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Safety and Tolerability of Tenapanor in Pediatric Patients With Irritable Bowel Syndrome With Constipation: An Analysis of Blinded Safety Data From a Phase 3 Study and Its Open-Label Extension

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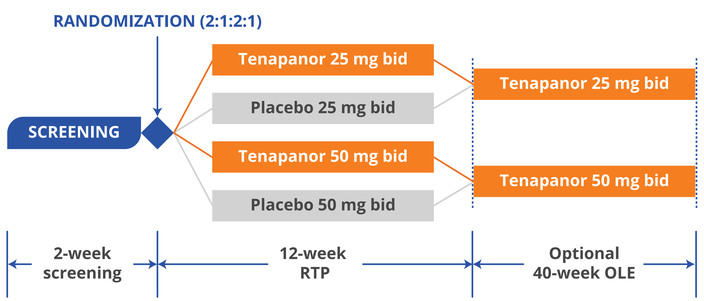
Introduction

- Irritable bowel syndrome (IBS) is a gastrointestinal disorder that affects approximately 5% of children in the United States, with IBS with constipation (IBS-C) being the most common subtype.[1,2]
- Tenapanor is a first-in-class, minimally absorbed inhibitor of intestinal sodium/hydrogen exchanger isoform 3 approved for the treatment of IBS-C in adults.[3]
- Tenapanor improves symptoms of IBS-C by increasing sodium and water retention in the gut, which facilitates softer stool consistency and faster transit. It also decreases intestinal permeability to macromolecules and reduces visceral hypersensitivity and abdominal pain in animal models.[3]
- In adult clinical trials, tenapanor demonstrated efficacy and was generally well tolerated, with diarrhea being the most commonly reported adverse event (AE).[3]
- The phase 3 R-ALLY (NCT05643534) study is ongoing and plans to enroll approximately 180 patients with the goal of evaluating the efficacy, safety, and tolerability of tenapanor in pediatric patients aged ≥12 and <18 years.[4]
- Patients who complete the 12-week R-ALLY randomized treatment period (RTP) may be able to enter a 40-week open-label safety extension (OLE) study (NCT05905926).[5]
- Here, we present preliminary, blinded, interim safety data from R-ALLY and its OLE.

Methods

- R-ALLY (TEN-01-304) is a randomized, double-blind, placebo-controlled study in patients (aged ≥12 to <18 years) meeting the Rome IV criteria for child/adolescent diagnosis of IBS-C (**Figure 1**).
  - During the 12-week RTP, patients are assessed on site every 2 or 4 weeks for safety.
- Patients who complete the 12-week RTP may enter a 40-week OLE study (TEN-01-306) (**Figure 1**).
  - Titrations are allowed between 25 mg bid and 50 mg bid during the OLE.
  - Patients are assessed on site approximately every 6 weeks for safety.

Figure 1: Study Design for Phase 3 R-ALLY and Optional 40-Week OLE Study



bid, twice daily; OLE, open-label extension; RTP, randomized treatment period.

Results

12-Week RTP

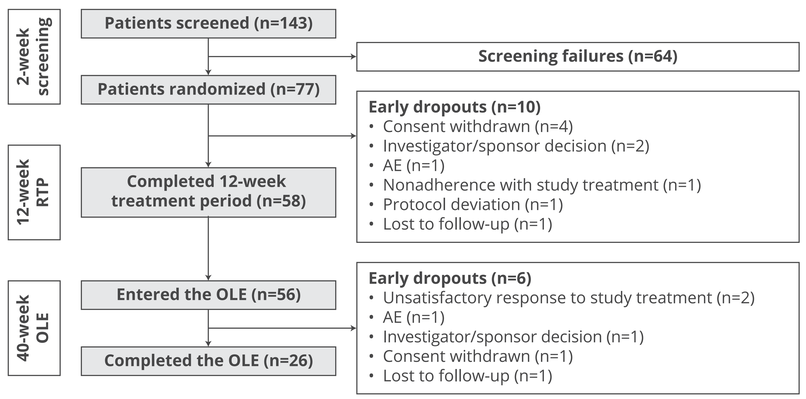
- **Table 1** summarizes the interim baseline demographics and treatment-emergent AEs (TEAEs) for the safety analysis set (SAS), which included 77 randomized and treated patients (**Figure 2**).
- All TEAEs were resolved or resolving and considered unrelated to study drug, except diarrhea.
  - One TEAE of severe diarrhea led to study drug discontinuation.

Table 1: R-ALLY Baseline Demographics and Blinded Data on TEAEs (Safety Analysis Set)

Baseline demographics (N=77)	
Age at informed consent, mean (SD), y	14.2 (1.71)
Female, n (%)	48 (62.3)
Race, n (%)	
White	54 (70.1)
Asian	11 (14.3)
Black or African American	9 (11.7)
Other	2 (2.6)
Multiple	1 (1.3)
Not Hispanic or Latino, n (%)	37 (48.1)
IBS-C duration at randomization, median (range), y	2.940 (0.05–17.26)
TEAEs (N=77) - all groups combined	
Patients with any..., n (%)	
TEAE	23 (29.9)
Serious TEAE	0
Severe TEAE	3 (3.9)
Drug-related TEAE	11 (14.3)
Severe, drug-related TEAE	1[a] (1.3)
TEAE leading to study drug discontinuation	1[a] (1.3)
Reported term	
Diarrhea/loose stool	12 (15.6)
Cold	4 (5.2)
Nausea	2 (2.6)
Worsening in IBS-C symptoms	2 (2.6)
Abdominal pain	1 (1.3)
Anal irritation	1 (1.3)
Anorexia	1 (1.3)
Bacterial vaginosis	1 (1.3)
Chest pain	1 (1.3)
Elevated protein	1 (1.3)
Gastroenteritis	1 (1.3)
Headache	1 (1.3)
Runny nose	1 (1.3)
Urinary tract infection	1 (1.3)
Vomiting	1 (1.3)

[a]From the same patient, who reported a TEAE of severe diarrhea that led to study drug discontinuation.
IBS-C, irritable bowel syndrome with constipation; TEAE, treatment-emergent adverse event.

Figure 2: Overview of Patient Flow Through the Study as of November 1, 2024



AE, adverse event; OLE, open-label extension; RTP, randomized treatment period.

40-Week OLE

- **Table 2** summarizes the interim baseline demographics and TEAEs for the SAS, which included 56 enrolled and treated patients (**Figure 2**).
- All TEAEs were resolved except 2 mild events: 1 overflow incontinence and 1 diarrhea.
- All TEAEs were considered unrelated to study drug except diarrhea.

Table 2: TEN-01-306 Baseline Demographics and TEAEs (Safety Analysis Set)

Baseline demographics (N=56)	
Age at 306 informed consent, mean (SD), y	14.8 (1.64)
Female, n (%)	35 (62.5)
Race, n (%)	
White	44 (78.6)
Asian	7 (12.5)
Black or African American	4 (7.1)
Other	1 (1.8)
Not Hispanic or Latino, n (%)	25 (44.6)
IBS-C duration at 306 enrollment, median (range), y	4.050 (0.28–15.41)
TEAEs (N=56)	
Patients with any..., n (%)	
TEAE	16 (28.6)
Serious TEAE	0
Severe TEAE	1 (1.8)
Drug-related TEAE[a]	3 (5.4)
TEAE leading to study drug discontinuation	1 (1.8)
Reported term	
Diarrhea/loose stool	4 (7.1)
Influenza	4 (7.1)
Headache	2 (3.6)
Abrasions, left lower leg	1 (1.8)
Cough	1 (1.8)
COVID-19	1 (1.8)
Dysmenorrhea (menstrual cramps)	1 (1.8)
Epistaxis	1 (1.8)
Fever	1 (1.8)
Labial abscess	1 (1.8)
Nausea	1 (1.8)
Overflow incontinence	1 (1.8)
Worsening in IBS-C symptoms	1 (1.8)
Yeast infection	1 (1.8)

[a]No patients reported a severe, drug-related TEAE in TEN-01-306.
IBS-C, irritable bowel syndrome with constipation; TEAE, treatment-emergent adverse event.

Limitation

- Phase 3 safety data are from a blinded, pooled data set that included placebo and tenapanor.

Conclusions

Preliminary blinded safety results of the R-ALLY study in pediatric patients with IBS-C and its open-label safety extension are consistent with those from previous studies of tenapanor in adult patients with IBS-C.

Diarrhea was the only AE related to study drug.

As of November 1, 2024, no unexpected safety concerns have been observed.

References

1. IBSRELA. Prescribing information. Ardelyx Inc.; 2025.
2. Thapar N et al. *Nat Rev Dis Primers*. 2020;6:89.
3. Self MM et al. *Clin Gastroenterol Hepat*. 2014;12:1468-73.
4. https://clinicaltrials.gov/study/NCT05643534. [Online]. Accessed February 19, 2025.
5. https://clinicaltrials.gov/study/NCT05905926. [Online]. Accessed February 19, 2025.

Acknowledgments

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Disclosures

Thomas Wallach is a consultant for Nutricia and has ownership interest in Kiwi Bioscience. Mihaela Ringheanu is a speaker for Nutricia. Ana Cantisano has nothing to disclose. Yang Yang, Karishma Raju, Jocelyn Tabora, and Susan Edelstein are full-time employees of Ardelyx, Inc.

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IBSRELA® (tenapanor) is indicated for 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.** ***[see PI Contraindications (4), Use in Specific Populations (8.4)]*****.**
- **Avoid use of IBSRELA in patients 6 years to less than 12 years of age.** ***[see PI Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*****.**
- **The safety and effectiveness of IBSRELA have not been established in pediatric patients less than 18 years of age.** ***[see PI Use in Specific Populations (8.4)]*****.**

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%).

For additional safety information, including the Boxed Warning, please see full Prescribing Information: click here.

MEDI-US-2500329

IBS-C, irritable bowel syndrome with constipation.

IBSRELA (tenapanor hydrochloride). Prescribing information. Ardelyx, Inc; 2025.
Available at: https://www.ibsrela-hcp.com/PI