Poster: Tu1663

Comparing the Efficacy of Tenapanor in Irritable Bowel Syndrome With Constipation in Hispanic vs Non-Hispanic Patients: A Post Hoc Analysis of Patients in the Phase 3 T3MPO-1 and T3MPO-2 Studies

Rosita Frazier,[1] William Hasler,[1] Yang Yang,[2] Suling Zhao,[2] Susan Edelstein,[2] and David P. Rosenbaum[2]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, AZ, USA; [2]Ardelyx, Inc., Waltham, MA, USA

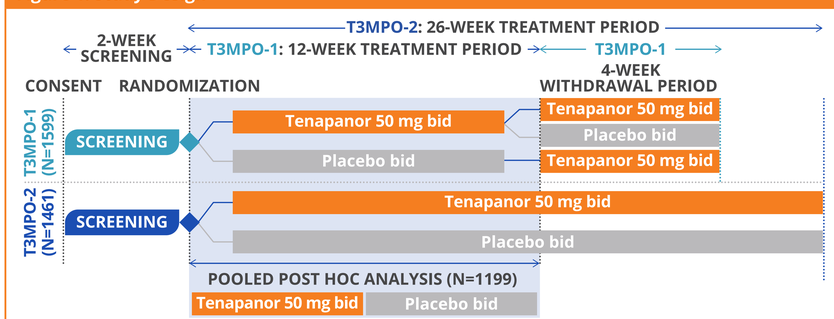
Introduction

- Irritable bowel syndrome with constipation (IBS-C) is a common disorder of gut-brain interaction characterized by abdominal pain, infrequent bowel movements, and hard/lumpy stools.[1]
- Ethnic differences have been identified among adults with IBS, with Hispanic patients reporting more perceived stigma, more concern about bowel issues, and spending more time attending to bowel function vs non-Hispanic patients, thus making it important to better understand IBS-C in the Hispanic patient population.[2-4]
- Tenapanor is a first-in-class, minimally absorbed, small-molecule inhibitor of intestinal sodium/hydrogen exchanger isoform 3 (NHE3) approved by the Food and Drug Administration (FDA) for the treatment of IBS-C in adults.[5,6]
- Through NHE3 inhibition, tenapanor reduces the absorption of sodium and increases water retention in the gut, leading to softer stool consistency and accelerated transit.[7-9]
- Tenapanor may also decrease visceral hypersensitivity and intestinal permeability to macromolecules, mast cells, and mast cell mediators, leading to less abdominal pain in patients with IBS-C.[10]
- Two multicenter, phase 3, randomized, double-blind, placebo-controlled clinical trials, T3MPO-1 (NCT02621892) and T3MPO-2 (NCT02686138), showed that patients treated with tenapanor 50 mg twice a day (bid) experienced both a significant increase in complete spontaneous bowel movements (CSBMs) and a decrease in abdominal pain compared with those receiving placebo.[11,12]
- While the Hispanic community represents the second largest ethnic cohort in the US, comprising over 60 million individuals (2020 US census), clinical trial enrollment of Hispanic patients has generally lagged, only representing an estimated 11% of clinical trial participants.[4,13,14]
- The phase 3 T3MPO-1 and T3MPO-2 studies included a large number of Hispanic patients with IBS-C (28% of participants), allowing for a post hoc evaluation of responses to tenapanor in Hispanic and non-Hispanic patients in this pooled patient population with IBS-C.

Methods

- Study methods for the phase 3 studies have been described previously.[11,12] To summarize, adults with IBS-C were randomized to tenapanor (50 mg bid) or placebo for 12- and 26-week treatment periods in T3MPO-1 and T3MPO-2, respectively (**Figure 1**).

Figure 1: Study Design[a]



[a]The association between treatment (tenapanor or placebo) and response status (Yes or No) was assessed using the Cochran–Mantel–Haenszel (CMH) test. The CMH *P* value was based on a 1 degree of freedom test for association between treatment (tenapanor and placebo), stratified by the pooled investigator site.
bid, twice a day.

- The following responder rates were evaluated in Hispanic and non-Hispanic, tenapanor-treated patients:
  - A 6 of 12–week overall response was defined as achieving a CSBM response and an abdominal pain response in the same week for ≥6 of the first 12 treatment weeks.
    - A CSBM response was defined as an increase of ≥1 weekly CSBMs from baseline.
    - An abdominal pain response was defined as a ≥30% decrease in average weekly worst abdominal pain from baseline.
  - A 9 of 12–week overall response was defined as achieving a CSBM response, an abdominal pain response, and ≥3 CSBMs in the same week for ≥9 of the first 12 treatment weeks.
  - A 9 of 12–week durable overall response was defined as achieving a CSBM response, an abdominal pain response, and ≥3 CSBMs in the same week for ≥9 of the first 12 treatment weeks and 3 of the last 4 weeks of the first 12 treatment weeks.

Results

Patients

- The pooled analysis included 600 tenapanor-treated patients from the intent-to-treat analysis set, 425 of whom were non-Hispanic and 175 of whom were Hispanic.
- The demographics and baseline characteristics of the Hispanic and non-Hispanic populations were generally well balanced (**Table 1**).

Table 1: Patient Demographics and Baseline Characteristics of Hispanic and Non-Hispanic Patients in the Pooled Data From the T3MPO-1 and T3MPO-2 Studies (Intent-to-Treat Analysis Set)

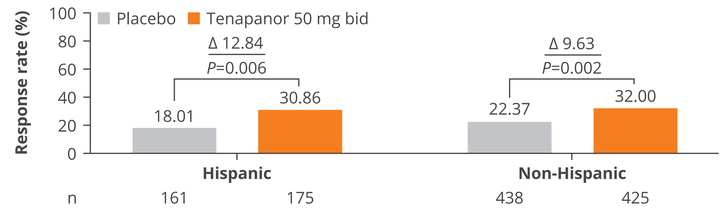
Demographic/characteristic	Hispanic		Non-Hispanic	
	Tenapanor (N=175)	Placebo (N=161)	Tenapanor (N=425)	Placebo (N=438)
Age, years	45.3 (13.0)	44.6 (13.8)	45.6 (13.4)	44.9 (13.3)
Sex, n (%)				
Female	133 (76.0)	130 (80.7)	351 (82.6)	366 (83.6)
Race, n (%)				
White	161 (92.0)	142 (88.2)	225 (52.9)	236 (53.9)
African American	9 (5.1)	11 (6.8)	171 (40.2)	181 (41.3)
Asian	1 (0.6)	0 (0.0)	21 (4.9)	13 (3.0)
Other[a]	4 (2.3)	8 (5.0)	8 (1.9)	8 (1.8)
Body mass index, kg/m²	29.6 (6.2)	29.0 (5.5)	30.4 (7.5)	30.5 (7.3)
Duration of IBS symptoms before randomization, years	10.0 (10.0)	9.9 (9.4)	11.2 (11.9)	11.6 (12.2)
Disease characteristic				
Abdominal pain[b]	6.6 (1.7)	6.5 (1.8)	6.1 (1.7)	6.2 (1.6)
CSBMs per week[c]	0.1 (0.5)	0.1 (0.3)	0.2 (0.4)	0.2 (0.4)

Data are shown as mean (SD) unless otherwise stated.
[a]Includes American Indian or Alaskan Native, multiple, and unknown. [b]Assessed daily using a 0-10–point scale, where 0 = none and 10 = very severe; the average weekly score was calculated from scores for all days during a week with ≥4 recorded diary days. [c]Data are shown as mean (SD) of the average of the weekly scores during the screening period for individual patients.
CSBM, complete spontaneous bowel movement; IBS, irritable bowel syndrome.

Responder Rates

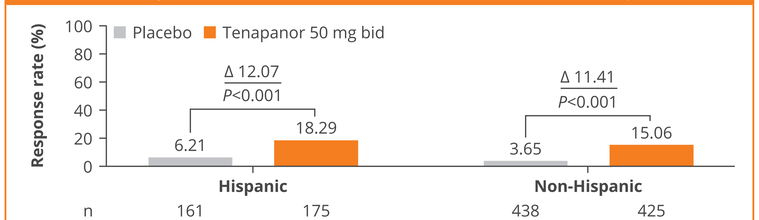
- The placebo-adjusted, 6 of 12–week overall response rate was higher in Hispanic than non-Hispanic patients on tenapanor (12.84%, *P*=0.006 vs 9.63%, *P*=0.002).
- The placebo-adjusted, 9 of 12–week overall response rate (12.07%, *P*<0.001 vs 11.41%, *P*<0.001) and durable overall response rate (11.50%, *P*<0.001 vs 11.16%, *P*<0.001) were similar between Hispanic and non-Hispanic patients on tenapanor.
- In general, the response to tenapanor was similar between Hispanic and non-Hispanic patients (**Figures 2-4**).

Figure 2: 6 of 12–Week Overall Response Rates in Hispanic and Non-Hispanic Patients in the Pooled Population From T3MPO-1 and T3MPO-2 Studies (ITT Analysis Set)[a]



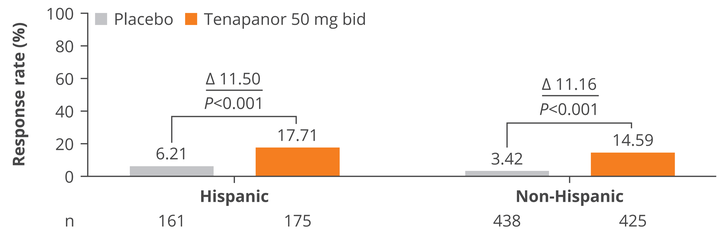
[a]A 6 of 12–week overall response was defined as achieving a CSBM response and an abdominal pain response in the same week for ≥6 of the first 12 treatment weeks.
bid, twice a day; CSBM, complete spontaneous bowel movement.

Figure 3: 9 of 12–Week Overall Response Rates in Hispanic and Non-Hispanic Patients in the Pooled Population From T3MPO-1 and T3MPO-2 Studies (ITT Analysis Set)[a]



[a]A 9 of 12–week overall response was defined as achieving a CSBM response, an abdominal pain response, and ≥3 CSBMs in the same week for ≥9 of the first 12 treatment weeks.
bid, twice a day; CSBM, complete spontaneous bowel movement.

Figure 4: 9 of 12–Week Durable Overall Response Rates in Hispanic and Non-Hispanic Patients in the Pooled Population From T3MPO-1 and T3MPO-2 Studies[a]



[a]A 9 of 12–week durable overall response was defined as achieving a CSBM response with an abdominal pain response and ≥3 CSBMs in the same week for ≥9 of the first 12 treatment weeks and 3 of the last 4 weeks of the first 12 treatment weeks.
bid, twice a day; CSBM, complete spontaneous bowel movement.

Safety

- Safety outcomes in T3MPO-1 and T3MPO-2 have been previously reported. Tenapanor was generally well tolerated with an acceptable safety profile.[11,12]
- Treatment-emergent adverse events (TEAEs) in the tenapanor group were reported by 26.9% of Hispanic patients and 48.2% of non-Hispanic patients (**Table 2**).
  - While the TEAE rate differs between ethnicity groups, further breakdown by race (Black/White) did not explain this difference. Therefore, in the absence of any other baseline demographic differences between ethnicity groups, the difference in TEAE rate based on ethnicity is likely attributable to randomness.
- The most common TEAE in the tenapanor group during the randomized treatment period was diarrhea in both Hispanic (8.6%) and non-Hispanic (18.0%) patients (**Table 2**).

Table 2: Treatment-Emergent Adverse Events Reported by Hispanic and Non-Hispanic Patients (Safety Analysis Set)

	Hispanic		Non-Hispanic	
	Tenapanor (N=175)	Placebo (N=161)	Tenapanor (N=427)	Placebo (N=440)
Patients with any TEAE, n (%)	47 (26.9)	37 (23.0)	206 (48.2)	161 (36.6)
TEAEs experienced by ≥3% patients				
Diarrhea	15 (8.6)	1 (0.6)	77 (18.0)	15 (3.4)
Nausea	2 (1.1)	2 (1.2)	14 (3.3)	14 (3.2)
Nasopharyngitis	5 (2.9)	3 (1.9)	13 (3.0)	13 (3.0)
Flatulence	1 (0.6)	1 (0.6)	14 (3.3)	9 (2.0)
Headache	3 (1.7)	5 (3.1)	5 (1.2)	7 (1.6)
Urinary tract infection	2 (1.1)	5 (3.1)	7 (1.6)	14 (3.2)

Data are n (%).
TEAE, treatment-emergent adverse event.

Conclusions

This post hoc analysis shows that the efficacy of tenapanor in Hispanic patients is comparable with that in non-Hispanic patients.

These observations indicate tenapanor is efficacious in patients with IBS-C, irrespective of ethnicity.

Overall, tenapanor demonstrated an acceptable safety and tolerability profile.

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Dr. Frazier can be contacted for further information on this study at Frazier.Rosita@mayo.edu

Disclosures

Rosita Frazier and William Hasler have no commercial interests or conflicts of interest to declare. Susan Edelstein, Yang Yang, Suling Zhao, and David Rosenbaum are employees of Ardelyx, Inc.

Acknowledgements

Medical writing support for the development of this poster, under the direction of the authors, was provided by Ashfield MedComms, an Inizio company, and funded by Ardelyx, Inc.