

A Phase 3, 26-Week Randomized Controlled Study to Assess Safety and Efficacy of Tenapanor for Treatment of Chronic Idiopathic Constipation in Adults: Design and Rationale

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Background

- Chronic idiopathic constipation (CIC), also known as chronic constipation, is characterized by infrequent bowel movements, difficult stool passage, and/or a sensation of incomplete evacuation that persists for several months without known cause, as defined by the Rome IV diagnostic criteria.¹
 - In a large, nationally representative survey of 88,607 adults in the United States conducted in 2020, the prevalence of Rome IV CIC was 6%.²
 - In the BURDEN-CIC study that surveyed 1223 patients with CIC, 59% of patients who received prescription treatment reported that they were not satisfied with their current chronic treatment. In addition, many patients reported feeling frustrated (42%), stressed (28%), or depressed (15%) about their condition.³
- Owing to the considerable burden of CIC, there is an unmet need for an effective, well-tolerated treatment that provides durable improvement in constipation symptoms.

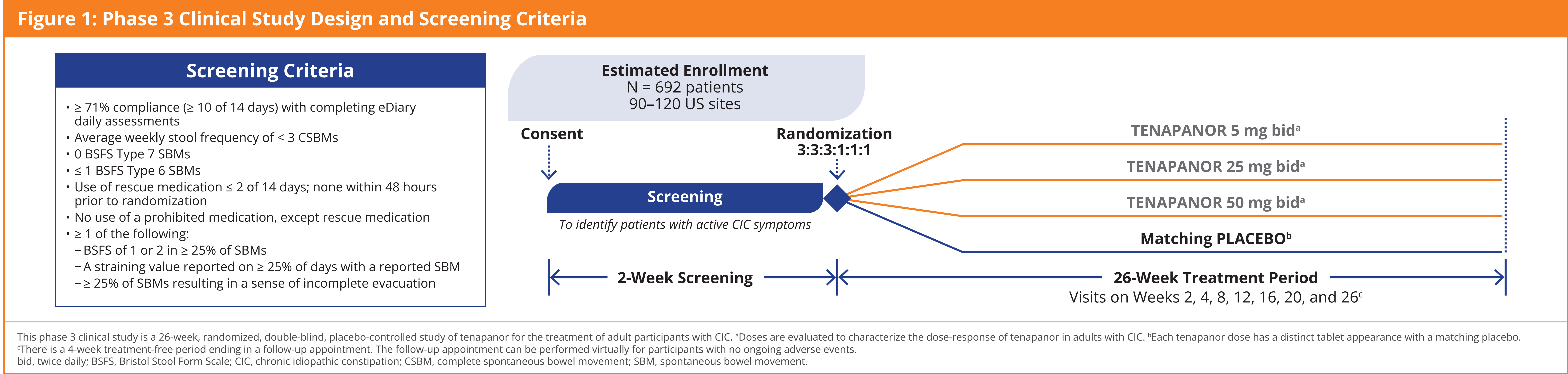
Rationale

- Tenapanor, a sodium/hydrogen exchanger 3 (NHE3) inhibitor, has been approved by the US Food and Drug Administration (FDA) for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.⁴
- In *post hoc* analyses of two phase 3 trials of tenapanor in patients with IBS-C (T3MPO-1 and T3MPO-2), tenapanor significantly improved CIC-relevant bowel function endpoints and constipation severity versus placebo.^{5,6}
- Given the symptom continuum between CIC and IBS-C, tenapanor warrants evaluation in patients with CIC.
- Here, we present the study design for a trial assessing the efficacy, safety, and tolerability of tenapanor in adults with CIC.

Methods

Study Design

- This is a phase 3, randomized, double-blind, placebo-controlled, multicenter study (NCT07382167; **Figure 1**).



Patient Population

Figure 2: Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Adult males or females (aged 18–80 years) • Informed consent prior to initiation of study-specific procedures • Diagnosis of CIC by Rome IV criteria – Must include ≥ 2 of the following:^a • Straining during > 25% of defecations • Lumpy or hard stools (BSFS 1–2) • Sensation of incomplete evacuation in > 25% of defecations • Sensation of anorectal obstruction/blockage in > 25% of defecations • Manual maneuvers to facilitate > 25% of defecations^b • Average weekly stool frequency of < 3 CSBMs – Loose stools rarely present without the use of laxatives – Insufficient criteria for IBS-C • Females of non-childbearing potential or using appropriate contraception^c • Males should use appropriate contraception • Daily access to eDiary via computer, tablet, or smartphone	• Loose (mushy) or watery stool (BSFS 6 or 7) in the absence of any laxative or medication that is known to affect stool consistency (ie, prohibited medicine) for > 25% of bowel movements during the 3 months prior to the screening visit • Fecal impaction within 6 months prior to the screening visit • Unexplained and clinically significant “alarm symptoms” including lower gastrointestinal bleeding, iron-deficiency anemia, weight loss, or fever of unknown origin • Functional diarrhea as defined by Rome IV criteria • IBS with constipation, IBS with diarrhea, mixed IBS, or unsubtyped IBS as defined by Rome IV criteria • Diagnosis or treatment of any clinically symptomatic biochemical or structural abnormality of the gastrointestinal tract within 6 months prior to the screening visit, or active disease within 6 months prior to the screening visit^d • Central nervous system disorder^e

^aCriteria fulfilled for the last 3 months with symptom onset ≥ 6 months prior to diagnosis. ^bIncluding digital evacuation, support of the pelvic floor. ^cPregnancy test must be negative at Visits 1 and 2. ^dIncluding but not limited to cancer, inflammatory bowel disease, diverticulitis, duodenal ulcer, dyssynergic defecation, erosive esophagitis, gastric ulcer, pancreatitis (within 12 months prior to the screening visit), ileus, or gastrointestinal obstruction. ^eIncluding Parkinson’s disease, spinal cord injury, or multiple sclerosis. BSFS, Bristol Stool Form Scale; CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement; IBS, irritable bowel syndrome; IBS-C, IBS with constipation.

Endpoints

Figure 3: Study Endpoints and Assessments

Primary Endpoint	Key Secondary Endpoints
• Durable CSBM response (defined as achieving weekly CSBM response^a for ≥ 9 out of the first 12 weeks of the RTP and for ≥ 3 of the last 4 weeks of the first 12 weeks of the RTP)	• 9/12-week CSBM response (defined as achieving the weekly CSBM response^a for ≥ 9 out of the first 12 weeks of the RTP) • Change from baseline over the first 12 weeks of the RTP in CSBM frequency, SBM frequency, stool consistency,^b and straining
Additional Secondary Endpoints	
• Change from baseline to each analysis week in average weekly CSBM frequency, SBM frequency, stool consistency,^b straining score, and constipation severity score	• Percent change from baseline to each analysis week in abdominal discomfort and bloating • Change from baseline in the total score and subscales of PAC-SYM and PAC-QOL at Weeks 12 and 26, and the End of Treatment visit or Early Termination visit
Safety and Other Assessments	
• Adverse events will be monitored throughout the study, including the 4-week follow-up period • A complete physical examination will be conducted at Screening, Weeks 12 and 26/Early Termination visit • A 12-lead ECG will be obtained at Screening, Weeks 12 and 26/Early Termination visit. For any patient who experiences severe diarrhea requiring medical intervention, a 12-lead ECG will be obtained at the next visit	• Vital signs, including heart rate, respiratory rate, sitting systolic and diastolic blood pressure, temperature, and body weight will be obtained at Screening, Day 1 (pre-dose), Weeks 12 and 26/Early Termination visit • Serology will be performed at Screening • Pharmacokinetic blood sampling will be performed at Weeks 12 and 26 for ~30 patients per treatment arm • Serum chemistries, hematology, and urinalysis will be conducted at Screening, Weeks 12 and 26/Early Termination visit. For any patient who experiences severe diarrhea requiring medical intervention, a serum chemistry panel will be obtained at the next visit

Efficacy endpoints are derived from daily and weekly eDiary assessments, including bowel movement frequency, stool consistency, straining, abdominal discomfort, bloating, constipation severity, and rescue medication use. ^aA weekly CSBM response is defined as an increase of ≥1 CSBM per week from baseline and an average of ≥3 CSBMs per week in a given week. ^bUsing the Bristol Stool Form Scale. CSBM, complete spontaneous bowel movement; ECG, echocardiogram; PAC-QOL, Patient Assessment of Constipation-Quality of Life; PAC-SYM, Patient Assessment of Constipation-Symptoms; RTP, randomized treatment period; SBM, spontaneous bowel movement.

Statistical Analyses

- Safety analyses will include all participants receiving ≥ 1 dose of study treatment.
- Efficacy analyses will include all randomized participants meeting eligibility criteria and receiving ≥ 1 dose of study treatment.
- Categorical endpoints will be analyzed using Cochran–Mantel–Haenszel tests stratified by sex.
- Continuous endpoints will be analyzed using an analysis of covariance (ANCOVA) model, an analysis of variance (ANOVA) model, or a mixed-effects model for repeated measures (MMRM), with treatment and sex as fixed effects and baseline value as a covariate, as appropriate.
- To control the overall Type I error rate at the 0.05 level (2-sided), a gatekeeping procedure will be followed.
- The statistical analysis plan is currently being reviewed by the FDA and may be subject to change.

Limitations

- The study will be conducted only in the United States, limiting the applicability of the findings for patients in other geographic regions.
- Study eligibility may be limited by the requirement for a pre-existing CIC diagnosis based on Rome IV criteria, potentially excluding patients with symptoms consistent with CIC who have not received a formal diagnosis.
- The screening criteria may restrict participation to patients with more severe CIC, which could limit the generalizability of the findings to patients with less severe disease.
- Efficacy assessments rely primarily on patient-reported outcomes collected via eDiary.

Summary



Although tenapanor has been shown to be effective for treating IBS-C, its role in CIC remains undefined.



This phase 3 study is designed to evaluate the efficacy, safety, and tolerability of tenapanor in adults with CIC.

- Primary completion is estimated in May 2027.



The results of this study will provide important data on the efficacy, safety, tolerability, and pharmacokinetic profile of tenapanor in adults with CIC.

Disclosures

This study was supported by Ardelyx, Inc. Susan Edelstein, Yang Yang, Jocelyn M. Tabora, Kenji Kozuka, and Karishma Raju are employees of Ardelyx, Inc. Anthony J. Lembo reports consulting payments from Ardelyx, Atmo, BioAmerica, Ironwood, Salix, Takeda, Vibrant, and Viscera Labs, and stock ownership in Bristol Myers Squibb, Johnson & Johnson, and MetaPhy Health.

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