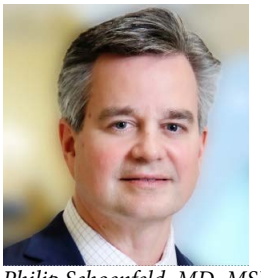
EVIDENCE-BASED GI
AN ACG PUBLICATION

Tenapanor (IBSRELA) for Treatment of IBS-C: Effective Over 26 Weeks



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This article reviews Chey WD, Lembo A, Yang Y, Rosenbaum DP. Efficacy of Tenapanor in Treating Patients With Irritable Bowel Syndrome with Constipation: A 26-Week, Placebo-Controlled Phase 3 Trial (T3MPO-2). Am J Gastroenterol 2021; 116: 1294-1303. https://doi.org/10.14309/ajg.0000000000001056

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STRUCTURED ABSTRACT

Question: Is tenapanor (IBSRELA), a first-in-class, small-molecule inhibitor of the GI sodium/hydrogen exchanger isoform 3 (NHE3) superior to placebo in patients with inflammatory bowel syndrome with constipation (IBS-C) for improving global IBS-C symptoms, abdominal discomfort, and complete spontaneous bowel movements (CSBM) based on FDA-defined responder endpoints?

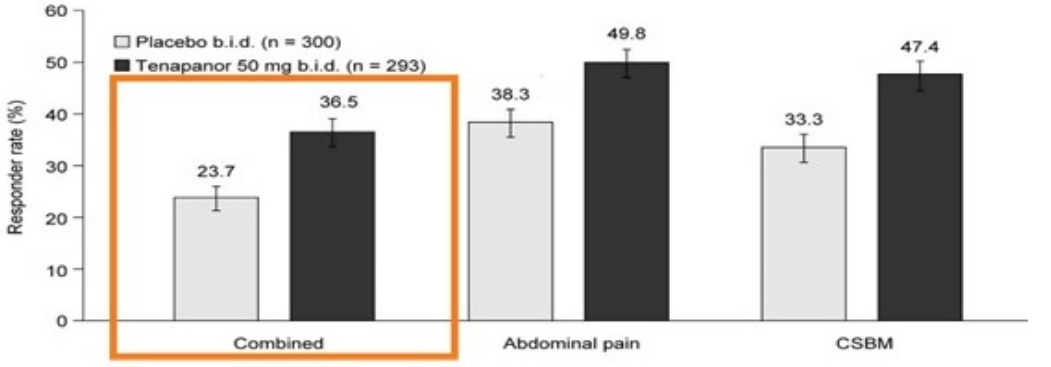
Design: Multicenter, double-blind, placebo-controlled randomized controlled trial.

Setting: Nintey-two United States centers conducted from December 2015 through August 2017.

Patients: Five hundred nintey-three outpatients meeting Rome III IBS-C criteria.

Interventions/Exposure: Tenapanor 50mg b.i.d. vs placebo b.i.d. for 26 weeks.

Outcome: The primary endpoint was the proportion of patients meeting the FDA-defined endpoint: $\geq$ 6 of first 12 weeks as combined responders for abdominal pain improvement and complete spontaneous bowel movements (CSBMs) in the same week. Per FDA requirements, patients used a touch-tone phone and an interactive voice response phone system to record symptoms daily. An abdominal pain responder was defined as $\geq$ 30% improvement in average weekly worst abdominal pain from baseline, and a CSBM responder had



Risk difference versus placebo, % (95% CI)	12.9 (5.5, 20.2)	11.5 (3.6, 19.4)	14.1 (6.3, 21.9)
P value	<0.001	0.004	<0.001

Figure 1. ≥ 6/12 week responders for FDA-combined endpoint, abdominal pain endpoint, and CSBM endpoint.

an increase of ≥1 weekly CSBM from baseline. Key secondary endpoints included 6/12 week responders for abdominal pain, 6/12 week responders for CSBM, 9/12 week combined responders, and 13/26 week combined responders.

Data Analysis: Intention-to-treat analyses were performed. For responder rates or proportions, Cochran-Mantel-Haenszel tests with pooled investigator site as a stratification (adjustment) variable were used. For degrees of relief of IBS symptoms and treatment satisfaction, analysis of variance models with terms for pooled investigator site and treatments as covariates were used.

Results: In all, 593 IBS-C patients were randomized and included in the intention-to-treat (ITT) analysis (mean age: 45.4 years old; 82.1% female; 63.6% White; Baseline Symptoms: Abdominal Score = 6.3 on 0-10 scale; 0.1 CSBMs/week; 1.6 SBMs/week). Approximately, 81.1% from the ITT analysis completed entire 26 weeks of treatment. Tenapanor-treated patients were more likely to be ≥ 6/12 week combined responders compared to placebo-treated patients: 36.5% vs 23.7% (aRR = 1.55, 95% CI: 1.20-1.99, $P< 0.0001$) (**Figure 1**) as well as ≥ 6/12 week abdominal pain responders and CSBM responders per FDA criteria (**Figure 1**). Significantly more tenapanor patients were 9/12 week responders: 18.4% vs 5.3% (aRR = 3.47, 95% CI: 2.03-5.94, $P<0.0001$). Mean improvement in CSBM and mean decrease in abdominal pain was maintained through 26 weeks (**Figure 2**). Diarrhea was more commonly reported by tenapanor-treated patients versus placebo-treated patients (16.0% vs 3.7%), although discontinuation of study medication due to diarrhea only occurred in 6.5% of tenapanor-treated patients.

Funding: Ardelyx Pharmaceuticals.

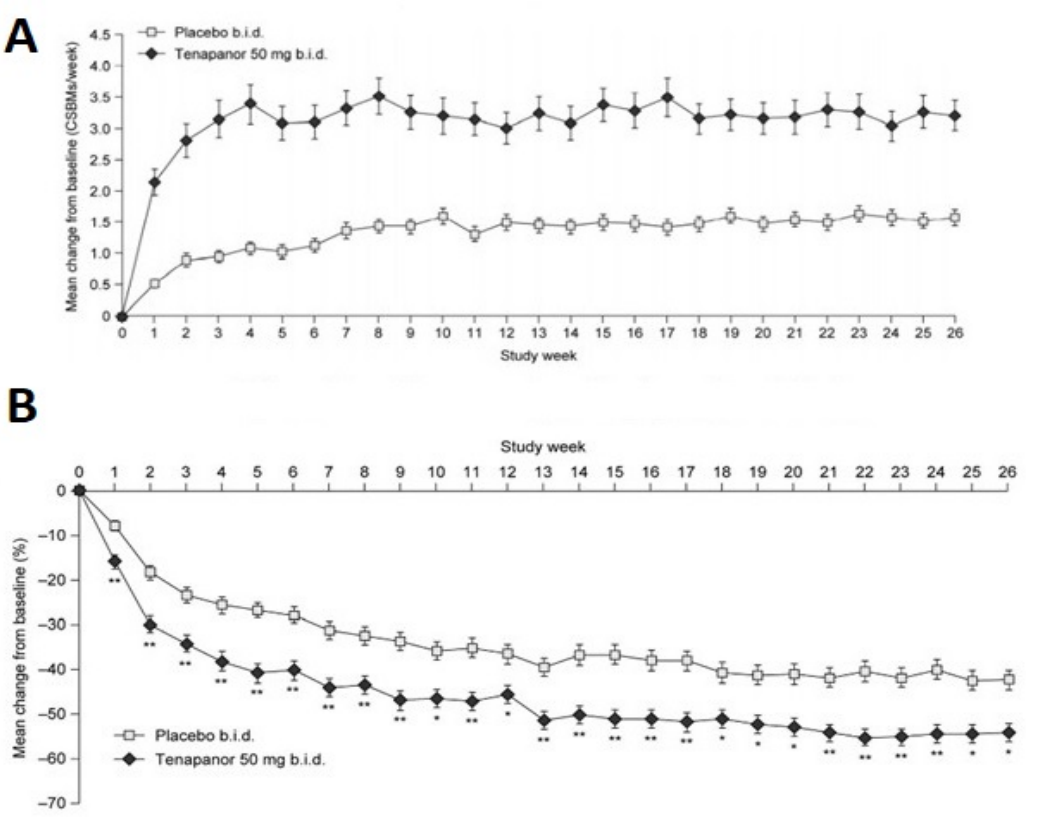


Figure 2. Weekly change in CSBMs (A) and abdominal pain (B).

COMMENTARY

Why Is This Important?

Although IBS is commonly characterized by altered intestinal motility and visceral hypersensitivity, the underlying pathophysiology is complex and may involve defective brain-gut interactions, alterations in gut flora, genetic predispositions, and defects in enteric nervous system functioning, among others. Thus, it's unsurprising that even the most effective IBS treatments rarely demonstrate efficacy in more than 50% of patients[1]. Therefore, it's heartening that we're getting more treatment options for IBS-C.

Tenapanor (IBSRELA) is the first sodium/hydrogen exchanger 3 (NHE3) inhibitor approved for use. NHE3 is expressed on the surface of the intestine, and tenapanor inhibits dietary sodium absorption by inhibiting NHE3[2]. Animal studies demonstrate that it also decreases intestinal permeability and visceral

hypersensitivity, although the mechanism for these actions is unclear since the pharmacologic action primarily blocks sodium absorption[2].

Key Study Findings

Tenapanor is clearly superior to placebo for improvement in abdominal discomfort, stool frequency and stool consistency.

Based on the FDA-required, ≥ 6/12 week combined response endpoint, tenapanor-treated patients were more likely to improve compared to placebo-treated patients: 36.5% vs 23.7% (aRR = 1.55, 95% CI: 1.20-1.99, $P < 0.0001$). Tenapanor-treated patients were also more likely to be 9/12 week responders: 18.4% vs 5.3% (aRR = 3.47, 95% CI: 2.03-5.94, $P < 0.0001$).

Some practitioners might be disappointed that only 36.5% of patients were "responders," but the complicated patient-reported outcomes required by the FDA are a high threshold for "success" and don't necessarily translate well to clinical care. It's notable that tenapanor-treated patients improved from mean of 0.1 CSBMs/week to more than 3 CSBMs/week, which was consistent through 26 weeks as well as achieving approximately 50% reduction in abdominal pain from baseline (**Figure 2**).

Caution

With respect to study design, this is an excellent clinical trial that meets all FDA-requirements for a Phase III RCT. Based on baseline characteristics (e.g., average of 0.1 CSBMs/week), study patients had fairly severe IBS-C symptoms, which might impact generalizability of study results. Since tenapanor works at the surface of the colonic mucosa, it's considered "minimally absorbed." This is consistent with finding no drug-drug interactions and no difference in adverse events between tenapanor- and placebo-treated patients with the exception of diarrhea.[2] As seen with most effective treatments for IBS-C, a minority of patients will experience diarrhea. Diarrhea was more commonly reported by tenapanor-treated patients vs placebo-treated patients (16.0% vs 3.7%), although discontinuation of study medication due to diarrhea only occurred in 6.5% of tenapanor-treated patients.

My Practice

Per the ACG Guideline on Management of IBS[1], guanylate cyclase-C agonists (i.e., linaclotide and plecanatide) are the only treatments that receive a strong recommendation based on high quality RCT evidence and they are the cornerstone of my treatment for IBS-C. Although I recognize that many practitioners may prefer to start IBS-C treatment with an osmotic laxative, it's worth remembering that the ACG Guideline suggests against using polyethylene-glycol products (e.g., MiraLax) to relieve global IBS symptoms in IBS-C since RCTs report no significant differences versus placebo for improvement in abdominal discomfort symptoms. Regardless, when patients are referred to me, they have invariably already tried osmotic laxatives, and most patients will have tried and failed these over-the-counter medications prior to seeing a gastroenterologist for IBS-C[1]. For patients who don't get adequate relief with linaclotide or plecanatide, I'll try tenapanor. Since tenapanor has a unique mechanism of action, I won't wait for patients to fail trials of linaclotide AND plecanatide. I'll simply switch to tenapanor after a patient fails their initial course of a guanylate cyclase-C agonist.

Consistent with the study findings, I'll emphasize to patients that it may take 8-12 weeks to achieve optimal decrease in abdominal discomfort symptoms and encourage patients to continue treatment even if there is only mild improvement in the first 1-2 weeks. I'll also proactively educate my patients that loose stools may occur in the first week of treatment, since this is when tenapanor-associated diarrhea is most likely to occur.

Since I treat more severe IBS-C patients, I frequently combine therapies. I doubt that I'd combine tenapanor with a guanylate cyclase-C agonist, but I will combine it with peppermint oil capsules as an on-demand or daily anti-spasmodic treatment or a neuromodulator, such as duloxetine (Cymbalta) at 30-60mg daily, and/or referral to our dietitician for instruction in low-FODMAP diets.

For Future Research

Comparative statements about the efficacy of tenapanor (IBSRELA) compared to other IBS-C treatments can't be made in the absence of head-

to-head trials. It would be optimal, albeit unlikely, to see these types of trials in the future. Also, RCT data about the efficacy of combination therapy (e.g., tenapanor plus neuromodulator) would be helpful. Based on my clinical experience, many patients will experiment by only using tenapanor 50 mg daily or even as a prn medication. Real-world data about this would be instructive.

Conflict of Interest

Dr. Schoenfeld reports that he sits on advisory boards and speakers bureaus, and is a consultant for Ironwood Pharmaceuticals, AbbVie Pharmaceuticals, and Salix Pharmaceuticals. He also serves as an advisory board member for Takeda Pharmaceuticals, Ardelyx Pharmaceuticals, and Phathom Pharmaceuticals.

REFERENCES

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