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A SPECIAL MEETING REVIEW EDITION

Highlights in IBS-C From Digestive Disease Week 2025

A Review of Selected Presentations From DDW 2025

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Special Reporting on:

- Safety and Tolerability of Tenapanor in Pediatric Patients With IBS-C: An Analysis of Blinded Safety Data From a Phase 3 Study and Its Open-Label Extension
- Efficacy and Safety of Linaclotide in Treating Pediatric Patients Aged 7-17 Years With IBS-C: Results From a Phase 3 Study
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Safety and Tolerability of Tenapanor in Pediatric Patients With IBS-C: An Analysis of Blinded Safety Data From a Phase 3 Study and Its Open-Label Extension

Tenapanor, a first-in-class retainagogue, is an inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3).[1] It was evaluated in 2 placebo-controlled, randomized, phase 3 studies conducted in adult patients with irritable bowel syndrome with constipation (IBS-C): T3MPO-1 (12-week trial) and T3MPO-2 (26-week trial).[2,3] The primary endpoint for both trials was the US Food and Drug Administration (FDA) combined endpoint for IBS-C, defined as an improvement of at least 30% from baseline in average daily worst abdominal pain score and an increase of at least 1 complete spontaneous bowel movement (CSBM) from baseline, both in the same week for 6 or more out of 12 weeks. This endpoint was significantly improved in both trials with tenapanor: 27.0% vs 18.7%, Cochran-Mantel-Haenszel [CMH] P=.020 for T3MPO-1; 36.5% vs 23.7%, CMH P<.001 for T3MPO-2. These T3MPO studies led to the FDA approval of tenapanor in adult patients with IBS-C.[4]

The efficacy and safety of tenapanor in pediatric patients with IBS-C remains to be established. R-ALLY, an ongoing randomized, double-blind, placebo-controlled, phase 3 study, aimed to evaluate the efficacy, safety, and tolerability of tenapanor specifically in pediatric patients from 12 to less than 18 years old. After completing the 12-week randomized treatment period, patients may be eligible for enrollment into a 40-week open-label safety extension study.

At DDW 2025, Wallach and colleagues presented preliminary blinded safety data from an interim analysis of the R-ALLY study and its open-label extension study (Table 1).[5] During the 12-week randomized treatment period, patients were randomized to receive twice-daily tenapanor 25 mg or 50 mg, or matched placebo. After completion of the 12-week treatment, patients could enter the open-label extension at the same dosage, which could be titrated to 25 mg or 50 mg twice daily. The safety follow-up included an on-site safety assessment every 2 to 4 weeks during the randomized treatment period, then every 6 weeks during the open-label safety extension. All enrolled patients met the Rome IV criteria for child and adolescent diagnosis of IBS-C.[6]

An interim analysis of the R-ALLY 12-week randomized treatment period was reported from a total of 77 randomized patients. Of these, 58 patients completed the randomized treatment period (mean age at screening: 14.2 years [SD, 1.71]; 62.3% female; 48.1% classified as not Hispanic or Latino). At the time of randomization, patients had a median duration of IBS-C of 2.9 years (range, 0.05-17.3 years).

During the R-ALLY 12-week randomized treatment period, the reported blinded safety data included 29.9% of patients experiencing a treatment-emergent adverse event (TEAE). No serious TEAEs were reported, and 3.9% were considered severe TEAEs. A drug-related TEAE was reported in 14.3% of patients. One severe drug-related TEAE, severe diarrhea, was associated with the only study drug discontinuation in the 12-week period. The most common TEAEs were diarrhea or loose stool (12 patients; 15.6%); cold (4 patients; 5.2%); nausea (2 patients; 2.6%); and worsening in IBS-C symptoms (2 patients; 2.6%). The remaining TEAEs were all reported in 1 patient (1.3%): abdominal pain, anal irritation, anorexia, bacterial vaginosis, chest pain, elevated protein, gastroenteritis, headache, runny nose, urinary tract infection, and vomiting.

Of the 58 patients who completed the R-ALLY trial, 56 patients entered the 40-week open-label extension. During this period, a similar rate of TEAEs were reported (28.6%). No serious TEAEs were reported, and 1 severe TEAE occurred. Three patients (5.4%) experienced a drug-related TEAE, but none were serious. A single patient experienced a TEAE that led to drug discontinuation. The most common TEAEs reported were diarrhea or

Table 1. TEAEs Reported With Tenapanor in Pediatric Patients With IBS-C

TEAE category, n (%)	12-week RTP in phase 3 R-ALLY study (n=77 [all groups combined])	Optional 40-week OLE (n=56)
TEAE	23 (29.9)	16 (28.6)
Serious TEAE	0	0
Severe TEAE	3 (3.9)	1 (1.8)
Drug-related TEAE	11 (14.3)	3 (5.4)
Severe drug-related TEAE	1[a] (1.3)	0
TEAE leading to study drug discontinuation	1[a] (1.3)	1 (1.8)

IBS-C, irritable bowel syndrome with constipation; OLE, open-label extension; RTP, randomized treatment period; TEAE, treatment-emergent adverse event.

[a]From the same patient, who reported a TEAE of severe diarrhea that led to study drug discontinuation.

Adapted from Wallach T et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa1643.[5]

loose stool (4 patients; 7.1%), influenza (4 patients; 7.1%), and headache (2 patients; 3.6%).

The study investigators concluded that the blinded safety results reported with tenapanor thus far in this pediatric patient population were consistent with the known safety profile in adult patients. As was observed in clinical studies in adults, diarrhea was the only adverse event considered to be related to the study drug.

Tenapanor was approved by the FDA for the treatment of IBS-C in adults in 2019 and was made available in the United States in 2022. Tenapanor has a unique mechanism of action: by inhibiting NHE3, it improves stool form, stool frequency, and abdominal pain in patients with IBS-C. The safety and efficacy of tenapanor in pediatric patients is unknown, although IBS affects approximately 6% to 14% of children. Data from the ongoing R-ALLY study, a double-blind, placebo-controlled study comparing 2 dosages of tenapanor (25 mg twice daily and 50 mg twice daily) to placebo, found that tenapanor was very safe in this age group (12-18 years), with no serious AEs. Only 1 severe drug-related TEAE was reported (diarrhea), which led to drug discontinuation. These reassuring results are important, as this medication will likely become an FDA-approved treatment option for adolescent patients with IBS-C.

—Brian E. Lacy, MD, PhD

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Efficacy and Safety of Linaclotide in Treating Pediatric Patients Aged 7-17 Years With IBS-C: Results From a Phase 3 Study

Two secretagogues, linaclotide and plecanatide, are used in the treatment of IBS-C. Both are peptides that act as agonists to the guanylate cyclase-C (GC-C) receptor.[1] Linaclotide was compared with placebo in 2 phase 3 trials, both of which included the FDA combined endpoint for IBS-C response as the primary endpoint.[2,3] This endpoint was significantly improved in both trials with linaclotide: 33.7% vs 13.9%, $P<.0001$ in the 26-week study; 33.6% vs 21.0%, $P<.0001$ in the 12-week study. These studies resulted in the FDA approval of linaclotide for the treatment of IBS-C in adults.[4] Additionally, linaclotide is indicated for the treatment of chronic idiopathic constipation (CIC) in adults and functional constipation in pediatric patients (6 to 17 years).

Hyams and colleagues reported the results from a multicenter, randomized, double-blind, parallel-group phase 3 trial that evaluated the use of linaclotide in pediatric patients with IBS-C (Table 2).[5] Patients were 7 to 17 years of age, weighed 18 kg or more, and met the Rome III IBS-C criteria for children and adolescents. During the 14 days prior to randomization, patients were required to have had an average daytime abdominal pain score of 1 or greater and fewer than 3 spontaneous bowel movements (SBMs) per week on average.

Patients were stratified by age group (7 to 11 years vs 12 to 17 years) and randomized to 2 arms, each of which received once-daily linaclotide (145 µg or 290 µg) for a 12-week period. All patients were treated with active study drug; therefore, the study results were compared with a placebo response extrapolated from the adult

studies of linaclotide. A prespecified 18% statistical superiority threshold (95% CI upper bound of the 16% placebo responder rate) was estimated based on a meta-analysis of 3 linaclotide studies conducted in adult patients. A total of 108 patients were randomized: 55 patients to the 145 µg arm and 53 patients to the 290 µg arm.

Patient demographics and baseline characteristics were balanced across the 2 linaclotide arms. The mean age was 12.7 years and 12.6 years; patients aged 7 to 11 years comprised 41.5% and 38.3% of the study population; and patients aged 12 to 17 years comprised 58.5% and 61.7% of the study population in the 145 µg and 290 µg arms, respectively. Females comprised 56.6% and 66.0% of each linaclotide arm, respectively. Across both arms, most patients were White (70%) or Black or African American (24%). At baseline in the linaclotide 145 µg and 290 µg arms, multiple disease characteristics were similar, including the SBM frequency (1.3 and 1.3 SBMs per week, respectively); CSBM frequency (0.5 and 0.4); abdominal pain score (1.9 and 1.9); and stool consistency score (2.5 and 2.8).

Abdominal pain was assessed by an abdominal pain (daytime and nighttime) score of 0 to 4, with 0 indicating no abdominal pain and 4 indicating a lot of abdominal pain. Stool consistency was scored using the 7-point ordinal pediatric Bristol Stool Form Scale score.[10] The primary efficacy endpoint was the abdominal pain and SBM (APS)+2 responder rate, which was defined as the proportion of patients who, for at least 6 out of the 12 treatment weeks, achieved both 30% or greater reduction in the mean abdominal pain score and an increase of 2 or more SBMs per week from baseline.

The primary endpoint, APS+2 rate, was 22.6% in the linaclotide 145 µg arm and 23.4% in the linaclotide 290 µg arm. These exceeded the adult placebo responder rate of 16% but not the superiority threshold of 18%.

More than one-third of patients were considered nonresponders owing to incomplete twice-daily eDiary entries. The mean compliance for 4 or more twice-daily eDiary entries per week during the 12-week treatment period was 64.1% (linaclotide 145 µg) and 63.0% (linaclotide 290 µg). A prespecified sensitivity analysis was performed to evaluate the impact of missed eDiary entries on the primary efficacy endpoint. To do this, a missing-at-random assumption was used to impute missing data. The results of this prespecified sensitivity analysis found that, when accounting for the missing eDiary entries, 34.1% and 38.9% of patients in the 145 µg and 290 µg arms, respectively, achieved the APS+2 rate. Statistical superiority was met in this sensitivity analysis. The 95% CI lower bound was greater than 18%, confirming statistical superiority (20.8% with linaclotide 145 µg and 23.8% with linaclotide 290 µg).

In addition, 2 post hoc analyses were performed to optimize the use of all available eDiary data collected. The first post hoc analysis included patients with at least 8 eDiary entries (either morning or evening) in the study week. In this post hoc analysis, 28.3% and 29.8% of patients in the 145 µg and 290 µg arms, respectively, achieved the primary endpoint. The 95% CI lower bound was 18.5% with linaclotide 145 µg and 19.2% with linaclotide 290 µg.

The second post hoc analysis included patients with at least 4 daytime symptom entries (captured in evening eDiary entries) in the study week. In this second post hoc analysis, 30.2% and 31.9% of patients in the 145 µg and 290 µg arms, respectively, achieved the primary endpoint. The 95% CI lower bound was 20.0% with linaclotide 145 µg and 20.8% with linaclotide 290 µg.

Several secondary endpoints were also assessed. One was the SBM+2 responder rate, defined as an increase of at least 2 SBMs during the study week for at least 6 of the 12 treatment weeks. The SBM+2 rate was 30.2% of

Table 2. 6/12 Weeks APS+2 Responder Rate of Linaclotide in Pediatric Patients Aged 7-17 Years With IBS-C[a,b]

Analysis	6/12 Weeks APS+2 Responder Rate	
	Linaclotide 145 µg	Linaclotide 290 µg
Primary endpoint analysis[c]	22.6%	23.4%
Prespecified sensitivity analysis[d]	34.1%	38.9%
Post hoc analysis[d]		
At least 8 eDiary entries/week	28.3%	29.8%
At least 4 daytime symptom eDiary entries/week	30.2%	31.9%

APS, abdominal pain and spontaneous bowel movement; IBS-C, irritable bowel syndrome with constipation; mITT, modified intention-to-treat; SBM, spontaneous bowel movement.

[a]The mITT population: all randomized patients who received at least 1 dose of study intervention, excluding those who were noncompliant with the study protocol and/or had an electronic clinical outcome assessment issue related to the inclusion criteria.

[b]A 6/12 weeks APS+2 responder is defined as a patient who, for ≥6 weeks of the 12-week treatment period, has an increase of at least 2 SBMs and a decrease of ≥30% in the mean abdominal pain score (combination of daytime and nighttime) from baseline during the same week.

[c]Statistical significance for primary endpoint not met, as more than one-third of patients defaulted to nonresponders because of incomplete twice-daily eDiary entries. Mean compliance for ≥4 twice-daily eDiary entries per week during the 12-week treatment period was 64.1% (linaclotide 145 µg) and 63.0% (linaclotide 290 µg).

[d]Prespecified and post hoc analyses addressed missing eDiary entries.

Adapted from Hyams JS et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract 624.[5]

Medication trials can be tricky to design and perform in the pediatric population for a number of reasons, including that responses are often provided by parents and not patients, and the use of placebo has to be carefully justified. In the novel study by Hyams and colleagues, 2 separate dosages of linaclotide (145 µg and 290 µg) were investigated for the treatment of IBS-C symptoms in pediatric patients (age 7-17 years; Rome III criteria). No placebo group was included in the 12-week study to avoid the ethical concerns of giving a placebo to pediatric patients. Both dosages improved stool consistency and stool frequency compared with baseline, and abdominal pain improved in 43% to 49% of patients compared with baseline. These positive findings should pave the way for a larger, multicenter study using either placebo or polyethylene glycol as a comparator.

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patients treated with linaclotide 145 µg and 29.8% of patients treated with linaclotide 290 µg. Another secondary endpoint was the abdominal pain responder rate, which was defined as 30% or greater reduction in mean abdominal pain score from baseline at least 6 of the 12 weeks of treatment. A total of 49.1% and 42.6% of patients in the 145 µg and 290 µg arms, respectively, were considered abdominal pain responders.

Additional secondary endpoints measured between the linaclotide 145 µg and 290 µg arms were the change from baseline over the 12-week treatment period in SBM frequency rate (2.3 vs 2.7, respectively), stool consistency score (1.0 vs 1.4, respectively), and change in abdominal pain score (–0.8 in both arms).

All TEAEs reported were considered mild or moderate in severity, and no TEAEs led to treatment discontinuation. TEAEs were reported by 20.0% of patients treated with linaclotide 145 µg and 15.1% of patients treated with linaclotide 290 µg. Diarrhea was the most frequent TEAE, reported in 7.3% and 7.5% of each treatment arm, respectively.

Overall, the results prompted the study authors to conclude that, in pediatric patients with IBS-C aged 7 to 17 years, once-daily treatment with linaclotide 145 µg or 290 µg demonstrated improvement in IBS-C symptoms from baseline.

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Patient-Reported IBS-C Symptom Severity Correlates Positively With Financial Burden: Results From the IBS in America 2024 Real-World Survey

The IBS in America 2024 survey was a 15-minute online survey conducted between January 15, 2024, and April 14, 2024, which included US residents aged 18 years or older. This real-world survey showed that, in addition to constipation (reported by 94% of respondents), many other symptoms were experienced by individuals with IBS-C.[1,2,3]

Shah and colleagues used data from the IBS in America 2024 survey to investigate the association between participant-reported IBS-C symptoms and financial toxicity, a description of the financial burden and distress that IBS-C can cause for patients and their family members.[4,5] All survey participants were US residents aged 18 years or older who met the following self-reported criteria: diagnosed with IBS-C; were currently seeing a health care provider to treat IBS-C; and had used either over-the-counter or prescription medication to treat IBS-C.

A total of 284 survey respondents were included in this analysis, with a

Table 3. Health-Related Economic Burden Reported in IBS in America 2024 Real-World Survey

FACIT-COST item	Respondents' answers of "very much/quite a bit" to FACIT-COST items		
	Total	Age <65 years (n=213)	Age ≥65 years (n=71)
I feel in control of my financial situation	28.5%	24.4%	40.8%
My out-of-pocket medical expenses are more than I thought they would be	29.2%	30.5%	25.4%
My illness has been a financial hardship to my family and me	29.9%	36.6%	9.9%
I worry about the financial problems I will have in the future as a result of my illness or treatment	39.1%	46.5%	16.9%
I am frustrated that I cannot work or contribute as much as I usually do	44.4%	49.3%	29.6%

FACIT-COST, Functional Assessment of Chronic Illness Therapy Comprehensive Score for Financial Toxicity; IBS, irritable bowel syndrome.
Adapted from Shah E et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Mo1257.[4]

mean age of 51.4 years and identifying as primarily female (92%) and White (87%). About one-third of respondents had received their IBS-C diagnosis within the previous 5 years; another 36% were diagnosed between 5 and 15 years earlier; and 31% were diagnosed 15 years previously or longer. IBS episodes occurred on a daily (36%), weekly (44%), or monthly (14%) frequency over the previous year; 6% of respondents reported IBS episodes every few months or less often.

Financial toxicity was measured using selected items from the Functional Assessment of Chronic Illness Therapy Comprehensive Score for Financial Toxicity (FACIT-COST) scale (version 2).[6] Several FACIT-COST items related to health-related economic burden were evaluated (Table 3). Only 28.5% of respondents agreed either "very much" or "quite a bit" with the statement "I feel in control of my financial situation." This response varied significantly by age, as significantly fewer respondents younger than 65 years agreed with this statement compared with respondents 65 years or older (24.4% vs 40.8%; *P*<.01). Survey respondents agreed either "very much" or "quite a bit" with the following statements: "My out-of-pocket medical expenses are more than I thought they would be" (29.2%); "My illness has been a financial hardship to my family and me" (29.9%); "I worry about the financial problems I will have in the future as a result of my illness or after treatment" (39.1%); and "I am frustrated that I cannot work or contribute as much as I usually do" (44.4%).

Symptoms of IBS-C were assessed using 2 Patient-Reported Outcomes Measurement Information System (PROMIS) gastrointestinal (GI) symptom scales.[7,8] The PROMIS GI Belly Pain scale uses 5 items to assess the frequency, intensity, and quality of abdominal pain over the previous 7 days as well as bothersomeness and interference with daily activities. The PROMIS GI Constipation scale uses 9 items to assess constipation-related symptoms over the previous 7 days as well as bothersomeness. Both PROMIS GI scales use T-scores; a T-score of 50 represents the average US population, whereas a T-score of 60 and 40 represent 1 standard deviation worse and better, respectively. The mean T-score was 62.3 for the PROMIS GI Belly Pain scale and 60.8 for the PROMIS GI Constipation scale.

Pearson correlations showed that each FACIT-COST measure of financial toxicity positively correlated with the PROMIS GI Belly Pain T-score and the PROMIS GI Constipation T-score as well as the frequency of IBS-C episodes. Additionally, each FACIT-COST measure correlated negatively with the degree of IBS control. A multivariate analysis showed that the overall financial toxicity, assessed by considering the FACIT-COST measures together, was significantly related to constipation severity (*P*<.001), abdominal pain severity (*P*<.001), the degree of IBS control (*P*<.001), and frequency of IBS episodes (*P*<.05).

Survey respondents with higher PROMIS GI Constipation T-scores (≥60) showed greater financial burden across each FACIT-COST measure compared with respondents with lower T-scores (<60). For respondents with higher vs lower T-scores, respectively, 54.1% vs 32.3% agreed with the phrase "I am frustrated that I cannot work or contribute as much as I usually do" (*P*<.001). Similarly, a total of 52.2% vs 22.8%, respectively, agreed with the phrase "I worry about the financial problems I will have in the future as a result of my illness or treatment" (*P*<.001); 40.1% vs 17.3%, respectively, agreed with the phrase "My illness has been a financial hardship to my family and me" (*P*<.001); 37.6% vs 18.9%, respectively, agreed with the phrase "My out-of-pocket medical expenses are more than I thought they would be" (*P*<.001). Fewer respondents with a higher vs lower T-score, respectively, agreed with the phrase "I feel in control of my

Widely recognized to have a significant impact on quality of life, IBS also has a significant economic impact on patients and the health care system. The IBS in America 2024 survey study took a unique approach to the financial impact of IBS by using a validated financial questionnaire (FACIT-COST) to evaluate the relationship between symptom severity and financial distress. Patients with greater symptom severity also reported greater financial distress, including concerns about out-of-pocket medical expenses, their ability to work, and their financial future. These results highlight that an integrated approach to the treatment of patients with IBS-C should include an assessment of the economic impact of this common disorder.

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financial situation" (21.7% vs 37.0%; *P*<.005). Similar outcomes were also observed among survey respondents with higher PROMIS GI Belly Pain T-scores (≥60) compared with respondents with lower T-scores (<60).

The study authors concluded that IBS-C adversely impacted the lives of the survey respondents, particularly with regard to their finances. They concluded that these results supported an association between greater IBS-C symptom severity and a larger degree of financial hardship and distress, thus driving financial toxicity. The study authors noted that their analysis was limited by unvalidated assessments. They also noted that a healthy control group was not included for comparison.

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Neither Tenapanor Nor Its Major Metabolite Were Detected in the Breast Milk of Healthy Lactating Females After 4 Days of Dosing: A Phase 1, Open-Label, Pharmacokinetic Study

Tenapanor is minimally absorbed following repeated twice-daily administration.[1] Further, the primary metabolite of tenapanor, M1, is not pharmacologically active and is present at a maximum observed concentration of 15 ng/mL at steady state.[2] Brenner and colleagues provided a summary of a study conducted to determine the pharmacokinetics of tenapanor and M1 in breast milk (Table 4).[3]

This phase 1 study enrolled 7 adult females in good health with a body mass index (BMI) between 18.0 kg/m^2 and 35.0 kg/m^2 who had been breastfeeding or actively pumping for at least 4 weeks or longer prior to study entry. All study participants received open-label twice-daily tenapanor (50 mg) on days 1 through 3, then once on day 4. Breast milk was collected prior to the first tenapanor dose (hour 0), then at 1, 2, 4, 6, 8, and 24 hours after the last dose.

The mean age of participants was 30.0 years. A total of 5 participants were White; a sixth participant was American Indian or Alaskan Native; and the seventh participant reported multiple races. Among the 7 participants, the mean weight was 80.2 kg, the mean height was 161.8 cm, the mean BMI was 30.9 kg/m^2, and the mean gestational age at delivery was 39.0 weeks.

Table 4. Summary of Breast Milk Pharmacokinetic Parameters Through 24 Hours Post Dose and TEAEs With Tenapanor

	Tenapanor 50 mg bid (n=7)
Breast milk pharmacokinetic parameters, mean (SD)[a]	
C_{max}, ng/mL	0.000 (0.0000)
C_{trough}, ng/mL	0.000 (0.0000)
DID, µg/kg/d	0.000 (0.0000)
Maternal dose, µg/kg/d	1275 (211.37)
RID, %	0.000 (0.0000)
Summary of TEAEs, n (%)	
TEAE	3 (42.9)
Gastrointestinal disorders	3 (42.9)
SAR	3 (42.9)
Serious TEAE	0
TEAE leading to tenapanor discontinuation	0

bid, twice daily; C_{max}, maximum observed concentration; C_{trough}, lowest observed concentration during a dosing interval; d, day; DID, daily infant dose; RID, relative infant dose; SAR, suspected adverse reaction; TEAE, treatment-emergent adverse event.

[a]Pharmacokinetic parameters were calculated following the last dose on day 4. Participants received tenapanor 50 mg bid on day 1 through day 3 and once before breakfast on day 4.

Adapted from Brenner D et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa1673.[3]

Tenapanor, an NHE3 inhibitor, does not have an assigned FDA pregnancy category. As the drug is minimally absorbed after oral administration (<0.5 ng/mL), it is not thought to be associated with a significant risk in pregnant women or in women who breastfeed. The first-in-kind open-label pharmacokinetic study by Brenner and colleagues in 7 healthy lactating females demonstrated that twice-daily tenapanor 50 mg did not lead to any appreciable levels of tenapanor in breast milk. These results should reassure women with IBS-C who require tenapanor while breastfeeding.

—Brian E. Lacy, MD, PhD

At all timepoints, in all samples, the concentrations of both tenapanor and its metabolite M1 were below the limit of quantitation (<1.00 ng/mL). Because these results were not quantifiable, neither the area under the curve or time-related pharmacokinetic parameters could be calculated.

There were no unexpected TEAEs reported among the 7 participants included in this study. GI disorders were reported by 3 participants, including diarrhea (n=3), flatulence (n=2), and nausea (n=1). All of these were considered mild in severity.

The study authors concluded that, after receiving repeated oral administration of tenapanor 50 mg twice daily, neither tenapanor nor its primary metabolite M1 were present at detectable levels in the breast milk of healthy lactating females. The safety profile of tenapanor among these participants was similar to that seen in prior clinical studies of tenapanor in healthy volunteers. The investigators noted that, although safety data could be different between healthy individuals and patients with IBS-C, any difference was not likely to affect the outcome of lack of detectable tenapanor levels in human breast milk.

References

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3. Brenner D, Raju K, Kozuka K, et al. Neither tenapanor nor its major metabolite were detected in the breast milk of healthy lactating females after 4 days of dosing: a phase 1, open-label, pharmacokinetic study. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa1673.

Long-Term Safety of Linaclotide in Treating Pediatric Patients Aged 7-17 Years With IBS-C: Interim Results From a Phase 3 Study

Saps and colleagues reported data from an ongoing multicenter, long-term 52-week safety study of linaclotide in pediatric patients with IBS-C (Table 5).[1] To be eligible for enrollment, patients were aged 7 to 17 years, weighed 18 kg or more, and met the modified Rome III criteria for pediatric IBS-C. All patients had completed the treatment period in prior studies of linaclotide. Patients who had previously completed the phase 2 study went on to receive open-label linaclotide at a dosage of 290 µg once-daily in the long-term safety study; if they had received linaclotide at a dosage of 145 µg or less, or placebo, they had the option of receiving open-label linaclotide at a dosage of 145 µg in the long-term safety study. Patients who had previously completed the phase 3 study had the option to either remain on the same blinded dosage of linaclotide or receive open-label linaclotide at a dosage of 290 µg.

The median age in the overall population was 14.0 years (range, 7 to 17 years); 30.6% of patients were aged 7 to 11 years, and 69.4% were aged 12 to 17 years. Most patients were female (61.2%) and White (71.4%). At baseline, the mean weight of patients was 54.4 kg, the mean height was 155.9 cm, and the mean BMI was 21.9 kg/m^2.

At the time of data cutoff in August 2024, a total of 98 patients had received linaclotide at a dosage of either 145 µg (n=22) or 290 µg (n=76). Among the linaclotide 145 µg group, 2 patients discontinued prematurely, whereas 16 of the 76 patients treated with linaclotide 290 µg discontinued prematurely. All safety outcomes were assessed in the safety population, defined as patients who had received at least 1 dose of linaclotide as part of the long-term phase 3 study. The primary safety endpoint of this long-term phase 3 safety study was the incidence of TEAEs over the 52-week study.

Overall, TEAEs were reported in 34.7% of patients (13.6% treated with 145 µg linaclotide and 40.8% treated with 290 µg linaclotide). Treatment-

Table 5. Summary of TEAEs With Linaclotide in Pediatric Patients Aged 7-17 Years With IBS-C[a]

	Linaclotide 145 µg (n=22)	Linaclotide 290 µg (n=76)	All doses (N=98)
TEAE category, n (%)			
Any TEAE	3 (13.6)	31 (40.8)	34 (34.7)
Treatment-related TEAEs	0 (0)	10 (13.2)	10 (10.2)
Serious TEAEs	0 (0)	2 (2.6)[b]	2 (2.0)[b]
Dose reduction owing to TEAEs	0 (0)	6 (7.9)	6 (6.1)
Treatment discontinuation owing to TEAEs	0 (0)	0 (0)	0 (0)
AESIs	0 (0)	0 (0)	0 (0)
Deaths	0 (0)	0 (0)	0 (0)
Common TEAEs reported by at least 2 patients in either treatment group, n (%)			
Diarrhea	0 (0)	6 (7.9)	6 (6.1)
Influenza	0 (0)	4 (5.3)	4 (4.1)
Syncope[c]	1 (4.5)	2 (2.6)	3 (3.1)
Anal incontinence[c]	0 (0)	2 (2.6)	2 (2.0)
COVID-19	0 (0)	2 (2.6)	2 (2.0)
Ear infection	0 (0)	2 (2.6)	2 (2.0)
Fall[c]	0 (0)	2 (2.6)	2 (2.0)
Headache	0 (0)	2 (2.6)	2 (2.0)

AESI, adverse event of special interest; IBS-C, irritable bowel syndrome with constipation; TEAE, treatment-emergent adverse event.

[a]Safety population included enrolled patients who received at least 1 dose of study drug.

[b]Serious TEAEs were not considered related to study treatment.

[c]Event not related to diarrhea.

Adapted from Saps M et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa2099.[1]

related TEAEs were reported in 10.2% of patients (all were in the group treated with linaclotide 290 µg). Two serious TEAEs were reported (both in the linaclotide 290 µg group); these were not considered related to the study treatment. The first event was in a 10-year-old male patient who had adenoid, nasal turbinate, and tonsillar hypertrophy; the patient later experienced a postprocedural hemorrhage following surgery. The second event was in a 17-year-old female patient who had migraine and mental status changes. No patients discontinued treatment owing to a TEAE.

The most common TEAE, defined as those reported by at least 2 patients in either linaclotide group, was diarrhea (6 cases, or 6.1%, all in the linaclotide 290 µg group). The next most frequent TEAEs were influenza (4 cases, or 4.1%, all in the linaclotide 290 µg group); syncope (3 cases, or 3.1%, 2 of whom were in the linaclotide 290 µg group and 1 in the linaclotide 145 µg group); anal incontinence, COVID-19, ear infection, fall, or headache (all occurred in 2 cases, or 2.0%, all in the linaclotide 290 µg group). Potentially clinically significant laboratory results and clinically significant vital signs were infrequent in both linaclotide groups, with no unexpected changes of clinical relevance reported.

The study authors concluded that linaclotide treatment was well tolerated in this pediatric population aged 7 to 17 years with IBS-C. The overall safety profile in this pediatric population was consistent with that established in prior linaclotide pediatric and adult studies, and no new safety concerns were identified. The authors noted that this was a multicenter study across 4 countries (including the United States), which allowed for observation and collection of data from patients representing a wider pediatric population with IBS-C. The authors further noted that the long-term treatment period in this study (52 weeks) allowed for an assessment of a relatively long-term exposure to linaclotide. The authors reported the lack of randomization between the 2 linaclotide dosages as a limitation, as was the lack of a placebo comparator.

Linaclotide, a GC-C agonist, was approved for the treatment of functional constipation in children aged 6 to 17 years in 2023. IBS affects approximately 6% to 14% of children, with IBS-C being the most common subtype. Saps and colleagues reported on the ongoing phase 3, 52-week study evaluating the safety and efficacy of linaclotide in children aged 7 to 17 years, with an emphasis on safety in this abstract. Only 10 of 98 patients (median age, 14 years) had treatment-related AEs, which is reassuring, and only 6.1% reported diarrhea. As no medication is approved for the treatment of children with IBS-C, these results are encouraging and may help lead to FDA approval in the future.

—Brian E. Lacy, MD, PhD

Reference

1. Saps M, Nurko S, Khlevner J, et al. Long-term safety of linaclotide in treating pediatric patients aged 7-17 years with IBS-C: interim results from a phase 3 study. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa2099.

The Clinical Efficacy of Linaclotide and Plecanatide in IBS-C and CIC: A Potential Benefit to Switching GC-C Agonists?

Like linaclotide, plecanatide is a GC-C agonist that functions as a secretagogue. Plecanatide was evaluated against placebo in 2 identically designed phase 3 clinical trials, both of which used the same FDA combined primary endpoint of overall response.[1] In Study 1, plecanatide treatment resulted in a significantly higher percentage of patients who achieved the primary endpoint vs placebo (30.2% [3 mg arm] and 29.5% [6 mg arm] vs 17.8%; $P<.001$). A similar outcome was achieved in Study 2 (21.5% [3 mg arm] and 24.0% [6 mg arm] vs 14.2%; $P=.009$). Plecanatide is FDA-approved for the treatment of IBS-C in adults; it is also indicated for the treatment of CIC in adults.[2]

Desai and colleagues investigated whether patients with either IBS-C or CIC who failed to respond to an initial GC-C agonist (either linaclotide or plecanatide) could derive benefit from switching to the other agent within the same class (Figure 1).[3] A total of 56 patients were identified from a retrospective chart review (29 patients with IBS-C and 27 patients with CIC) between 2018 and 2024.

The mean patient age was 57.9 ± 15.0 years, just over one-half (55.4%) were female, and most were White (48.2%). The mean BMI at baseline was 28.5 kg/m^2, and 53.6% had a mood disorder at baseline, with

41.1% reporting neuromodulator or antidepressant use. Most patients had initially been treated with plecanatide (n=42; 75.0%); the other 14 patients (25.0%) were initially treated with linaclotide. Both symptom severity at baseline as well as response to treatment was scored on the global symptom Likert scale, which has a 4-point (0-3) range.

At baseline, the median global symptom severity was 2.0 (moderately bothersome). This improved to 1.0 (slight symptom improvement) after initial treatment with the GC-C agent for a median of 170 days (range, 9 to 2165 days). There was a greater initial response observed with linaclotide compared with plecanatide (1.36 ± 0.93 vs 0.64 ± 0.49, respectively; *P*=.002). This higher initial response was observed regardless of diagnosis (*P*=.50) or baseline symptom severity (*P*=.69).

Switching to the alternative GC-C agent (patients initially treated with linaclotide were switched to plecanatide, and vice versa) was associated with a median response of 2.0 (moderate improvement). No difference was observed between the 2 agents (*P*=.17). The response observed with GC-C agent switching was not associated with diagnosis (*P*=.99), baseline symptom severity (*P*=.09), mood comorbidity (*P*=.16), or neuromodulator use (*P*=.85). A high percentage of patients (60.8%) experienced at least a moderate level of symptom improvement after switching agents, without any significant difference attributable to either GC-C agent (*P*=.54).

References

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2. Trulance (plecanatide) [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; March 2024.
3. Desai N, Singerman C, Elwing JE, Sayuk GS. The clinical efficacy of linaclotide and plecanatide in IBS-C and CIC: a potential benefit to switching GC-C agonists? Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa1650.

Despite a strong body of evidence documenting that secretagogues (the GC-C agonists linaclotide and plecanatide) are effective at treating symptoms of IBS-C and chronic constipation, there are no data to help guide clinicians in the treatment of patients who may not respond to the initial secretagogue of choice. This is important because, although these 2 agents are similar, nuances in their mechanisms of action and treatment effects have been identified. The retrospective review by Desai and colleagues is clinically relevant because it demonstrates that, if an incomplete response occurs with the use of one secretagogue, then switching to the other secretagogue is a reasonable treatment option with a good chance of success.

—Brian E. Lacy, MD, PhD

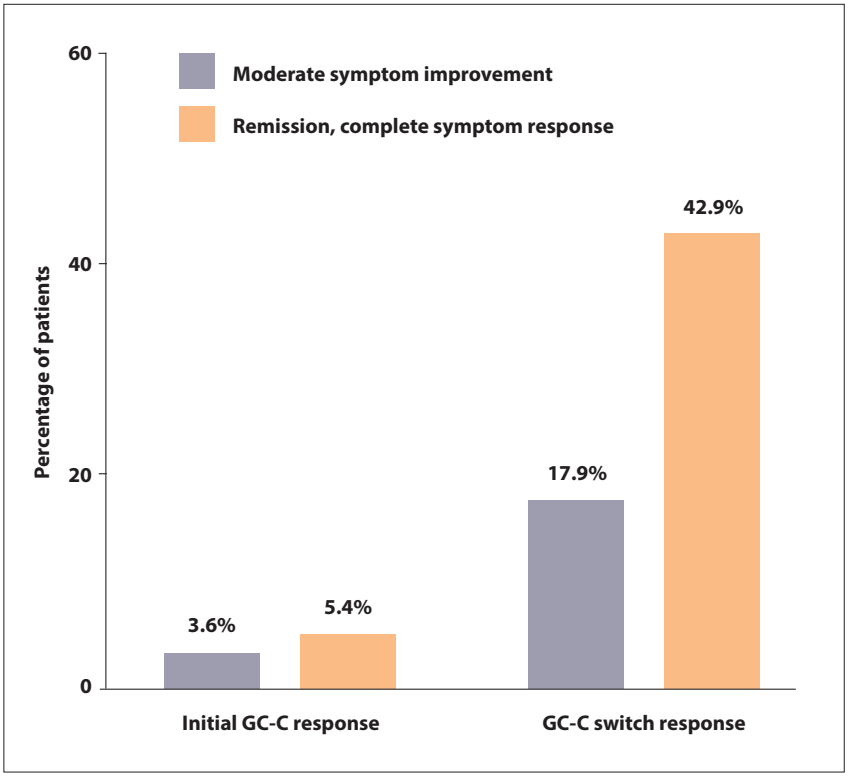

Figure 1. Percentage of patients achieving at least moderate symptom improvement (Likert = 2) or symptom remission (Likert = 3) from initial treatment and following GC-C switch.

GC-C, guanylate cyclase-C.

Adapted from Desai N et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa1650.[3]

IBS-C Patient Experiences With Pharmacologic Therapies: Qualitative Analysis of Online Posts From X (Twitter) and E-health Forums

Khalil and colleagues reported the results of a study aimed to use social netnography to analyze online interactions and behaviors collected from social media and e-health forums.[1] This social network analysis focused on patients who self-reported an IBS-C diagnosis and treatment with an FDA-approved therapy.

This analysis surveyed publicly available posts collected from X (formerly known as Twitter) as well as IBS-specific subforums on sites such as Reddit, WebMD, and ibspatient.org. Posts were filtered using the name of FDA-approved IBS-C medications (linaclotide, lubiprostone, plecanatide, tegaserod, and tenapanor). Posts from January 2009 to April 2024 were included in this analysis, yielding a total of 8830 posts. An open coding technique was used for qualitative analysis of the identified posts, which reached saturation after analyzing 600 random posts.

The thematic network that emerged from this analysis is shown in Figure 2. Four main themes were identified: perceived medication efficacy, burden related to taking IBS-C medications, intentional nonadherence, and barriers to adherence. Regarding the theme of perceived medication efficacy, patients reported mixed experiences, with some individuals believing that the medications were effective whereas others considered them ineffective or only partially effective. The biophysical burden of IBS-C medications was also wide-ranging and included nausea, frustration, and social anxiety related to potential diarrheal side effects when away from home. This burden may relate to the nonadherence noted. Additional barriers to adherence were identified and included adverse effects, personal beliefs, and insurance coverage. These barriers led many patients to discontinue medications, seek alternative treatments, or adjust their medication dosages.

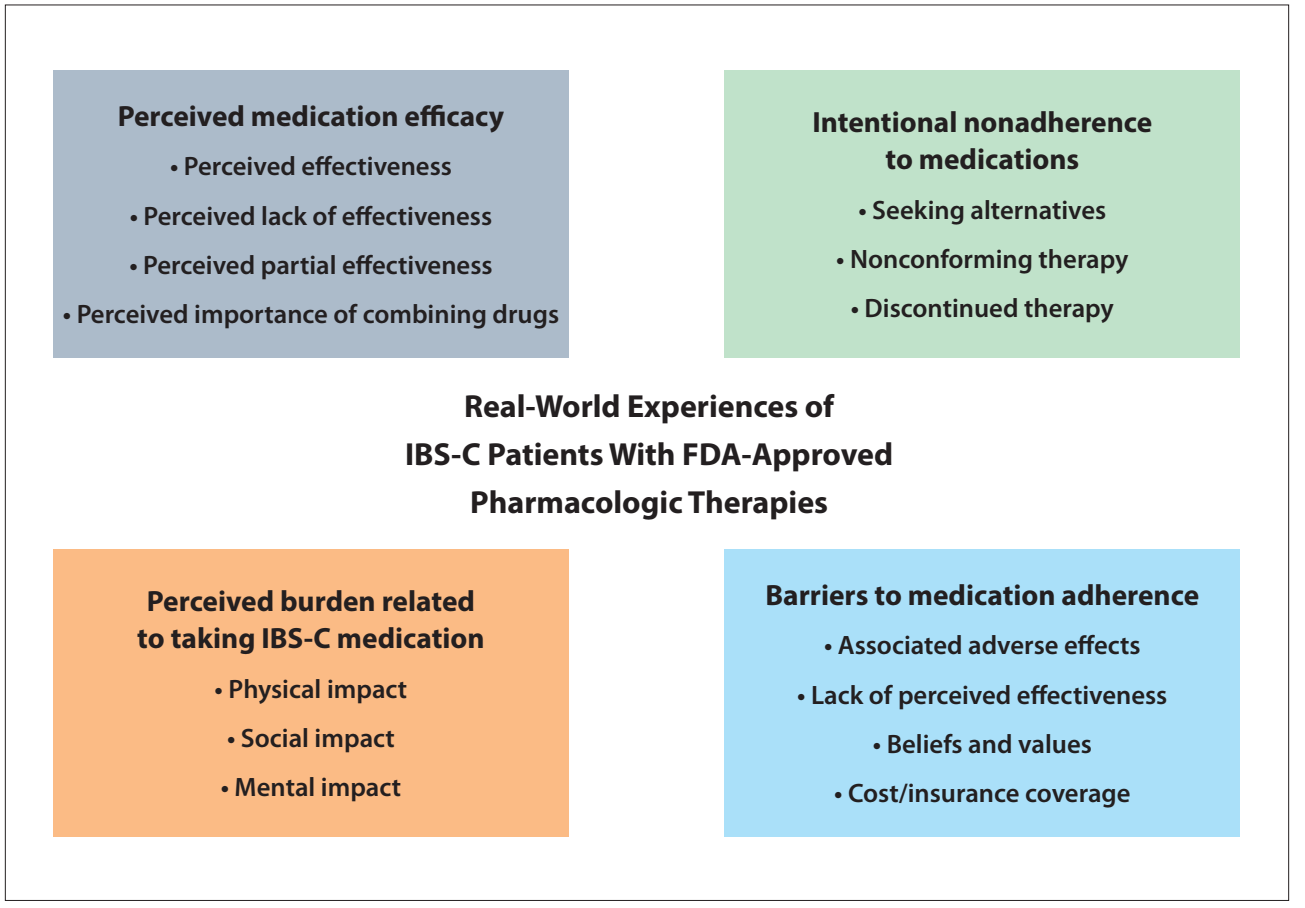

Figure 2. Diverse real-world experiences of IBS-C patients with FDA-approved pharmacologic therapies.

FDA, US Food and Drug Administration; IBS-C, irritable bowel syndrome with constipation.

Adapted from Khalil C et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa1671.[1]

Analysis of online posts and social media is an emerging field of scientific inquiry. One concept supporting netnography (the research of online data) qualitative analysis is that individuals may post views and opinions that they might not report to their health care provider. The caveat, of course, is that social media posts represent individual views that may not accurately reflect the population at risk; additionally, bias and confounders may be present, including the potential for the introduction of fake news or multiple postings of the same data. The analysis by Khalil and colleagues of over 7000 posts (with data saturation achieved at 600 posts) confirmed the high biopsychosocial burden of IBS-C and reinforced the need for health care providers to involve patients in shared decision-making, in an attempt to address medication efficacy, side effects, and insurance issues.

—Brian E. Lacy, MD, PhD

The study authors concluded that there is a high degree of variability in real-world experiences of patients treated with FDA-approved therapies for IBS-C. They noted that these findings support the need for shared decision-making in the management of patients with IBS-C, so that patient perceptions of efficacy, side effects, cost, and personal beliefs can be incorporated and addressed. This will allow patients and their clinicians to identify the best treatment option for each individual, potentially improving adherence and outcomes.

Reference

1. Khalil C, Suchak K, Krut Z, et al. IBS-C patient experiences with pharmacologic therapies: qualitative analysis of online posts from X (Twitter) and e-health forums. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Sa1671.

IBSRELA (tenapanor) tablets, for oral use

Brief Summary of Full Prescribing Information

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- **IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration [*see Contraindications (4), Use in Specific Populations (8.4)*].**
- **Avoid use of IBSRELA in patients 6 years to less than 12 years of age [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].**
- **The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age [*see Use in Specific Populations (8.4)*].**

1 INDICATIONS AND USAGE

IBSRELA is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

4 CONTRAINDICATIONS

IBSRELA is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].
- Patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients

IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).

Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.4)*].

5.2 Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients [*see Adverse Reactions (6.1)*]. If severe diarrhea occurs, suspend dosing and rehydrate patient.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 1203 adult patients with IBS-C in two randomized, double-blind, placebo-controlled clinical trials (Trial 1 and Trial 2). Patients were randomized to receive placebo or IBSRELA 50 mg twice daily for up to 52 weeks. Demographic characteristics were comparable between treatment groups in the two trials [*see Clinical Studies (14)*].

Most Common Adverse Reactions

The most common adverse reactions reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo during the 26-week double-blind placebo-controlled treatment period of Trial 1 are shown in Table 1.

Table 1: Most Common Adverse Reactions* in Patients With IBS-C in Trial 1 (26 Weeks)

Adverse Reactions	IBSRELA N=293 %	Placebo N=300 %
Diarrhea	16	4
Abdominal Distension	3	<1
Flatulence	3	1
Dizziness	2	<1

*Reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo.

The adverse reaction profile was similar during the 12-week double-blind placebo-controlled treatment period of Trial 2 (610 patients: 309 IBSRELA-treated and 301 placebo-treated) with diarrhea (15% with IBSRELA vs 2% with placebo) and abdominal distension (2% with IBSRELA vs 0% with placebo) as the most common adverse reactions.

Adverse Reaction of Special Interest – Severe Diarrhea

Severe diarrhea was reported in 2.5% of IBSRELA-treated patients compared to 0.2% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 [*see Warnings and Precautions (5.2)*].

Patients with Renal Impairment

In Trials 1 and 2, there were 368 patients (31%) with baseline renal impairment (defined as eGFR less than 90 mL/min/1.73m^2). In patients with renal impairment, diarrhea, including severe diarrhea, was reported in 20% (39/194) of IBSRELA-treated patients and 0.6% (1/174) of placebo-treated patients. In patients with normal renal function at baseline, diarrhea, including severe diarrhea, was reported in 13% (53/407) of IBSRELA-treated patients and 3.5% (15/426) of placebo-treated patients. No other differences in the safety profile were reported in the renally impaired subgroup.

The incidence of diarrhea and severe diarrhea in IBSRELA-treated patients did not correspond to the severity of renal impairment.

Adverse Reactions Leading to Discontinuation

Discontinuations due to adverse reactions occurred in 7.6% of IBSRELA-treated patients and 0.8% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2. The most common adverse reaction leading to discontinuation was diarrhea: 6.5% of IBSRELA-treated patients compared to 0.7% of placebo-treated patients.

Less Common Adverse Reactions

Adverse reactions reported in less than 2% of IBSRELA-treated patients and at an incidence greater than placebo during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 were: rectal bleeding and abnormal gastrointestinal sounds.

Hyperkalemia

In a trial of another patient population with chronic kidney disease (defined by eGFR from 25 to 70 mL/min/1.73m^2) and Type 2 diabetes mellitus, three serious adverse reactions of hyperkalemia resulting in hospitalization were reported in 3 patients (2 IBSRELA-treated patients and 1 placebo-treated patient).

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 [*see Clinical Pharmacology (12.3)*]. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with IBSRELA. Monitor for signs related to loss of efficacy and adjust the dosage of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with tenapanor (30 mg twice daily for five days, a dosage 0.6 times the recommended dosage), the peak exposure (C_{max}) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by approximately 50% to 65% compared to when enalapril was administered alone [*see Clinical Pharmacology (12.3)*].

Monitor blood pressure and increase the dosage of enalapril, if needed, when IBSRELA is coadministered with enalapril.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. Therefore, maternal use is not expected to result in fetal exposure to the drug. The available data on IBSRELA exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.1 times the maximum recommended human dose and in rabbits at doses up to 8.8 times the maximum recommended human dose (based on body surface area).

Data

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.1 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 8.8 times the maximum recommended human dose, based on body surface area).

In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 9.7 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IBSRELA and any potential adverse effects on the breastfed infant from IBSRELA or from the underlying maternal condition.

8.4 Pediatric Use

IBSRELA is contraindicated in patients less than 6 years of age. Avoid IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.1)*].

The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week-old rats approximate human age equivalent of less than 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats [post-natal day (PND) 5] at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups [*see Contraindications (4), Warnings and Precautions (5.1)*].

8.5 Geriatric Use

Of the 1203 patients in placebo-controlled clinical trials of IBSRELA, 100 (8%) were 65 years of age and older. No overall differences in safety or effectiveness were observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Based on nonclinical data, overdose of IBSRELA may result in gastrointestinal adverse effects such as diarrhea as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged [*see Warnings and Precautions (5.1)*].

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Medication Guide).

Diarrhea

Instruct patients to stop IBSRELA and contact their healthcare provider if they experience severe diarrhea [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of IBSRELA in children, especially children less than 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to store IBSRELA securely and out of reach of children [*see Contraindications (4), Warnings and Precautions (5.1)*].

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FLIP THE SCRIPT ON IBS-C

In a survey of adults with IBS-C, only 25% were very satisfied with their prescription treatment.[1]*

Treatment for IBS-C is not one size fits all.[2] When your patients aren't getting adequate relief, try a therapy with a different mechanism of action,† in a different class.[3]

IBSRELA® (tenapanor) tablets

IBSRELA WORKS DIFFERENTLY TO IMPROVE THE CONSTIPATION AND ABDOMINAL PAIN OF IBS-C.

INDICATION

IBSRELA (tenapanor) is indicated for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in adults.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration. Avoid use of IBSRELA in patients 6 years to less than 12 years of age. The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age.

CONTRAINDICATIONS

- IBSRELA is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.
- IBSRELA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

WARNINGS AND PRECAUTIONS

Risk of Serious Dehydration in Pediatric Patients

- IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).
- Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age.

Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients. If severe diarrhea occurs, suspend dosing and rehydrate patient.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions in IBSRELA-treated patients (incidence ≥2% and greater than placebo) were: diarrhea (16% vs 4% placebo), abdominal distension (3% vs <1%), flatulence (3% vs 1%) and dizziness (2% vs <1%).

References: 1. Rangan V et al. *Gastroenterology.* 2020;158(3):786-788.e1. **2.** Saha L. *World J Gastroenterol.* 2014;20(22):6759-6773. **3.** IBSRELA [prescribing information]. Waltham, MA: Ardelyx, Inc.;2022.

*Based on data from a 2015 online survey of 1,667 patients with IBS-C, 311 of the 1,667 patients were prescription-treated and responded to a 5-point scale where 1 is very dissatisfied and 5 is very satisfied.[1]

†Mechanism of action=sodium/hydrogen exchanger isoform 3 (NHE3) inhibitor.

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IBSRELA® (tenapanor) tablets 50 mg BID

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