontaneous bowel movements (SBM), and weekly worst abdominal pain score ≥3 (0-10 numerical rating scale) during a 2-week screening period.
  - Patients were randomized to tenapanor 50 mg or placebo twice a day for a randomized treatment period of 12 weeks in T3MPO-1 and 26 weeks in T3MPO-2.
- Patients self-reported information about the status of their IBS symptoms daily using an eDiary (**Box**).

Box. Interactive Voice Response System (IVRS) Diary

The IVRS diary collected information on daily stool frequency, stool consistency, and straining. Constipation severity was assessed weekly through the IVRS diary.[a] Example questions:[b]

- *How many bowel movements have you had in the past 24 hours?* For each bowel movement:
  - *Please enter the time of the bowel movement using the 12 hours AM/PM format and indicate if it occurred today or yesterday.*
  - *Did you feel like you completely emptied your bowels?* Yes/No
  - *Refer to the Bristol Stool Form Scale (BSFS) given to you in this pamphlet. Please enter the number that best describes the consistency of bowel movement following the scale.*
  - *How much did you strain during the bowel movement?* Assessed on a scale of 1 (not at all) to 5 (an extreme amount).
- *How would you rate the severity of your constipation over the past week?* Assessed on a scale of 1 (none) to 5 (very severe).

[a]Entries into the IVRS diary must have been recorded between 6:00 PM and 11:59 PM (local time). [b]Sample questions reflect questions relevant to the analysis presented. The full IVRS diary included 4 weekly questions and 7 daily questions (with sub-questions for each bowel movement and each use of rescue medication). IBS, irritable bowel syndrome.

- Data from the first 12 weeks of both trials were used to calculate the durable CSBM responder rate, which is the endpoint used in clinical trials to evaluate treatments for CIC.
  - A durable CSBM response was defined as an increase of ≥1 CSBM per week from baseline and ≥3 CSBMs per week in the same week for ≥9 of 12 weeks, including ≥3 of the last 4 weeks of the study treatment, up to week 12.
    - An additional post hoc analysis was completed where durable CSBM response was defined as an increase of ≥2 CSBMs per week from baseline and ≥3 CSBMs per week in the same week for ≥9 of 12 weeks, including ≥3 of the last 4 weeks of the study treatment, up to week 12.
- The percentages of patients with a first CSBM or SBM by end of study day 2 (ie, early CSBM and SBM responders) were calculated for each trial.
- Change from baseline in mean stool consistency, mean stool consistency by Bristol Stool Form Scale (BSFS),[8] straining score, and constipation severity were analyzed for the 12- and 26-week treatment periods of T3MPO-1 and T3MPO-2, respectively.
- Analyses were completed in the intent-to-treat (ITT) population that included all patients who met the study eligibility criteria, were randomized, and received ≥1 dose of study drug.

Results

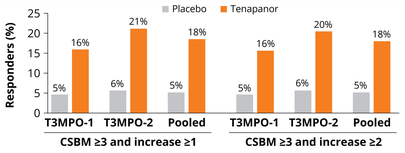
Patients

- The T3MPO-1 ITT population included 307 patients with IBS-C who received tenapanor and 299 patients with IBS-C who received placebo. The T3MPO-2 ITT population included 293 and 300 patients with IBS-C who received tenapanor or placebo, respectively.[4,5]
  - The pooled ITT population included 600 patients who received tenapanor and 599 patients who received placebo.
- Demographics and baseline characteristics were similarly well balanced between the tenapanor and placebo groups in both T3MPO-1 and T3MPO-2.[4,5]
  - For the T3MPO-1 ITT population, most patients were women (81.4%), the mean age was 45.0 years, and the average weekly CSBM was 0.2 at baseline.[4]
  - For the T3MPO-2 ITT population, most patients were women (82.1%), the mean age was 45.4 years, and the average weekly CSBM was 0.1 at baseline.[5]

Durable CSBM response

- The durable responder rate for the pooled ITT population was similar to the durable responder rates of the individual ITT populations of T3MPO-1 and T3MPO-2 (**Figure 1**).
  - The durable responder rates were also similar across populations using an increase of either ≥1 or ≥2 CSBMs per week as from baseline one of the criteria to determine weekly response (**Figure 1**).

Figure 1. Durable Response in ITT Populations From T3MPO-1 and T3MPO-2, Individually and Pooled



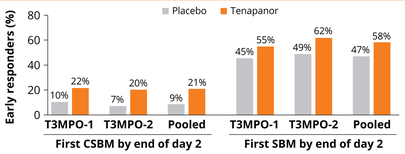
	CSBM ≥3 and increase ≥1			CSBM ≥3 and increase ≥2		
	T3MPO-1	T3MPO-2	Pooled	T3MPO-1	T3MPO-2	Pooled
Risk difference (95% CI)	11.28 (6.53, 16.02)	15.49 (10.13, 20.85)	13.32 (9.75, 16.90)	10.95 (6.24, 15.67)	14.81 (9.50, 20.12)	12.82 (9.28, 16.37)
Adjusted relative risk (95% CI)	3.37 (1.90, 5.96)	3.77 (2.25, 6.31)	3.58 (2.44, 5.25)	3.29 (1.86, 5.84)	3.65 (2.18, 6.12)	3.48 (2.37, 5.11)
CMH *P* value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Durable CSBM response was defined as an increase of ≥1 or ≥2 CSBMs/week from baseline and ≥3 CSBMs/week both in the same week for ≥9 of 12 weeks, including ≥3 of the last 4 weeks of the 12-week period. In T3MPO-2, the 12-week period was the first 12 weeks of the study. Risk differences, adjusted relative risk difference, and CMH *P* values are for tenapanor vs placebo.
CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CSBM, complete spontaneous bowel movement; ITT, intent-to-treat.

CSBMs by end of study day 2

- Within each treatment group, the early CSBM and SBM responder rates were similar between the individual ITT populations of T3MPO-1 and T3MPO-2 and the pooled ITT population (**Figure 2**).
  - In all cases, the early CSBM or SBM responder rate was significantly higher with tenapanor compared with placebo.

Figure 2. Early CSBM and SBM Response in ITT Populations From T3MPO-1 and T3MPO-2, Individually and Pooled



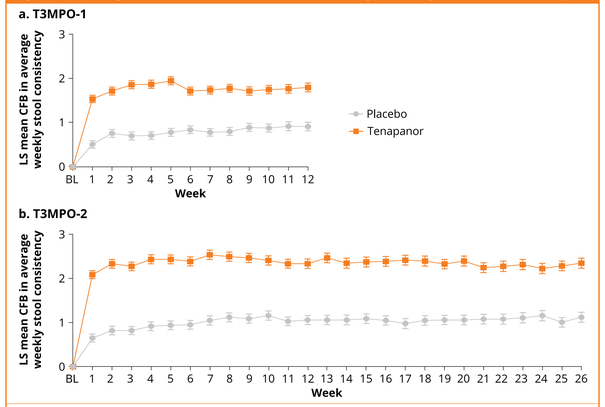
	First CSBM by end of day 2			First SBM by end of day 2		
	T3MPO-1	T3MPO-2	Pooled	T3MPO-1	T3MPO-2	Pooled
Risk difference (95% CI)	11.13 (5.38, 16.88)	13.14 (7.71, 18.56)	12.15 (8.20, 16.11)	9.56 (1.64, 17.49)	13.11 (5.17, 21.04)	11.25 (5.64, 16.87)
Adjusted relative risk (95% CI)	2.06 (1.39, 3.06)	2.89 (1.80, 4.63)	2.39 (1.77, 3.23)	1.21 (1.03, 1.41)	1.27 (1.09, 1.47)	1.24 (1.11, 1.38)
CMH *P* value	<0.001	<0.001	<0.001	0.020	0.001	<0.001

Early responders had their first CSBM or SBM after initiating treatment by the end of study day 2. Risk differences, adjusted relative risk difference, and CMH *P* values are for tenapanor vs placebo.
CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CSBM, complete spontaneous bowel movement; ITT, intent-to-treat; SBM, spontaneous bowel movement.

Additional endpoints related to chronic constipation

- In both studies, average weekly stool consistency improved from baseline for both tenapanor and placebo groups. The improvement was greater with tenapanor with the least squares (LS) mean reduction significantly greater with tenapanor compared with placebo in each week during the 12-week treatment period of T3MPO-1 (**Figure 3a**) and the 26-week treatment period of T3MPO-2 (**Figure 3b**).

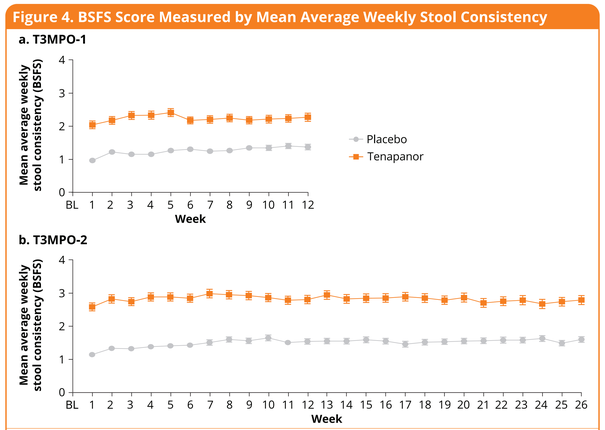
Figure 3. Change from Baseline in LS Mean Average Weekly Stool Consistency



Error bars represent SE. *P*≤0.001 at all weeks.
CFB, change from baseline; LS, least squares.

- Mean BSFS score (calculated as the mean of reported average weekly stool consistency) was around 1 with placebo and around 2-3 with tenapanor across weeks in both T3MPO-1 (**Figure 4a**) and T3MPO-2 (**Figure 4b**).

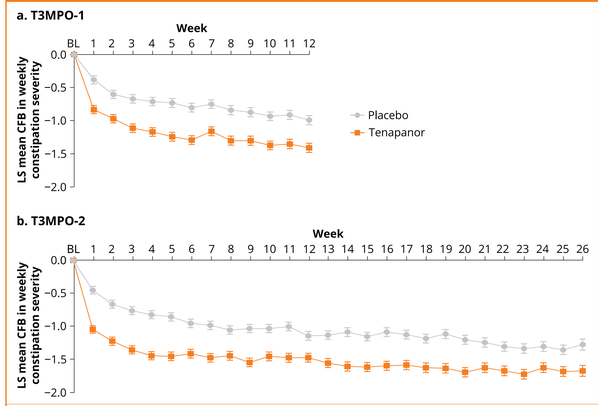
Figure 4. BSFS Score Measured by Mean Average Weekly Stool Consistency



Error bars represent SE. SEs <0.08 are too small to visualize relative to the circles and squares. On the BSFS, scores of 1 (separate hard lumps) or 2 (sausage shaped, lumpy) are considered constipation, scores of 3 (sausage with cracks), 4 (smooth snake) or 5 (soft blobs with edges) are considered normal, and scores of 6 (fluffy pieces) or 7 (watery) are considered diarrhea.[8]
BSFS, Bristol Stool Form Scale.

- Average weekly straining scores did not differ significantly from baseline to end of study or between tenapanor and placebo groups during the treatment periods of T3MPO-1 and T3MPO-2.[4,5]
- Constipation severity score improved from baseline in both treatment groups and the LS mean reduction was significantly greater with tenapanor compared with placebo in each week during the 12-week treatment period of T3MPO-1 (**Figure 5a**) and 26-week treatment period of T3MPO-2 (**Figure 5b**).

Figure 5. Change from Baseline in Constipation Severity



Error bars represent SE. *P*<0.001 for all weeks in a; *P*≤0.002 for all weeks in b.
BL, baseline; CFB, change from baseline; LS, least squares.

Conclusions

- Based on results from this post hoc analysis of the phase 3 T3MPO-1 and T3MPO-2 studies for IBS-C in adults, tenapanor, with its novel mechanism of action, shows promise as a potential therapeutic option for CIC.
  - Treatment with tenapanor significantly improved durable and early CSBM and SBM responses by end of study day 2 compared with placebo.
  - Additional measures of constipation, stool consistency, and constipation severity also improved significantly with tenapanor treatment compared with placebo.
- Future clinical trials are needed to evaluate tenapanor in patients with CIC to confirm these results.

Acknowledgments

Special thanks to Yang Yang, PhD, of Ardelyx, Inc., for her assistance with data analysis for this poster. Medical writing support for the development of this poster, under the direction of the authors, was provided by Ashfield MedComms US, an Inizio company, and funded by Ardelyx, Inc.

Disclosures

Lucinda A. Harris has received financial support from Ardelyx, AbbVie, Alnylam, Ironwood, Gemelli Biotech, and Takeda. David P. Rosenbaum is an employee of Ardelyx, Inc.

References

1. Spencer AG et al. *Sci Transl Med*. 2014;6:227ra36.
2. Johansson S et al. *Clin Exp Nephrol*. 2017;21:407-16.
3. IBSRELA (tenapanor hydrochloride). Prescribing information. Ardelyx, Inc.; 2022.
4. Chey WD et al. *Am J Gastroenterol*. 2020;115:281-93.
5. Chey WD et al. *Am J Gastroenterol*. 2021;116:1294-303.
6. Lacy BE et al. *Gastroenterology*. 2016;150:1393-407.
7. Wong RK et al. *Am J Gastroenterol*. 2010;105:2228-34.
8. Lewis SJ et al. *Scand J Gastroenterol*. 1997;32:920-4.

Contact Information
The presenting author, Dr. Lucinda A. Harris, can be reached at Harris.Lucinda@mayo.edu.