Efficacy and Safety of Tenapanor in Patients with Constipation-Predominant Irritable Bowel Syndrome: A 12-Week, Double-Blind, Placebo-Controlled, Randomized Phase 3 Trial

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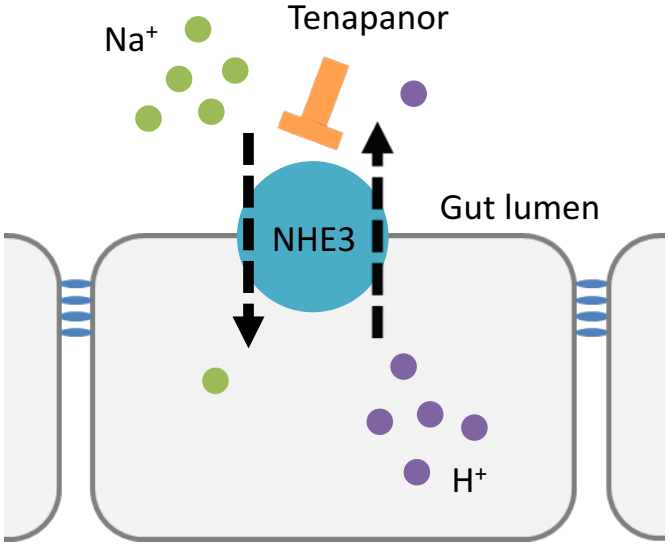
Tenapanor is a First-in-Class, Minimally Systemic, Small-Molecule Inhibitor of Gastrointestinal NHE3

- Na^+/H^+ exchanger isoform 3 (NHE3) is the major absorptive Na^+/H^+ exchanger in the gut[1]
- Specific inhibitor of NHE3 that reduces absorption of dietary sodium and phosphate (via a downstream effect) in preclinical and clinical studies[2,3]
- Undergoing evaluation in clinical trials as a potential treatment for IBS-C and for hyperphosphatemia in patients with end-stage renal disease on dialysis[4,5]

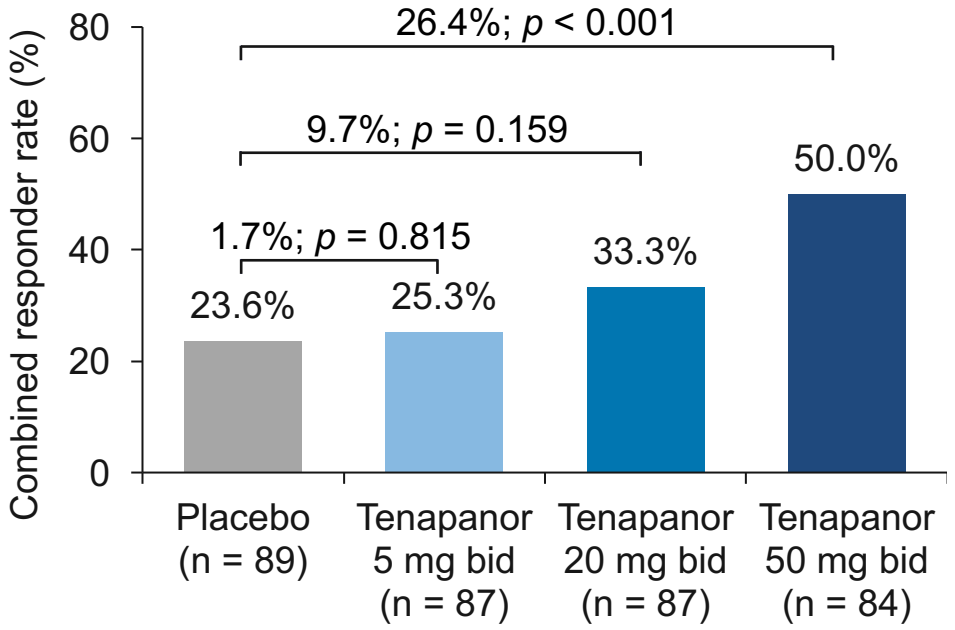


IBS-C, constipation-predominant irritable bowel syndrome; NHE3, sodium/hydrogen (Na^+/H^+) exchanger isoform 3

1. Girardi ACC *et al. Am J Physiol Cell Physiol* 2012;302:C1569–87; 2. Spencer AG *et al. Sci Transl Med* 2014;6:227ra36; 3. Labonté ED *et al. J Am Soc Nephrol* 2015;26:1138–49; 4. Chey WD *et al. Am J Gastroenterol* 2017;112:763–74; 5. Block GA *et al. J Am Soc Nephrol* 2017;28:1933–42

Phase 2b Study Results: Rationale for Phase 3

- Randomized study in 356 patients with IBS-C (Rome III criteria)
- Results provided clinical rationale for a phase 3 study with similar design
  - Combined, CSBM and abdominal pain responder rates (6 of 12 and 9 of 12 weeks) significantly greater with tenapanor 50 mg bid vs placebo
  - Tenapanor was well tolerated; most frequent adverse event was diarrhea



Chey WD *et al. Am J Gastroenterol* 2017;112:763–774; ClinicalTrials.gov ID: NCT01923428. Available from https://clinicaltrials.gov/ct2/show/NCT01923428

CSBM, complete spontaneous bowel movement

T3MPO-1 Phase 3 Study: Aims, Participants and Design

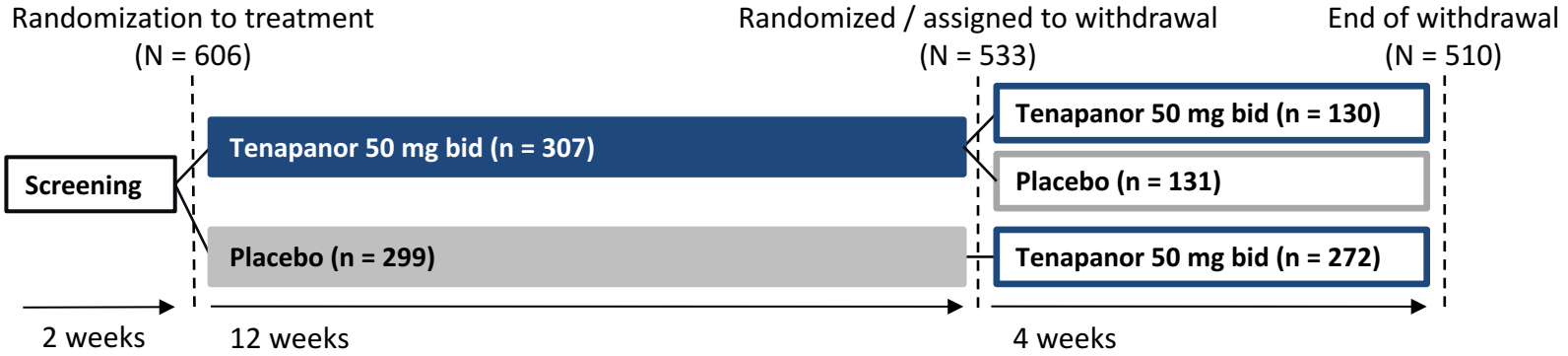
Aim

- Efficacy and safety of tenapanor 50 mg bid for the treatment of patients with IBS-C

Main eligibility criteria

- IBS-C diagnosis (modified Rome III criteria)
- Two-week screening criteria:
  - Mean average: < 3 CSBMs and ≤ 5 SBMs per week
  - Mean weekly abdominal pain score[a] ≥ 3

111 sites in the USA



[a]Assessed daily using a 10-point Likert scale: 0 = none to 10 = very severe; mean weekly score was calculated from scores for all days during a valid week.
ClinicalTrials.gov ID: NCT02621892. Available from: https://clinicaltrials.gov/ct2/show/NCT02621892
SBM, spontaneous bowel movement

Main Study Endpoints

Primary endpoint

- Combined responder rate
  - Proportion reporting ≥ 30% abdominal pain reduction and an increase of ≥ 1 CSBM from baseline in the same week for ≥ 6 of 12 treatment weeks

Key secondary endpoints

- CSBM responder rate
  - Proportion with an increase of ≥ 1 CSBM per week from baseline (≥ 6 of 12 weeks, ≥ 9 of 12 weeks, sustained response[a])
- Abdominal pain responder rate
  - Proportion with a decrease in abdominal pain of ≥ 30% from baseline (≥ 6 of 12 weeks, ≥ 9 of 12 weeks, sustained response[a])
- Combined responder rate (≥ 9 of 12 weeks, sustained response[a])

[a]Responder for ≥ 9 of 12 weeks and ≥ 3 of the last 4 weeks

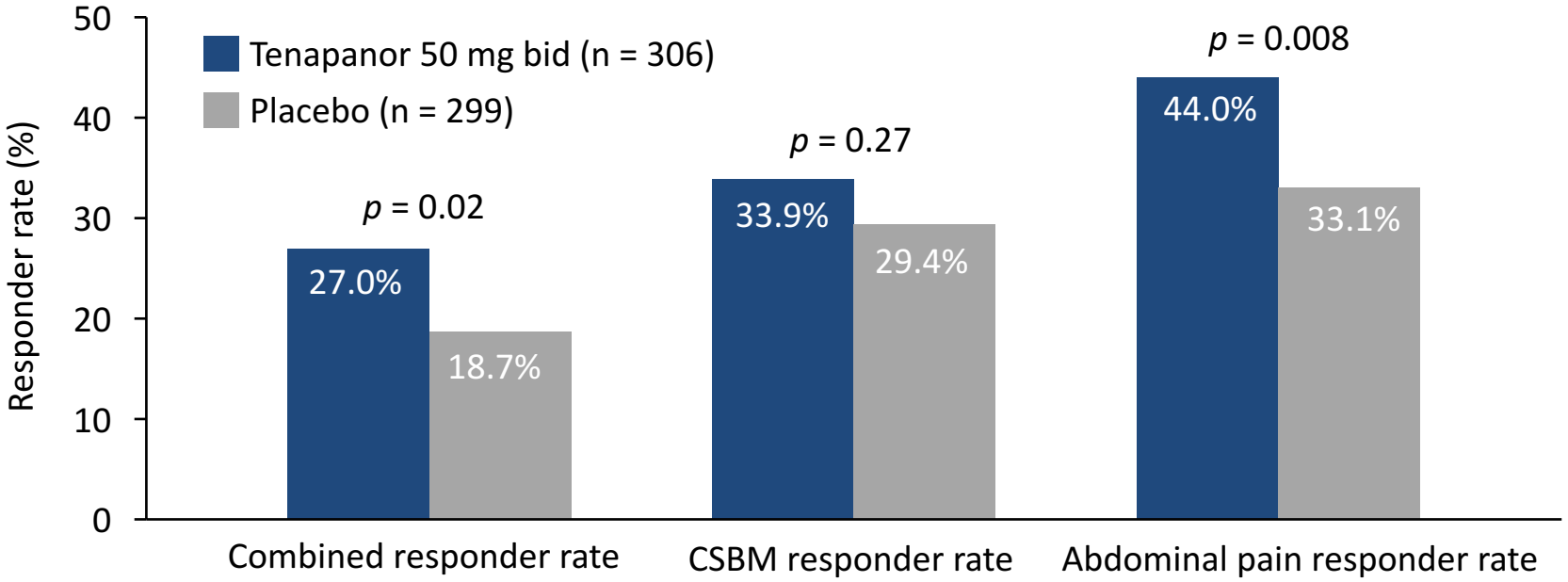
Patient Baseline Demographics and Disease Characteristics

	Tenapanor 50 mg bid (n = 307)	Placebo (n = 299)	Overall (n = 606)
Age (years), mean	45.0	44.9	45.0
Women (%)	79.5	83.3	81.4
Caucasian (%)	65.5	62.2	63.9
Body mass index (kg/m^2), mean	29.9	29.3	29.6
Number of CSBMs per week, mean	0.18	0.21	0.2
Number of SBMs per week, mean	1.76	1.69	1.7
Abdominal pain, weekly mean[a]	6.29	6.32	6.3

[a]Assessed daily using a 10-point Likert scale: 0 = none to 10 = very severe; mean weekly score was calculated from scores for all days during a valid week.

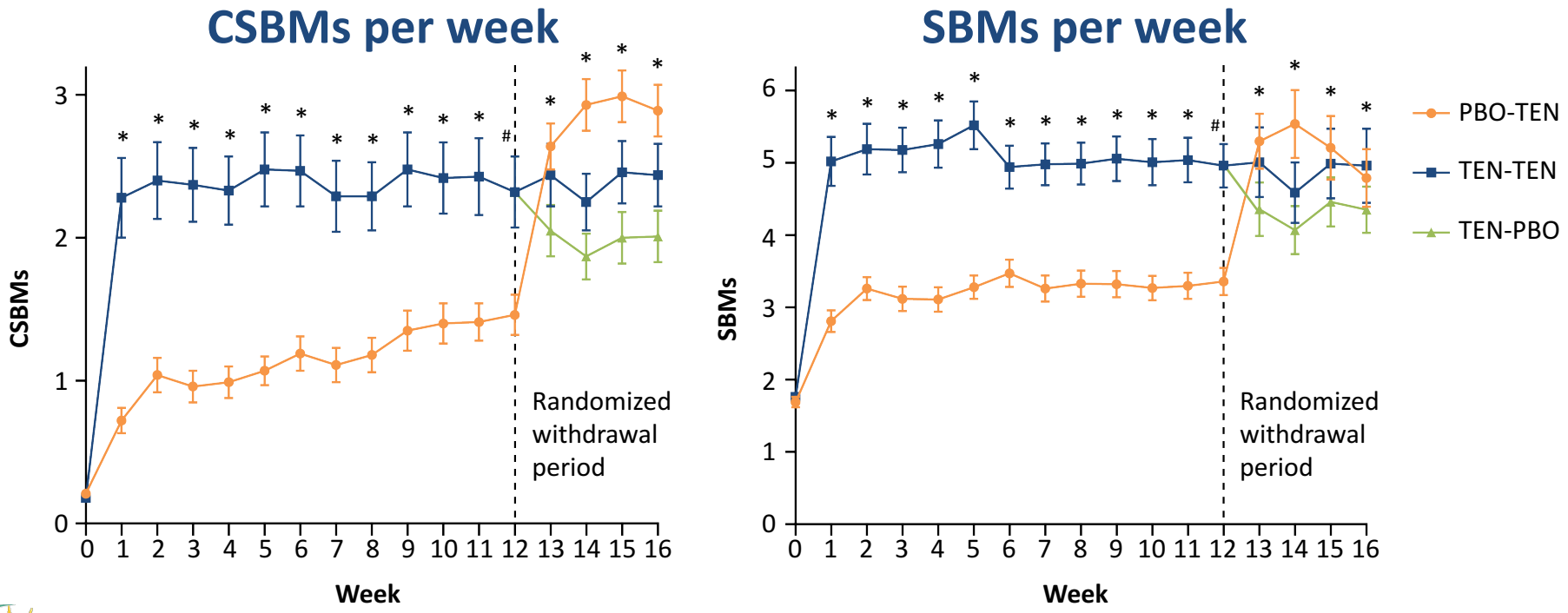
Primary and Key Secondary Endpoints

Responder Analysis ≥ 6 of 12 Weeks



Cochran–Mantel–Haenszel test, stratified by pooled investigator site; intention-to-treat analysis

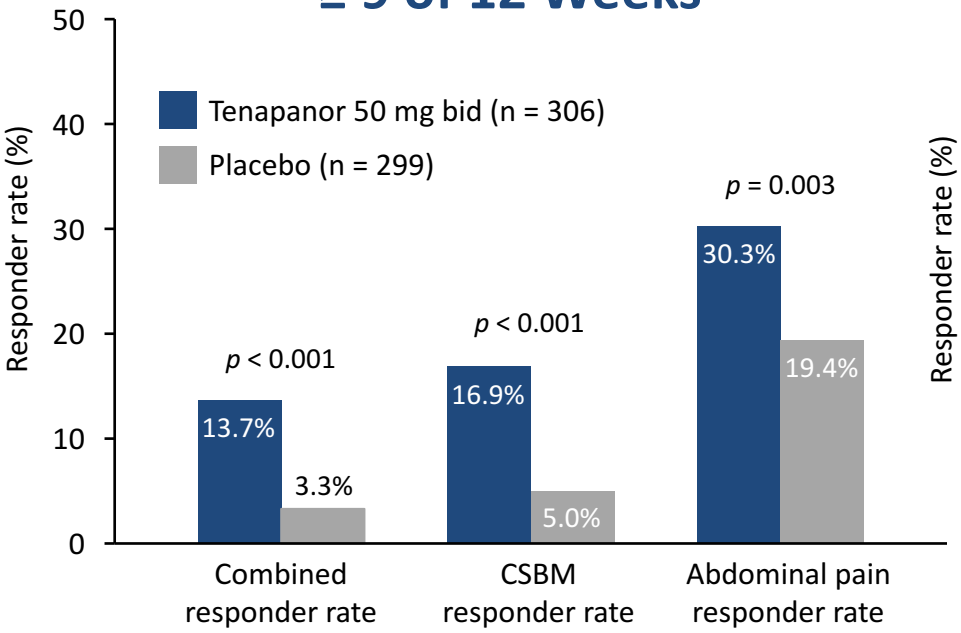
CSBM and SBM Frequency Over 16 Weeks



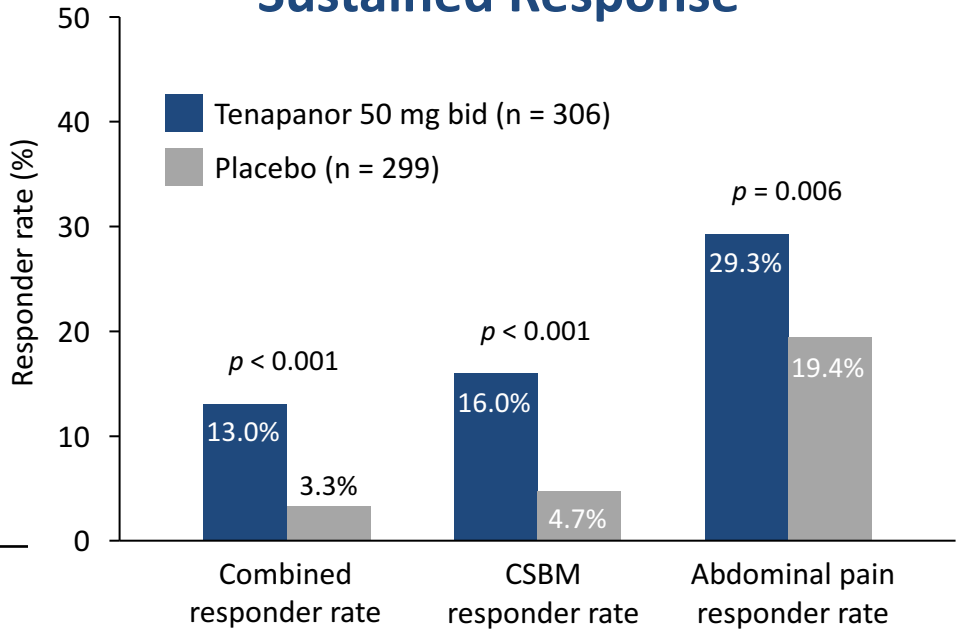
Intention-to-treat population; data are mean ± standard error; *$p < 0.001$; #$p = 0.001$ vs placebo
PBO, placebo; TEN, tenapanor

Key Secondary Endpoints

≥ 9 of 12 Weeks



Sustained Response[a]



Cochran–Mantel–Haenszel test, stratified by pooled investigator site; intention-to-treat analysis
[a]Responder for ≥ 9 of 12 weeks and ≥ 3 of the last 4 weeks

Summary of Adverse Events

	Tenapanor 50 mg bid (n = 309)	Placebo (n = 301)
Any AE	110 (35.6)	74 (24.6)
Treatment-related AEs	57 (18.4)	18 (6.0)
Serious AEs	4 (1.3)	0
AEs leading to discontinuation	23 (7.4)	2 (0.7)
AEs occurring in ≥ 2% of patients in any treatment group and more frequently than in the placebo arm		
Diarrhea	45 (14.6)	5 (1.7)
Nausea	8 (2.6)	5 (1.7)

- No drug-related serious AEs
- No clinically meaningful changes from baseline in clinical laboratory parameters, vital signs, electrocardiographic parameters, or physical examination findings
- The majority of AEs leading to discontinuation of tenapanor were diarrhea (6.5%)

Safety analysis population; data are n (%)
AE, adverse event

Conclusions

- Tenapanor is a first-in-class, minimally systemic NHE3 inhibitor
- In patients with IBS-C, treatment with tenapanor 50 mg bid produced a statistically significant improvement in the combined responder (≥ 6 of 12 weeks) primary endpoint, comprised of CSBM and abdominal pain responders
  - Significant improvements were seen in CSBMs, abdominal pain and the combined response in the ≥ 9 of 12 weeks responder analysis, with similar, clinically relevant improvements in the sustained responder analysis
- Tenapanor was generally well tolerated, with diarrhea the most common adverse event
- Additional phase 3 trials in patients with IBS-C are ongoing
  - T3MPO-2 efficacy and safety study (6 months)[1]
  - T3MPO-3 long-term safety study (1 year)[2]
- Tenapanor, with a novel mechanism of action, may offer a new treatment option for patients with IBS-C

1. ClinicalTrials.gov ID: NCT02686138. Available from: https://clinicaltrials.gov/ct2/show/NCT02686138
2. ClinicalTrials.gov ID: NCT02727751. Available from: https://clinicaltrials.gov/ct2/show/NCT02727751

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