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Efficacy of Tenapanor in Treating Patients With Irritable Bowel Syndrome With Constipation: A 26-Week, Placebo-Controlled Phase 3 Trial (T3MPO-2)

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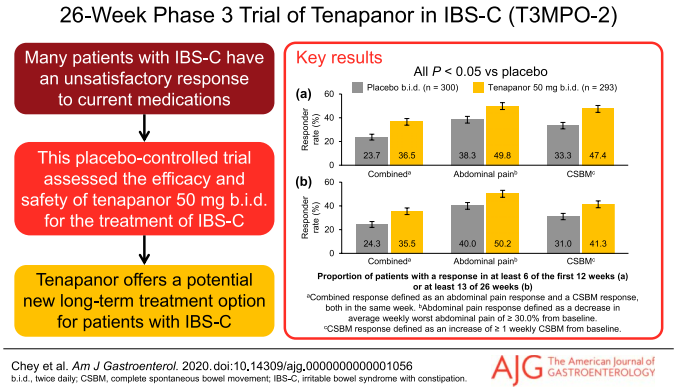
INTRODUCTION: **Tenapanor is a first-in-class, minimally absorbed, small-molecule inhibitor of the gastrointestinal sodium/hydrogen exchanger isoform 3. This phase 3 trial assessed the long-term efficacy and safety of tenapanor 50 mg b.i.d. for the treatment of patients with irritable bowel syndrome with constipation (IBS-C).**

METHODS: **In this randomized double-blind study (ClinicalTrials.gov identifier: NCT02686138), patients with IBS-C received tenapanor 50 mg b.i.d. or placebo b.i.d. for 26 weeks. The primary endpoint was the proportion of patients who had a reduction of ≥30.0% in average weekly worst abdominal pain and an increase of ≥1 weekly complete spontaneous bowel movement from baseline, both in the same week, for ≥6 of the first 12 treatment weeks (6/12-week combined responder).**

RESULTS: **Of the 620 randomized patients with IBS-C, 593 (95.6%) were included in the intention-to-treat analysis set (tenapanor: n = 293; placebo: n = 300) and 481 patients (77.6%) completed the 26-week treatment period. In the intention-to-treat analysis set (mean age: 45.4 years; 82.1% women), a significantly greater proportion of patients treated with tenapanor were 6/12-week combined responders than those treated with placebo (36.5% vs 23.7%; $P < 0.001$). Abdominal symptoms and global symptoms of IBS were significantly improved with tenapanor compared with placebo. Diarrhea, the most common adverse event, was typically transient and mild to moderate in severity. Diarrhea led to study drug discontinuation for 19 (6.5%) and 2 patients (0.7%) receiving tenapanor and placebo, respectively.**

DISCUSSION: **Tenapanor 50 mg b.i.d. improved IBS-C symptoms over 26 weeks and was generally well tolerated, offering a potential new long-term treatment option for patients with IBS-C (see Visual abstract, Supplementary Digital Content 1, http://links.lww.com/AJG/B797).**



SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B789, http://links.lww.com/AJG/B797

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INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic, symptom-based disorder characterized by abdominal pain and altered bowel movements (1). IBS is estimated to affect 11.2% of the world population (1,2), and IBS with constipation (IBS-C) accounts for approximately one-third of these cases (2).

The pathogenesis of IBS is believed to be heterogeneous, potentially involving abnormalities in gut motility, visceral sensation, gut microbiota, intestinal permeability, and/or gut immune activation (2). Symptoms of IBS can fluctuate over time in frequency and severity and are associated with considerable morbidity, impaired health-related quality of life (HRQoL), and decreased work productivity (1,3).

Although dietary interventions and over-the-counter medicines can improve bowel movement frequency and stool consistency in patients with IBS-C, symptoms such as abdominal pain and bloating often remain unaddressed (3–5), causing patients considerable distress (6,7). Some patients with IBS-C may benefit from prescription medications such as guanylate cyclase C agonists, including linaclotide and plecanatide, and type-2 chloride channel activators such as lubiprostone, all of which can address the full range of IBS-C symptoms. Although these medications have been shown to be more effective than placebo in clinical trials, many patients with IBS-C have an unsatisfactory response to treatment (8–10), demonstrating the need for additional effective treatment options.

Tenapanor, which has recently been approved by the US Food and Drug Administration (FDA) for the treatment of IBS-C, is a first-in-class, minimally absorbed, small-molecule inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3; Figure 1), expressed on the luminal surface throughout the small intestine and proximal colon (11). In animal studies, genetic knockouts confirm that NHE3 is the dominant NHE responsible for transepithelial sodium absorption (12). By inhibiting NHE3, tenapanor is therefore expected to reduce sodium absorption and increase the excretion of sodium and fluid in stool (13,14). In the 12-week T3MPO-1 study (ClinicalTrials.gov identifier: NCT02621892), a significantly greater proportion of patients with IBS-C treated with tenapanor reported improvements in global and individual IBS symptoms, including abdominal pain and bloating, than those treated with placebo (15). Tenapanor was generally well tolerated; the most frequent adverse event (AE) was diarrhea (15).

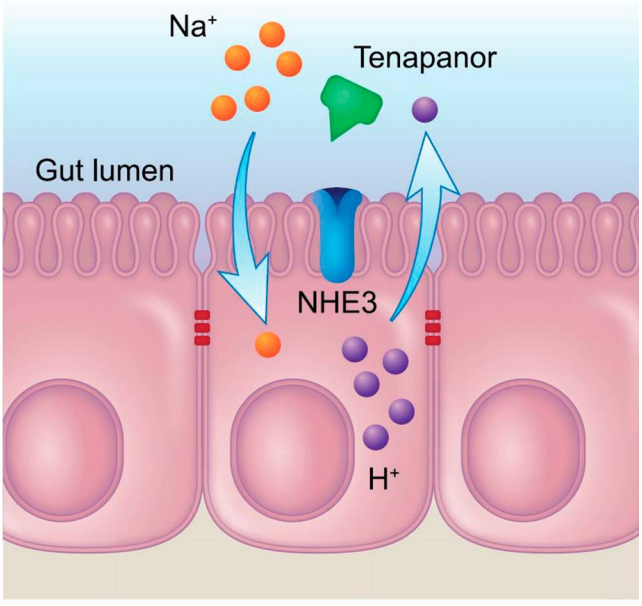


Figure 1. Mechanism of action. Tenapanor inhibits NHE3, which transports luminal sodium in exchange for cellular protons. NHE3, sodium/hydrogen exchanger isoform 3.

The current study, T3MPO-2, was designed to evaluate the efficacy and safety of tenapanor 50 mg b.i.d. compared with placebo over 26 weeks in patients with IBS-C.

METHODS

Study design

T3MPO-2 (ClinicalTrials.gov identifier: NCT02686138) was a multicenter, phase 3, randomized, double-blind, placebo-controlled study enrolling patients from 92 centers in the United States between December 2015 and August 2017 (last patient randomized on February 9, 2017). After a 2-week screening period, eligible patients were randomly assigned to receive 1 of 2 treatments for 26-weeks: tenapanor hydrochloride (hereafter referred to as tenapanor) 50 mg b.i.d. or placebo b.i.d. Scheduled study visits after randomization took place at weeks 2, 4, 8, 12, 16, 20, and 26.

Patients recorded data on efficacy variables, including daily bowel movement frequency and abdominal symptoms, using a touch-tone telephone diary with an interactive voice response system (IVRS).

The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry. All participating sites obtained independent ethics committee/institutional review board approval.

Patients

Full inclusion, exclusion, and study entry criteria used in this trial have been described previously (15). Briefly, men and women aged 18–75 years who met the Rome III criteria for IBS-C (16) were eligible for study enrollment.

To be randomly assigned to study treatment, patients also had to complete their IVRS telephone diary on ≥11 of 14 days during the 2-week screening period to demonstrate diary adherence and the following outcomes: weekly stool frequency of ≤5 spontaneous bowel movements (SBMs; defined as bowel movements occurring without the use of a laxative within the preceding 24 hours) and <3 complete spontaneous bowel movements (CSBMs; defined as SBMs accompanied by a sensation of complete evacuation); average weekly stool consistency score of <3 using the Bristol Stool Form Scale (BSFS) (17); average weekly abdominal pain score of ≥3 on a scale of 0–10; no use of a prohibited medication, except rescue medication; and no liquid stools for any SBM or mushy stools for >1 SBM, in accordance with the BSFS.

Rescue medications

Rescue medication use (bisacodyl 5 mg oral tablet or 10 mg suppository) was permitted for no more than 2 of the 14 screening period days and was not permitted within 48 hours of being randomly assigned to the study treatments. Throughout the treatment period, rescue medication was permitted to relieve severe constipation, defined as ≥72 hours without a bowel movement or when symptoms became intolerable. A bowel

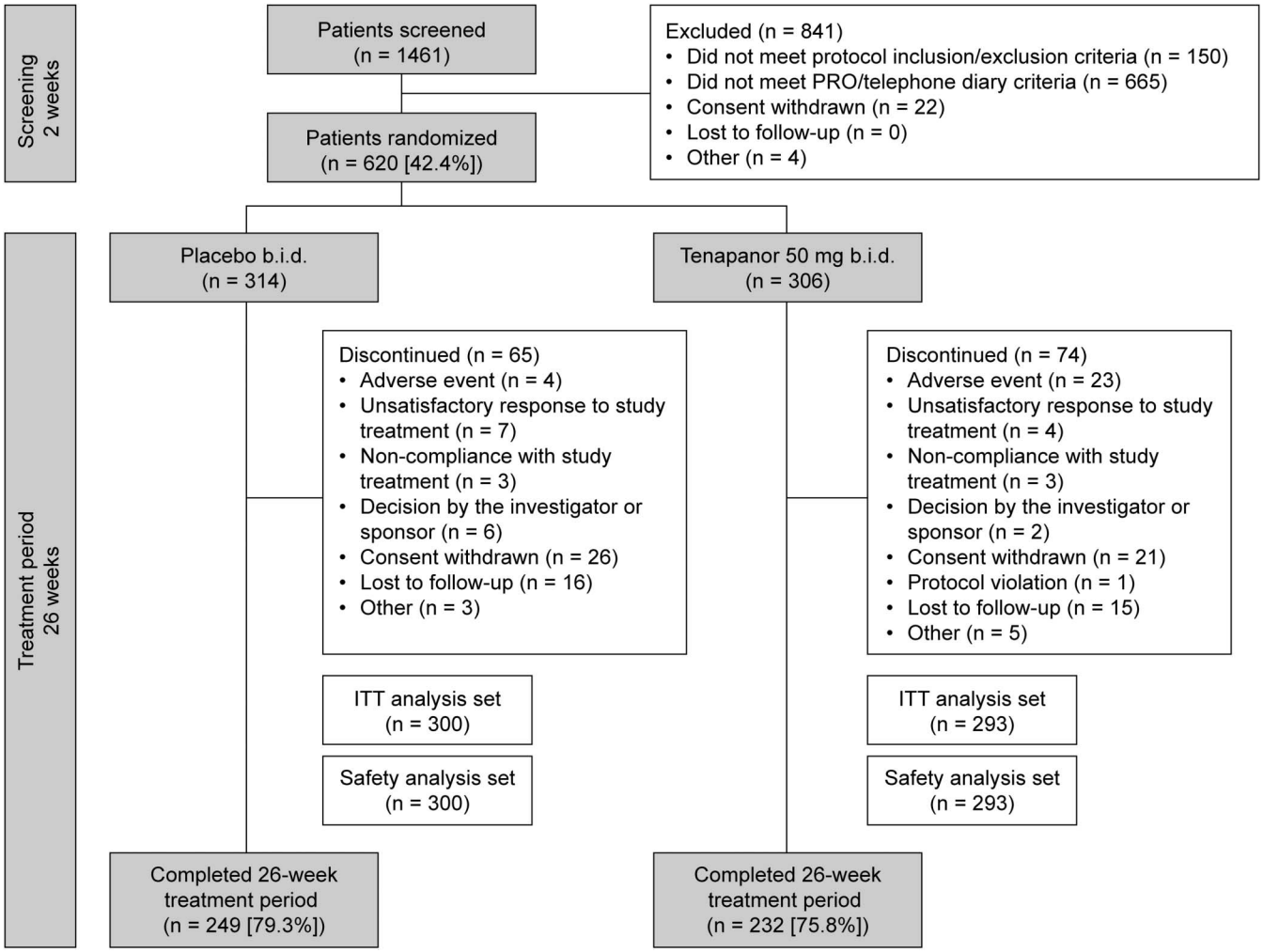


Figure 2. Overview of patient flow through the study. The safety analysis set includes all patients who received ≥1 dose of treatment. The ITT analysis set includes all patients who met the study entry inclusion/exclusion criteria, were randomized, and received ≥1 dose of study drug. b.i.d., twice daily; ITT, intention-to-treat; PRO, patient-reported outcome.

movement was not considered to be "spontaneous" if it was reported within 24 hours of the use of a rescue medication.

Efficacy variables and assessments

The primary endpoint was the 6/12-week combined responder rate, defined as the proportion of patients who had a weekly combined response for ≥6 of the first 12 weeks of the treatment period. A weekly combined response was defined as a decrease in average weekly worst abdominal pain of ≥30.0% from baseline (abdominal pain response) and an increase of ≥1 weekly CSBM from baseline (CSBM response), both in the same week. Baseline was defined as the average of values obtained during the 2-week screening period (i.e., weeks −1 and −2).

Key secondary endpoints included the 6/12-week CSBM and abdominal pain responder rates, the 9/12-week combined responder rate (the proportion of patients with a weekly combined response and ≥3 average weekly CSBMs for at least 9 of the first 12 weeks of the treatment period), and the 13/26-week combined responder rate (the proportion of patients with a weekly combined response for at least 13 weeks of the 26-week treatment period). Other secondary endpoints included "durable" combined CSBM and abdominal pain responder rates (the proportion of patients with a 9/12-week combined response who also met the response criteria for at least 3 of the final 4 weeks of the first 12 weeks of the treatment period); weekly proportion of patients with ≥3 CSBMs; average weekly CSBMs, SBMs, stool consistency, and straining score; 6/12-, 9/12-, and 13/26-week responder rates for abdominal symptoms (discomfort, bloating, cramping, and fullness); weekly IBS severity and constipation severity scores; weekly adequate relief and degree of relief of IBS symptoms; HRQoL assessed using the Irritable Bowel Syndrome Quality of Life questionnaire (IBS-QOL); and treatment satisfaction.

Patients recorded data for all efficacy variables using the IVRS telephone diary. Variables recorded daily included the frequency and time of each bowel movement, sensation of complete bowel emptying (1 = yes, 2 = no), stool consistency (measured using the BSFS), abdominal symptom scores (pain, bloating, cramping, discomfort, and fullness; each on a 0–10-point scale: 0 = absent, and 10 = very severe), straining score (1–5-point scale: 1 = not at all and 5 = an extreme amount), and use and time of rescue medication. Variables scored weekly included constipation severity, IBS severity (each on a 1–5-point scale: 1 = none and

5 = very severe), adequate relief of IBS (1 = yes and 2 = no), degree of relief from IBS symptoms (1–7-point scale: 1 = completely relieved and 7 = as bad as I can imagine), and treatment satisfaction (1–5-point scale: 1 = not at all satisfied and 5 = very satisfied). Patients were asked to complete the IBS-QOL at randomization (day 1) and at treatment weeks 12 and 26.

Safety outcomes and assessments

Safety assessments were based on AEs (all visits), clinical laboratory tests, comprising serum chemistry, hematology, and urinalysis (weeks −2, 4, 12, and 26), vital signs (weeks −2, 12, and 26), electrocardiograms (ECGs; weeks −2, 12, and 26), and physical examinations (weeks −2 and 26), as described previously (15).

AEs were spontaneously reported by the patient and/or disclosed in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Investigators defined AEs as mild (the event does not interfere in a significant manner with the patient's normal functioning level; it may be an annoyance but does not cause any limitation in usual activity), moderate (the event produces some impairment of functioning but is not hazardous to health; it is uncomfortable or an embarrassment and may cause some limitation in usual activity), or severe (the event produces significant impairment or incapacitation and is a definite hazard to the subject's health). All AEs were recorded on the appropriate page of the electronic case report form.

Statistical methods

Scores for weekly SBMs and weekly CSBMs were standardized to 7-day frequencies, with missing days during the week being imputed with the average for the recorded days. A valid week required ≥4 recorded diary days; patients with <4 days' input were treated as nonresponders for that week.

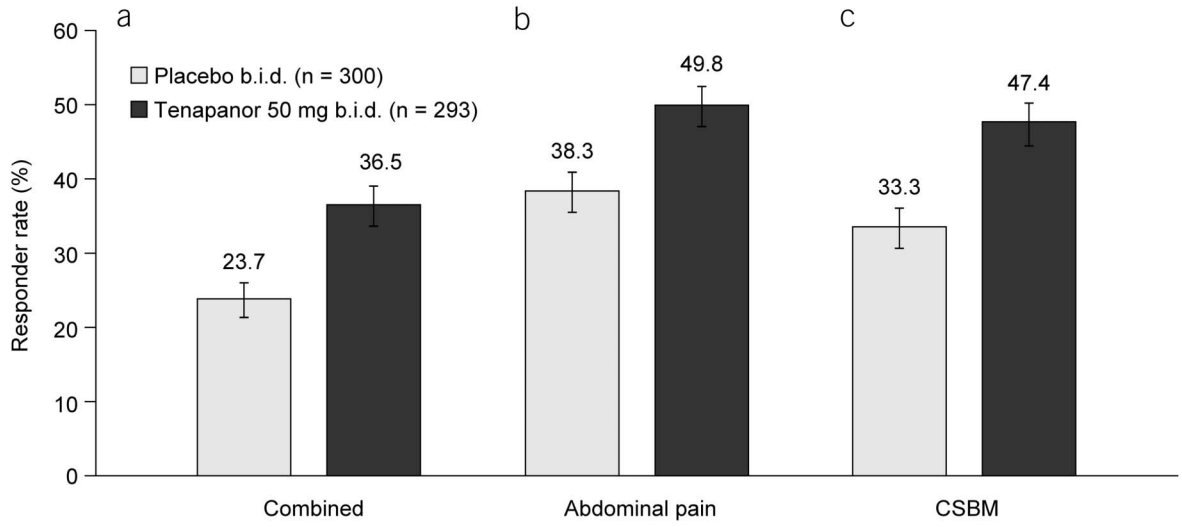
All patients who met the study eligibility criteria, were randomized, and received ≥1 dose of study drug were included in the intention-to-treat (ITT) analysis set. The ITT analysis set was used for the evaluation of all efficacy variables. All patients who received ≥1 dose of study drug were included in all analyses of safety data (safety analysis set).

A sample size of 300 in each treatment group was expected to achieve 95% power to detect a difference of 0.15 (15.0%) in the 6/12-week combined responder rate (primary endpoint) between the tenapanor and placebo groups. This assumed (under the alternative hypothesis) that the 6/12-week combined responder rate in the tenapanor group would be ≥45.0% and no closer than 15.0% to that in the placebo group.

Table 1. Patient demographics and baseline IBS-related characteristics (ITT analysis set)

Demographic/characteristic	Placebo (n = 300)	Tenapanor 50 mg b.i.d. (n = 293)	Overall (N = 593)
Age, yr	44.8 (13.8)	46.1 (13.1)	45.4 (13.5)
Sex, n (%)			
Women	247 (82.3)	240 (81.9)	487 (82.1)
Race, n (%)			
White	192 (64.0)	185 (63.1)	377 (63.6)
Black or African American	92 (30.7)	92 (31.4)	184 (31.0)
Asian	9 (3.0)	12 (4.1)	21 (3.5)
Body mass index, kg/m^2	30.9 (7.3)	30.5 (7.2)	30.7 (7.2)
Duration of IBS symptoms before randomization, yr	11.1 (11.6)	11.1 (11.1)	11.1 (11.3)
Disease characteristic[a]			
Abdominal pain[b]	6.3 (1.7)	6.3 (1.7)	6.3
CSBMs per week	0.1 (0.3)	0.1 (0.3)	0.1
SBMs per week	1.7 (1.1)	1.6 (1.0)	1.6
Stool consistency[c]	0.5 (0.4)	0.5 (0.4)	0.5
Straining[d]	0.9 (0.6)	0.9 (0.6)	0.9
IBS severity[e]	3.9 (0.7)	3.9 (0.7)	3.9
Constipation severity[e]	4.0 (0.7)	4.1 (0.7)	4.0

b.i.d., twice daily; BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; IBS, irritable bowel syndrome; ITT, intention-to-treat; SBM, spontaneous bowel movement.
Data are shown as mean (SD) unless otherwise stated.
[a]Data are shown as mean (SD) of the average of the weekly scores during the screening period for individual patients.
[b]Assessed daily using a 0–10-point scale: 0 = none, 10 = very severe; the average weekly score was calculated from scores for all days during a valid week.
[c]Assessed using the 7-point BSFS (17); the average weekly score calculated from scores for all valid SBMs during the week. For the purpose of calculating an average score, days with no stools were assigned a score of 0.
[d]Assessed for each SBM using a 1–5-point scale: 1 = not at all, 5 = an extreme amount; the average weekly score was calculated from scores for all valid SBMs during the week.
[e]Assessed weekly using a 1–5-point scale: 1 = none, 5 = very severe.



Responder rate, n (%)	71 (23.7)	107 (36.5)	115 (38.3)	146 (49.8)	100 (33.3)	139 (47.4)
Risk difference vs placebo, %	–	12.9	–	11.5	–	14.1
95% CI	–	(5.5–20.2)	–	(3.6–19.4)	–	(6.3–21.9)
Adjusted RR[a]	–	1.55	–	1.3	–	1.42
95% CI	–	(1.20–1.99)	–	(1.09–1.57)	–	(1.16–1.73)
CMH *P* value[b]	–	< 0.001	–	0.004	–	< 0.001

Figure 3. Six of 12-week responder rates (ITT analysis set): proportions of patients with (**a**) combined response for ≥6 of the first 12 treatment weeks (primary efficacy endpoint), (**b**) abdominal pain response for ≥6 of the first 12 treatment weeks (key secondary efficacy endpoint), and (**c**) CSBM response for ≥6 of the first 12 treatment weeks (key secondary efficacy endpoint). [a]The adjusted RR was based on the ratio of responder rates for tenapanor 50 mg b.i.d. vs placebo b.i.d. stratified by pooled investigator sites using the Mantel–Haenszel method. [b]The CMH *P* value was based on a 1 degree of freedom test for association between treatment (tenapanor and placebo), stratified by pooled investigator sites. b.i.d., twice daily; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CSBM, complete spontaneous bowel movement; ITT, intention-to-treat; RR, relative risk.

All efficacy variables involving responder rates or proportions were analyzed using a Cochran–Mantel–Haenszel test with pooled investigator site as a stratification (adjustment) variable. All changes from baseline in continuous efficacy variables derived from the daily IVRS telephone diary, and the weekly IBS severity, constipation severity, and IBS-QOL data, were analyzed using an analysis of covariance model, with terms for pooled investigator site and treatment and baseline values as the covariates. The degrees of relief of IBS symptoms and treatment satisfaction were analyzed using an analysis of variance model, with terms for pooled investigator site and treatment as the covariates. Statistical analyses were performed using a 2-sided significance level of 0.050.

RESULTS

Patients

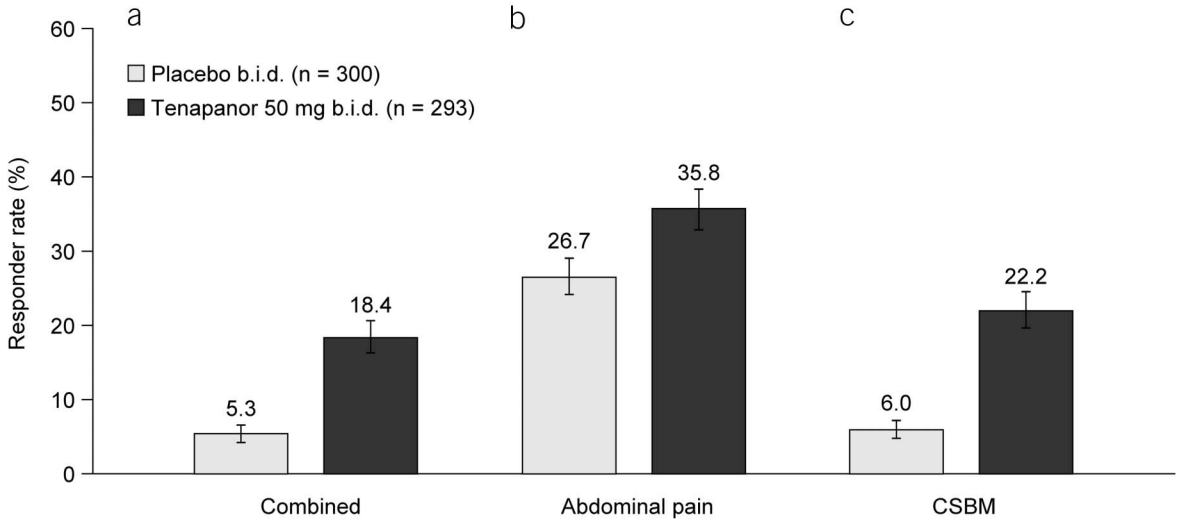
Of 1,461 patients who were screened, 620 (42.4%) were randomly assigned to treatment with tenapanor or placebo for 26 weeks (Figure 2). In total, 593 patients were included in the ITT and safety analysis sets, of whom 293 received tenapanor and 300 received placebo. Patients who were randomized but excluded from the ITT and safety analysis sets (n = 27) were associated with a clinical site judged by the sponsor to be in serious breach of Good Clinical Practice. At the time the breach was identified, 21 of these 27 patients had completed the study and 6 had discontinued (consent withdrawn, lost to follow up or citing other reasons).

The entire 26-week treatment period was completed by 232 of the 306 patients (75.8%) assigned to tenapanor and by 249 of the 314 patients (79.3%) assigned to placebo. Treatment groups were well balanced regarding patient demographics and baseline IBS-related characteristics (Table 1). The mean age of patients was 45.4 years, with most patients being women (82.1%) and White (63.6%).

Efficacy

A significantly greater proportion of patients in the tenapanor treatment group were 6/12-week combined responders than those in the placebo group (primary endpoint; 36.5% vs 23.7%; $P < 0.001$; Figure 3a). The 6/12-week abdominal pain responder rate was also significantly higher with tenapanor treatment than with placebo (49.8% vs 38.3%; $P = 0.004$; Figure 3b). Similarly, a significantly greater proportion of patients in the tenapanor treatment group were 6/12-week CSBM responders than those in the placebo group (47.4% vs 33.3%; $P < 0.001$; Figure 3c).

The 9/12-week combined responder rate was also significantly higher for patients receiving tenapanor than for those receiving placebo (18.4% vs 5.3%; $P < 0.001$; Figure 4a). Likewise, a significantly greater proportion of patients in the tenapanor treatment group than those in the placebo group were 9/12-week abdominal pain responders (35.8% vs 26.7%; $P = 0.015$; Figure 4b) and 9/12-week CSBM responders (22.2% vs 6.0%; $P < 0.001$; Figure 4c). Compared with the placebo group, a significantly greater proportion of patients in the tenapanor treatment group were 13/26-week combined responders (35.5% vs 24.3%; $P = 0.003$; Figure 5a). Similarly, a significantly greater proportion of patients in the tenapanor treatment group than those in the placebo group were 13/26-week abdominal pain responders (50.2% vs 40.0%; $P = 0.013$; Figure 5b) and 13/26-week CSBM responders (41.3% vs 31.0%; $P = 0.010$; Figure 5c).



Responder rate, n (%)	16 (5.3)	54 (18.4)	80 (26.7)	105 (35.8)	18 (6.0)	65 (22.2)
Risk difference vs placebo, %	–	13.1	–	9.2	–	16.2
95% CI	–	(8.0–18.2)	–	(1.7–16.6)	–	(10.7–21.7)
Adjusted RR[a]	–	3.47	–	1.35	–	3.71
95% CI	–	(2.03–5.94)	–	(1.06–1.73)	–	(2.25–6.12)
CMH *P* value[b]	–	< 0.001	–	0.015	–	< 0.001

Figure 4. Nine of 12-week responder rates (ITT analysis set; key secondary efficacy endpoint): proportions of patients with (**a**) combined response and ≥3 average weekly CSBMs for ≥9 of the first 12 treatment weeks, (**b**) abdominal pain response for ≥9 of the first 12 treatment weeks, and (**c**) CSBM response and ≥3 average weekly CSBMs for ≥9 of the first 12 treatment weeks. [a]The adjusted RR was based on the ratio of responder rates for tenapanor 50 mg b.i.d. vs placebo b.i.d., stratified by pooled investigator sites using the Mantel–Haenszel method. [b]The CMH *P* value was based on a 1 degree of freedom test for association between treatment (tenapanor and placebo), stratified by pooled investigator sites. b.i.d., twice daily; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CSBM, complete spontaneous bowel movement; ITT, intention-to-treat; RR, relative risk.

The durable combined responder rate was significantly higher with tenapanor treatment than with placebo (18.1% vs 5.0% for placebo; $P < 0.001$; Figure 6a). A significantly greater proportion of patients in the tenapanor treatment group than those in the placebo group were also durable abdominal pain responders (34.8% vs 26.7%; $P = 0.028$; Figure 6b) and durable CSBM responders (21.2% vs 5.7%; $P < 0.001$; Figure 6c). Compared with placebo, patients treated with tenapanor had a significantly greater mean increase from baseline in the average weekly number of CSBMs ($P < 0.001$; Figure 7) and a significantly greater mean decrease from baseline in average weekly abdominal pain scores ($P < 0.01$; Figure 8), from week 1 onward. A greater proportion of patients receiving tenapanor also met other secondary endpoints than patients receiving placebo (see Tables 1 and 2, Supplementary Digital Content 2, http://links.lww.com/AJG/B789). Improvements in overall HRQoL from baseline at week 26 were significantly greater with tenapanor than with placebo (least-squares means of 21.5 and 17.3, respectively; least-square mean difference = 4.2; 95% confidence interval = 0.95–7.39; $P = 0.011$).

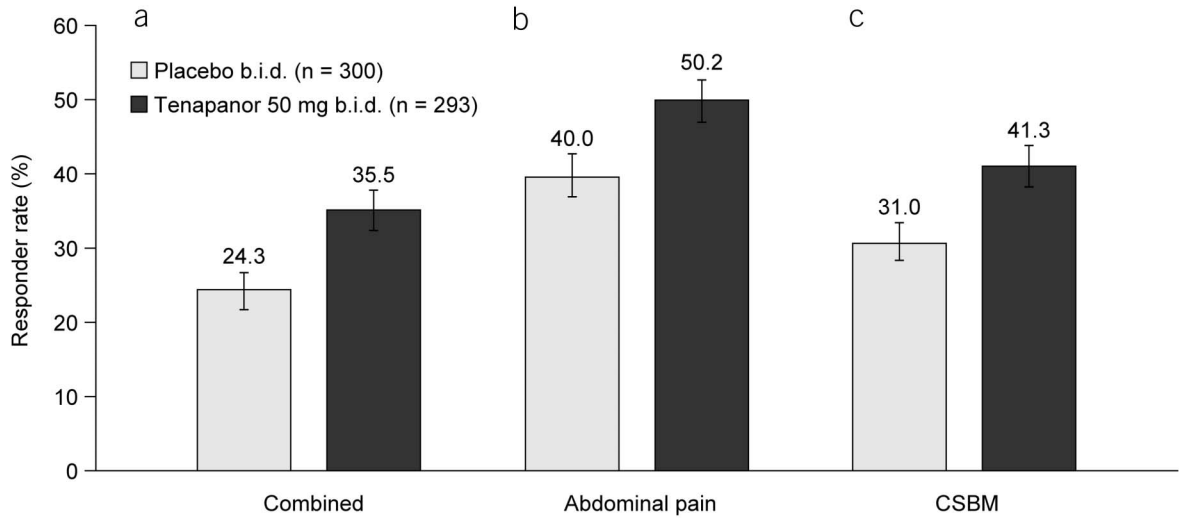
During the treatment period, 117 patients (39.9%) in the tenapanor group and 155 patients (51.7%) in the placebo group reported rescue medication use. The number of patients reporting the use of rescue medication generally decreased in both treatment groups over the course of the treatment period.

Safety

Mean study drug adherence in the safety analysis set was 98.1% for tenapanor and 99.2% for placebo during the treatment period. Most patients in the tenapanor group (93.5%) and the placebo group (93.3%) demonstrated a greater than 80% adherence rate.

Table 2 gives an overview of the AEs that occurred during the treatment period. Four patients in the tenapanor group experienced serious AEs (SAEs). By the preferred term, the SAEs were abdominal pain, diarrhea, nausea, and chronic obstructive pulmonary disease. Only the SAE of diarrhea reported in the tenapanor group was judged to be "possibly related" to treatment. No deaths occurred over the course of the study.

Treatment-related AEs were reported for 64 patients (21.8%) receiving tenapanor and 28 patients (9.3%) receiving placebo during the 26-week treatment period. By system organ class, most treatment-related AEs were gastrointestinal in nature, with diarrhea, abdominal distension, and flatulence the only treatment-related AEs by the preferred term reported for ≥3.0% of patients receiving tenapanor. Diarrhea was the most common AE, by the preferred term, and was reported by 47 patients (16.0%) receiving tenapanor and 11 patients (3.7%) receiving placebo during the treatment period. Diarrhea was typically transient (≤1 week's duration) and mild to moderate in severity. In approximately half of the cases, diarrhea occurred within a week of treatment commencement, and two-thirds of cases occurred within the first 3 weeks of treatment. Diarrhea was judged to be treatment related in 44 patients (15.0%) in the tenapanor group and 8 patients (2.7%) in the placebo group and led to study drug discontinuation for 19 patients (6.5%) in the tenapanor group and 2 patients (0.7%) in the placebo group. Generally, there was no evidence of clinically significant differences between treatment groups in electrolytes and other laboratory parameters (serum chemistry,



Responder rate, n (%)	73 (24.3)	104 (35.5)	120 (40.0)	147 (50.2)	93 (31.0)	121 (41.3)
Risk difference vs placebo, %	–	11.2	–	10.2	–	10.3
95% CI	–	(3.8–18.5)	–	(2.2–18.1)	–	(2.6–18.0)
Adjusted RR[a]	–	1.46	–	1.25	–	1.33
95% CI	–	(1.13–1.88)	–	(1.05–1.50)	–	(1.07–1.65)
CMH *P* value[b]	–	0.003	–	0.013	–	0.010

Figure 5. Thirteen of 26-week responder rates (ITT analysis set; key secondary efficacy endpoint): Proportions of patients with (**a**) combined response for ≥13 of 26 treatment weeks, (**b**) abdominal pain response for ≥13 of 26 treatment weeks, and (**c**) CSBM response for ≥13 of 26 treatment weeks. [a]The adjusted RR was based on the ratio of responder rates for tenapanor 50 mg b.i.d. vs placebo b.i.d., stratified by pooled investigator sites using the Mantel–Haenszel method. [b]The CMH *P* value was based on a 1 degree of freedom test for association between treatment (tenapanor and placebo), stratified by pooled investigator sites. b.i.d., twice daily; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CSBM, complete spontaneous bowel movement; ITT, intention-to-treat; RR, relative risk.

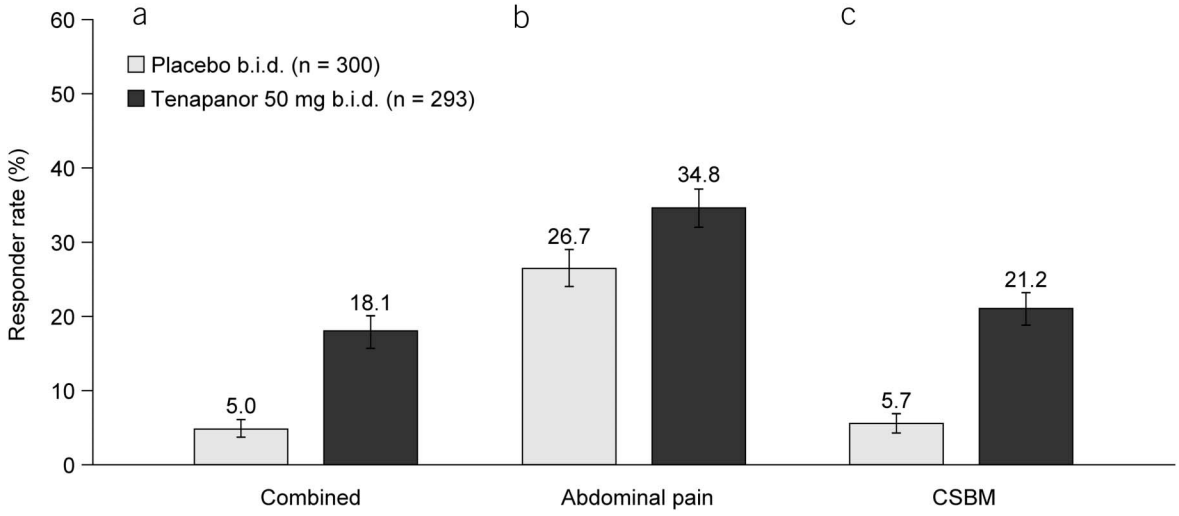
hematology, and urinalysis parameters), ECG parameters, vital signs, and physical examinations during the study.

DISCUSSION

In this randomized, phase 3 study, tenapanor treatment significantly improved IBS-C symptoms compared with placebo, with no evidence of decreasing efficacy over the 26-week study period. Compared with placebo, a significantly higher proportion of patients receiving tenapanor experienced an increase in CSBM frequency and a reduction in abdominal pain in the same week for ≥6 of the first 12 weeks of the treatment period (the primary endpoint). A statistically significant difference between tenapanor and placebo was also achieved for the more stringent endpoints requiring ≥9/12 and ≥13/26 treatment weeks of combined response. Overall, our study confirms the results from the previously published phase 3 T3MPO-1 trial, which assessed the effects of 12 weeks of tenapanor treatment in patients with IBS-C (13). That said, there were some differences in the results despite the similar endpoints used in these trials. Response rates for many of the key endpoints were greater for the T3MPO-2 cohort compared with T3MPO-1. Perhaps the most notable difference was the statistically significant improvement with tenapanor compared with placebo for the 6/12-week CSBM responder endpoint in T3MPO-2, but not in T3MPO-1; tenapanor did, however, offer a statistically significant benefit compared with placebo for the 9/12-week CSBM responder endpoint in both T3MPO-1 and T3MPO-2. The exact reasons for these differences are unclear but may include statistical variation, differences in study populations reflecting involvement of different study sites, or other unforeseen factors that may occur in the context of a clinical trial. Indeed, other phase 3 programs conducted in patients with IBS have also reported variation in trial results despite evaluating the same drug (8,9,18,19).

In both T3MPO-1 and T3MPO-2, robust improvements in average weekly CSBMs and abdominal pain were observed by week 1 and maintained through to the end of the treatment period (15). At the week 12 and 26 assessments of this study, the tenapanor treatment group had a significantly greater proportion of CSBM responders and a significantly greater mean increase from baseline in the average weekly number of CSBMs than the placebo group. From week 1, ≥30.0% of patients treated with tenapanor achieved at least 3 CSBMs per week. This CSBM frequency, according to a population-based study conducted in a representative sample in the United States, falls within the healthy range for adults (20). In our study, a significantly greater proportion of patients treated with tenapanor had ≥3 CSBMs per week throughout the treatment period than those treated with placebo.

A significantly greater proportion of patients receiving tenapanor experienced improvements in abdominal symptoms (discomfort, bloating, cramping, and fullness) for ≥6 and ≥9 of the first 12 weeks, and ≥13 of 26 weeks of the treatment period than those receiving placebo. Similarly, patients receiving tenapanor had a significantly greater improvement in global IBS treatment measures than those receiving placebo. Notably, patients receiving tenapanor reported a significant improvement from baseline in treatment satisfaction at week 26 compared with placebo. At the 26-week time point, 80.5% of patients receiving tenapanor were at least moderately satisfied with their



Responder rate, n (%)	15 (5.0)	53 (18.1)	80 (26.7)	102 (34.8)	17 (5.7)	62 (21.2)
Risk difference vs placebo, %	–	13.1	–	8.2	–	15.5
95% CI	–	(8.0–18.1)	–	(0.7–15.6)	–	(10.1–20.9)
Adjusted RR[a]	–	3.63	–	1.31	–	3.75
95% CI	–	(2.09–6.31)	–	(1.03–1.68)	–	(2.24–6.27)
CMH *P* value[b]	–	< 0.001	–	0.028	–	< 0.001

Figure 6. Durable responder rates (ITT analysis set; other secondary efficacy endpoint): Proportions of patients with (**a**) durable combined response, (**b**) durable abdominal pain response, and (**c**) durable CSBM response. [a]The adjusted RR was based on the ratio of responder rates for tenapanor 50 mg b.i.d. vs placebo b.i.d., stratified by pooled investigator sites using the Mantel–Haenszel method. [b]The CMH *P* value was based on a 1 degree of freedom test for association between treatment (tenapanor and placebo), stratified by pooled investigator sites. A durable abdominal pain response is defined as a decrease in average weekly worst abdominal pain of ≥30.0% from baseline for ≥9 of the first 12 treatment weeks, including ≥3 of the final 4 weeks of the first 12 weeks of the treatment period. A durable CSBM response is defined as an increase of ≥1 CSBM/week from baseline and ≥3 CSBM/week for ≥9 of the first 12 treatment weeks, including ≥3 of the final 4 weeks of the first 12 weeks of the treatment period. b.i.d., twice daily; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CSBM, complete spontaneous bowel movement; ITT, intention-to-treat; RR, relative risk.

treatment, compared with 61.2% of patients receiving placebo. The benefits of tenapanor in patients with IBS-C were also seen for quality of life parameters, with clinically meaningful improvements observed at weeks 12 and 26 across all IBS-QOL subscales, although these improvements were not always statistically significant compared with placebo.

Overall, tenapanor was associated with an acceptable safety profile over the course of our study, consistent with the results of

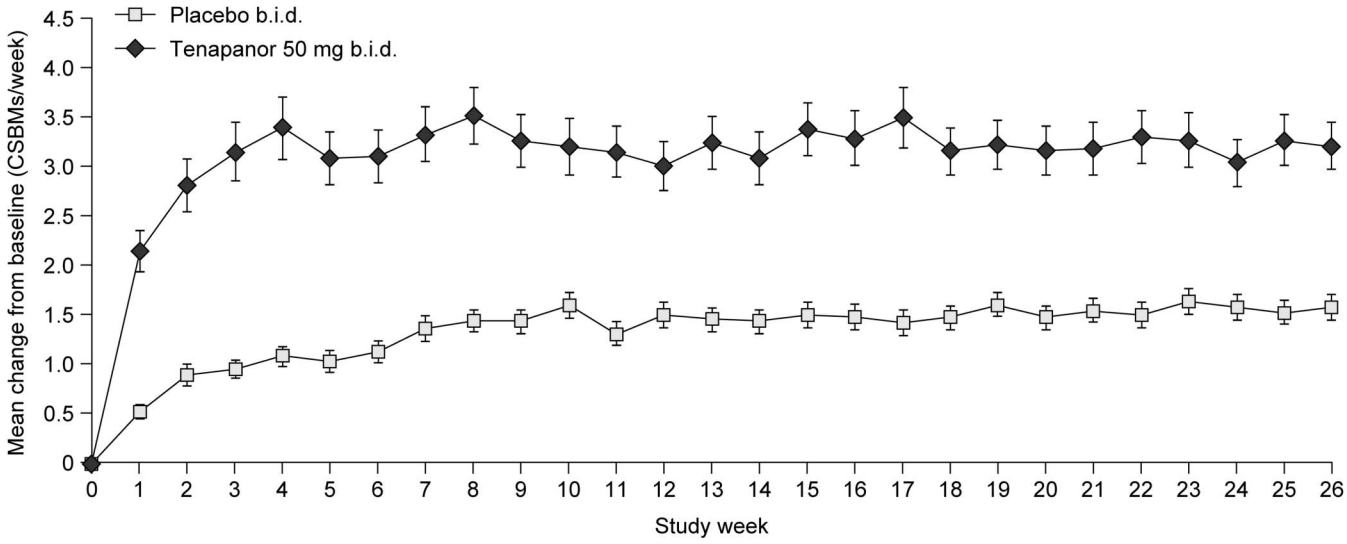


Figure 7. Mean change from baseline in the average weekly number of CSBMs over time (ITT analysis set). $P < 0.001$ vs placebo for all time points. *P* values were based on an ANCOVA model with treatment and pooled investigator site as factors and baseline value as a covariate. ANCOVA, analysis of covariance; b.i.d., twice daily; CSBM, complete spontaneous bowel movement; ITT, intention-to-treat.

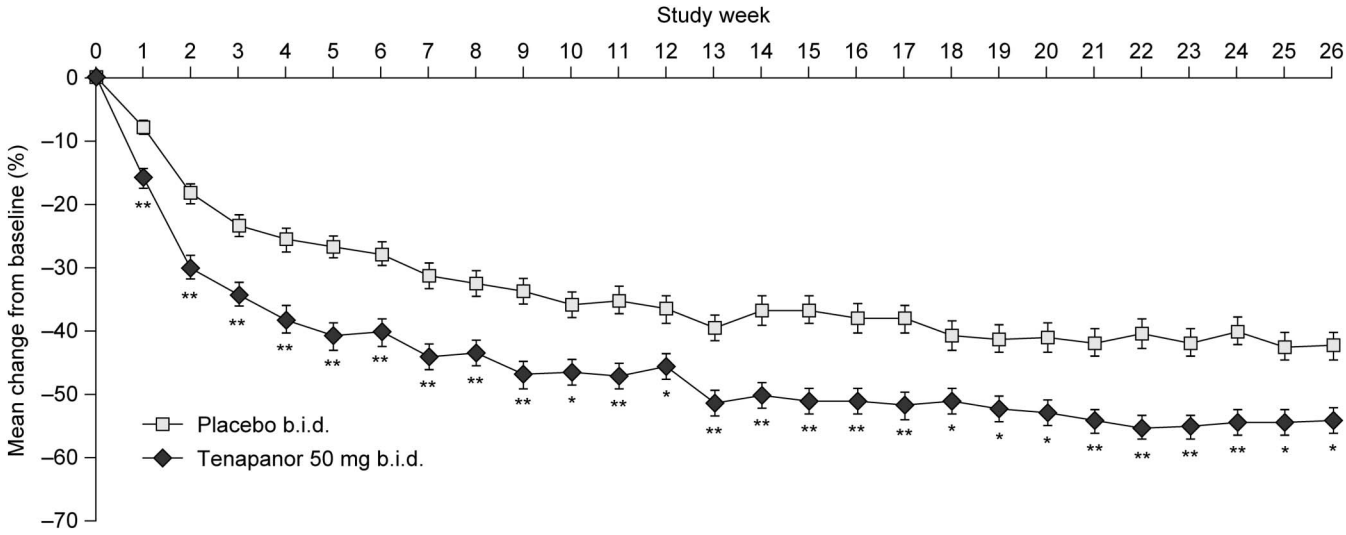


Figure 8. Mean change from baseline in the average weekly abdominal pain score over time (ITT analysis set). *$P < 0.01$, **$P < 0.001$ vs placebo. *P* values were based on an ANCOVA model with treatment and pooled investigator site as factors and baseline value as a covariate. ANCOVA, analysis of covariance; b.i.d., twice daily; ITT, intention-to-treat.

previously reported phase 2b and 12-week phase 3 trials (15,21). Diarrhea occurred in 16.0% of tenapanor-treated patients (47/293) during the 26-week treatment period, with onset within 1 week of treatment commencement in approximately half of cases. Diarrhea was typically transient and mild to moderate in severity, leading to study drug discontinuation for 19 (6.5%) and 2 patients (0.7%) receiving tenapanor and placebo, respectively. Four patients in the tenapanor group experienced SAEs during the 26-week treatment period; however, only 1 SAE (diarrhea) was judged to be possibly treatment related. No deaths were reported in either of the study groups. A study in which patients received 52–55 weeks of tenapanor has recently been completed (T3MPO-3; ClinicalTrials.gov identifier: NCT02727751) to understand the gastrointestinal AE profile of tenapanor over a prolonged treatment period.

Table 2. Overview of AEs (safety analysis set)

AEs, n (%)	Placebo (n = 300)	Tenapanor 50 mg b.i.d. (n = 293)
Any AE	124 (41.3)	143 (48.8)
Treatment-related AEs	28 (9.3)	64 (21.8)
Serious AEs	6 (2.0)	4 (1.4)
Deaths	0	0
AEs leading to study drug discontinuation	3 (1.0)	23 (7.8)
AEs by preferred term[a]		
Diarrhea	11 (3.7)	47 (16.0)
Abdominal distension	1 (0.3)	10 (3.4)
Flatulence	3 (1.0)	9 (3.1)
Nasopharyngitis	11 (3.7)	13 (4.4)

AE, adverse event; b.i.d., twice daily.
[a]AEs by the preferred term occurring in ≥3.0% of patients in the tenapanor treatment group and at a higher incidence than in the placebo group.

Potential limitations of the study should be acknowledged. Related to the timing of the study, the Rome III criteria, rather than the current Rome IV criteria, were used to identify patients for this study. However, recent research suggests that most patients fulfilling the Rome III criteria will also fulfill the Rome IV criteria for IBS-C (22). In addition to meeting these criteria, we also required that patients with IBS-C pass no more than 5 SBMs and fewer than 3 CSBMs per week to be eligible for randomization. Thus, our study population, similar to other recently completed phase 3 studies of patients with IBS-C (8–10), may represent a more severely affected population than the patients with typical IBS-C encountered in routine clinical practice (23). In our study, study drug adherence was far greater than what might be expected in clinical practice (24); further studies will assist in determining adherence to tenapanor in a real-world setting.

In conclusion, this methodologically rigorous, randomized, placebo-controlled phase 3 trial demonstrates the efficacy and tolerability of tenapanor over 26 weeks in patients with IBS-C. The results from T3MPO-2, together with T3MPO-1, provided robust support for the recent FDA approval of tenapanor for the treatment of IBS-C. Tenapanor is an effective and generally well tolerated new treatment option for patients with IBS-C.

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CONFLICTS OF INTEREST

Guarantor of the article: William D. Chey, MD, AGAF, FACG, FACP, RFF.

Specific author contributions: W.D.C. and A.J.L.: contributed to the planning of the study, interpretation of the data, and critical revision of the manuscript for important intellectual content. Y.Y.: reviewed the manuscript critically for statistical content and contributed to the interpretation of the data and critical revision of the manuscript for

important intellectual content. D.P.R.: contributed to the planning of the study, conduct of the study, interpretation of the data, and critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript for submission.
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Potential competing interests: W.D.C. is a consultant for Allergan, Biomerica, IM Health, Humphries Pharmaceuticals, Ironwood Pharmaceuticals, Phathom, QOL Medical, Ritter Pharmaceuticals, Salix/Valeant, and Urovant and has received research funding from Biomerica, Commonwealth Diagnostics International, QOL Medical, Salix/Valeant, Vibrant, and Zespri. A.J.L. is a consultant for Allergan, Ardelyx, Biomerica, Ironwood Pharmaceuticals, Prometheus Laboratories, and Valeant and has received research funding from Prometheus Laboratories, Biomerica, Vibrant, and Ironwood Pharmaceuticals. Y.Y. is an employee of Ardelyx. D.P.R. is an employee of and has an ownership interest in Ardelyx.
ClinicalTrials.gov identifier: NCT02686138.

Study Highlights

WHAT IS KNOWN

- ✓ People living with IBS-C can suffer considerable morbidity owing to abdominal and bowel symptoms.
- ✓ There are few evidence-based treatments that address the spectrum of IBS-C symptoms.
- ✓ Tenapanor is a first-in-class, minimally absorbed, small-molecule inhibitor of the gastrointestinal sodium/hydrogen exchanger isoform 3.
- ✓ In a previously published 12-week phase 3 study, a significantly greater proportion of patients with IBS-C reported a combined response, consisting of improvements in abdominal pain and stool frequency, when treated with tenapanor compared with placebo.

WHAT IS NEW HERE

- ✓ Consistent with the previously published phase 3 trial, tenapanor improved the combined response rate for at least 6 and 9 of the first 12 weeks, relative to placebo.
- ✓ Tenapanor also improved combined response rates for at least 13 of 26 weeks, compared with placebo.
- ✓ Tenapanor was generally well tolerated for up to 26 weeks; the most common adverse event was transient and mildto-moderate diarrhea.

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