Efficacy and safety of tenapanor in patients with constipation-predominant irritable bowel syndrome: a 12-week, double-blind, placebo-controlled, randomized phase 2b trial

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Disclosures

- William D Chey
  - Consultancy: Ardelyx, Asubio Pharmaceuticals, AstraZeneca, Forest Laboratories (Actavis), Ironwood Pharmaceuticals, Nestlé Health Science, Prometheus Laboratories, QOL Medical, Salix Pharmaceuticals, SK Biopharmaceuticals, Sucampo and Takeda
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- Anthony J Lembo
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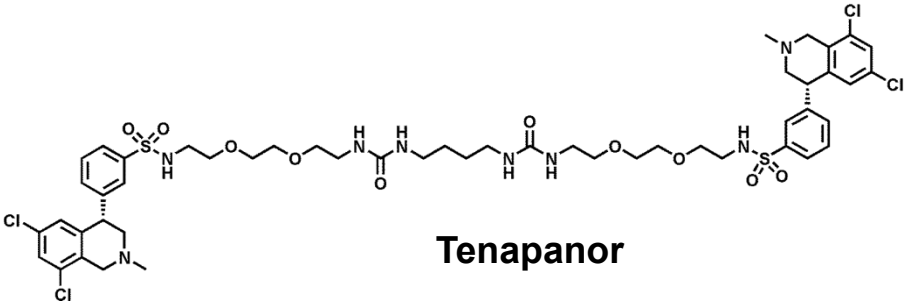
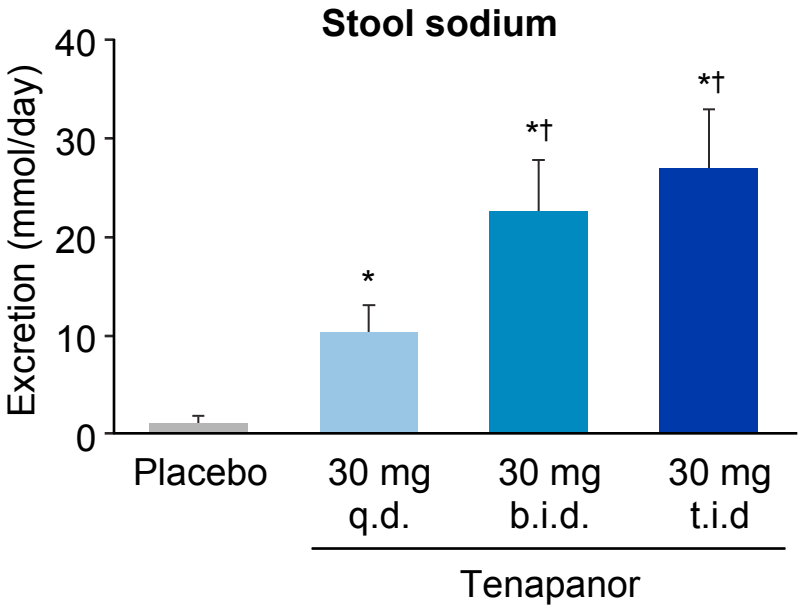
- James A Phillips
  - Consultancy: Ardelyx
- David P Rosenbaum
  - Employment and ownership interests: Ardelyx
- This study was funded by AstraZeneca and Ardelyx

Tenapanor (AZD1722) acts locally in the gut to reduce sodium absorption

- Sodium/hydrogen exchanger isoform 3 (NHE3) plays an important role in intestinal sodium/fluid homeostasis
- Tenapanor is a small-molecule inhibitor of NHE3
- Preclinical and phase 1 studies show that tenapanor reduces sodium absorption and has minimal systemic availability
- In a preclinical model, tenapanor showed antinociceptive effects on stress-induced mechanical colorectal hypersensitivity





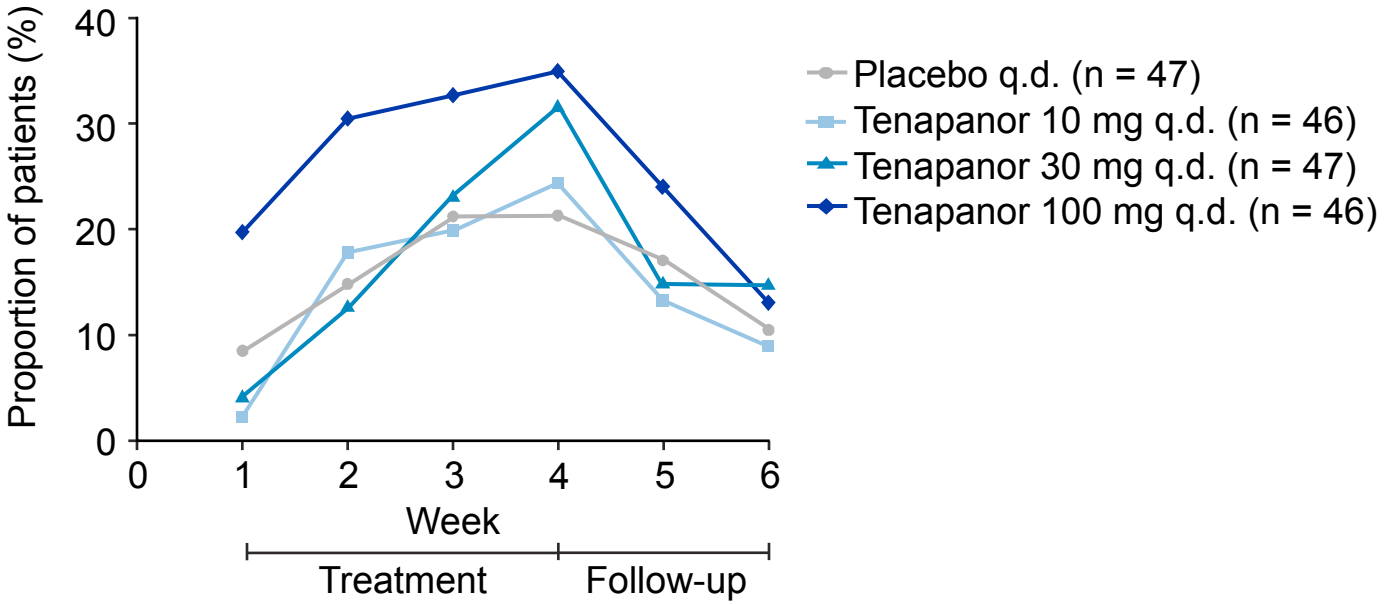
*$p < 0.05$ versus placebo; †$p < 0.05$ versus tenapanor 30 mg q.d. b.i.d., twice daily; q.d., once daily; t.i.d., three times daily

Eutamene H *et al*. *Gastroenterology* 2011;140:S-57–8; Schultheis PJ *et al*. *Nat Genet* 1998;19:282–5; Spencer AG *et al*. *Sci Transl Med* 2014;6:27ra36; Tse CM *et al*. *J Biol Chem* 1992;267:9340–6

Tenapanor is a potential treatment for constipation-predominant irritable bowel syndrome (IBS-C)

- IBS is a common, symptom-based condition defined by the presence of abdominal pain and altered bowel habits
  - In IBS-C, stools are hard/lumpy in ≥ 25% of bowel movements and loose/watery in < 25% of bowel movements
- Phase 2a data suggest that tenapanor improves IBS-C symptoms

Patients with a ≥ 30% decrease in abdominal pain and an increase of ≥ 1 in complete spontaneous bowel movements (CSBM) per week



IBS-C, constipation-predominant irritable bowel syndrome; CSBM, complete spontaneous bowel movement; q.d., once daily

ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT01340053 (accessed 20 April 2015); Longstreth GF *et al. Gastroenterology* 2006;130:1480–91

12-week dose-ranging study evaluating tenapanor 5 mg, 20 mg or 50 mg b.i.d. vs placebo (1/2)

Study aim

- To evaluate the efficacy and safety of tenapanor for the treatment of IBS-C

Key inclusion criteria ✓

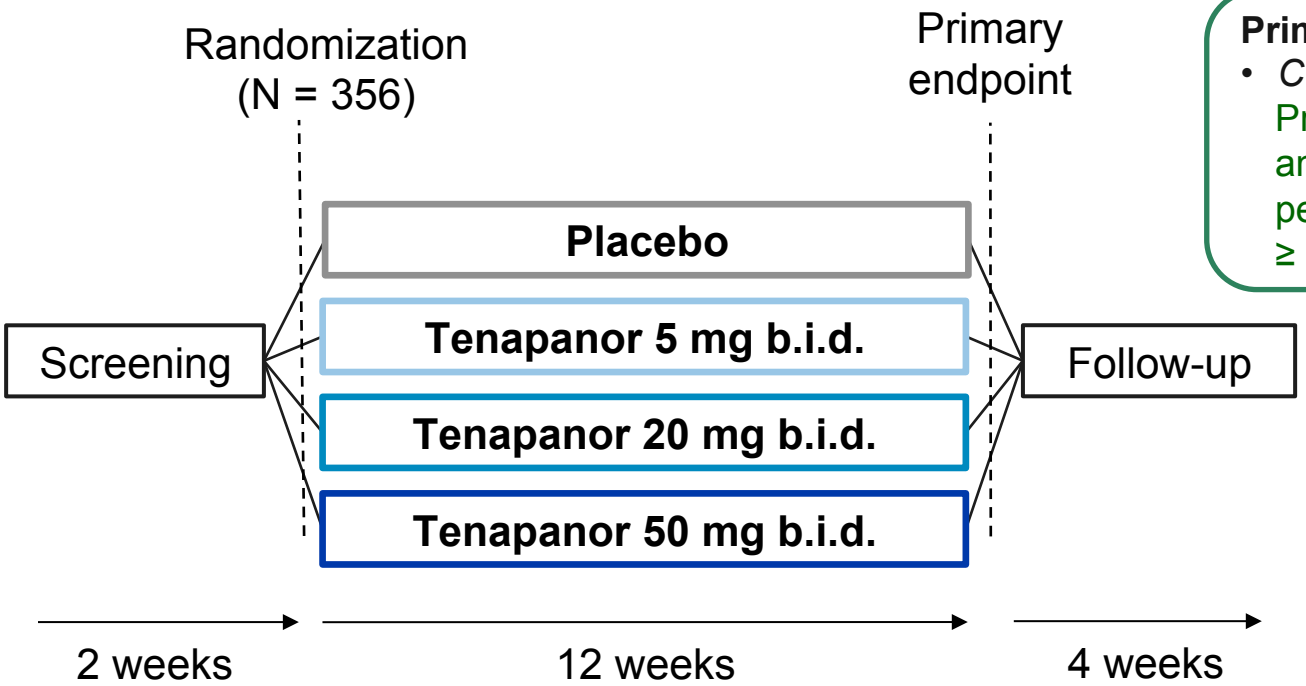
- Age 18–75 years
- IBS-C as defined by Rome III criteria
- Active disease during the screening period
  - < 3 CSBMs/week
  - < 5 SBMs/week
  - abdominal pain ≥ 3 (0–10 rating scale)

Key exclusion criteria ✗

- IBS with diarrhea (IBS-D), mixed IBS (IBS-M) or unsubtyped IBS as defined by Rome III criteria
- Diagnosis or treatment of any clinically symptomatic biochemical or structural abnormality of the gastrointestinal tract in the 6 months before screening
- Use of medication known to affect stool consistency

SBM, spontaneous bowel movement
ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT01923428 (accessed 29 April 2015)

12-week dose-ranging study evaluating tenapanor 5 mg, 20 mg or 50 mg b.i.d. vs placebo (2/2)



Primary endpoint

- *CSBM responder rate*
  Proportion of patients with an increase of ≥ 1 CSBM per week from baseline for ≥ 6/12 treatment weeks

Key secondary endpoints

- *Overall responder rate*[a]
- *Abdominal pain responder rate*[b]

Exploratory endpoints

- *Abdominal bloating, straining, IBS severity, constipation severity*

Safety assessments

- *Adverse event reporting throughout the trial*
- *Clinical laboratory tests (serum chemistry, hematology and urinalysis)*
- *Vital signs*
- *12-lead ECG*
- *Physical examinations*

[a]Proportion of patients with a ≥ 30% decrease in abdominal pain and an increase of ≥ 1 CSBM per week versus baseline for ≥ 6/12 treatment weeks

[b]Proportion of patients with a ≥ 30% decrease in abdominal pain from baseline for ≥ 6/12 treatment weeks

Statistical analysis methods (1/2)

- CSBM responder rate (primary endpoint), overall responder rate and abdominal pain responder rate (key secondary endpoints)
  - Treatment comparisons versus placebo are presented as risk differences (slides 8, 10, 11)
  - A screening test was performed based on a 2-degree of freedom Cochran–Mantel–Haenszel test for an association between treatment (placebo, tenapanor 20 mg b.i.d. and tenapanor 50 mg b.i.d.) and responder rate, stratified by pooled investigator sites
  - If this test was significant, a Cochran–Mantel–Haenszel test was used to calculate *p* values based on 1 degree of freedom for the association between treatment (placebo paired with each dose group separately) and responder rate, stratified by pooled investigator sites

Statistical analysis methods (2/2)

- Stool consistency (secondary endpoint), abdominal bloating, straining, IBS severity and constipation severity (exploratory endpoints)
  - Treatment comparisons versus placebo are presented as differences in LS mean changes from baseline (slide 11, 12)
  - A screening test was performed based on a 2-degree of freedom F-test from a full ANCOVA model to test for differences in mean changes from baseline among the placebo, tenapanor 20 mg b.i.d. and tenapanor 50 mg b.i.d. groups
  - LS means, 95% confidence intervals and *p* values were calculated using an ANCOVA model, with treatment and pooled investigator site as factors and baseline value as a covariate

Patient demographics and baseline disease characteristics

- 356 patients with IBS-C were randomized
  - The majority of patients were women (87%), < 65 years old (93%; mean age 45.7 years) and white (76%)

Baseline disease parameter	Placebo (n = 89)	Tenapanor 5 mg b.i.d. (n = 87)	Tenapanor 20 mg b.i.d. (n = 87)	Tenapanor 50 mg b.i.d. (n = 84)
CSBMs per week	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)
SBMs per week	2.0 (1.2)	1.9 (1.3)	1.9 (1.1)	2.0 (1.3)
Stool consistency[a]	1.8 (1.0)	1.8 (1.0)	1.6 (0.8)	1.8 (0.9)
Straining[b]	3.1 (1.2)	3.1 (1.1)	3.1 (1.3)	3.2 (1.3)
Constipation severity[c]	4.1 (0.7)	4.2 (0.6)	4.0 (0.7)	4.0 (0.8)
IBS severity[c]	3.8 (0.7)	3.9 (0.7)	3.9 (0.8)	3.8 (0.7)
Abdominal pain[d]	6.1 (1.5)	6.1 (1.6)	6.3 (1.5)	6.0 (1.5)

ITT, intention-to-treat; SD, standard deviation. Data are mean (SD) for the ITT population. Baseline was defined as the mean of weeks -1 and -2

[a]Assessed using the 7-point Bristol Stool Form Scale; weekly mean calculated from scores for all SBMs during the week

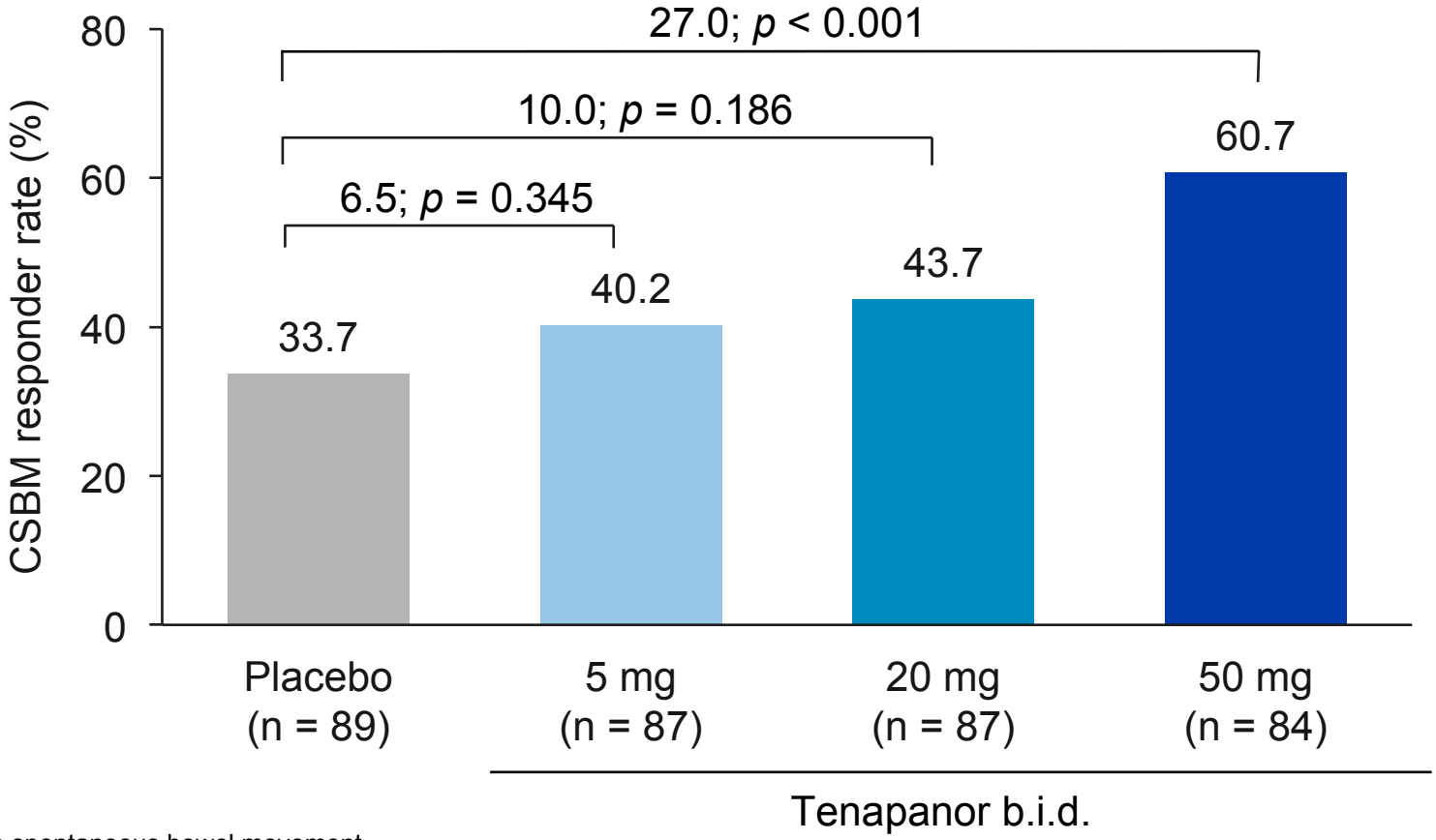
[b]Assessed for each SBM using a 5-point scale: 1 = not at all, 2 = a little bit, 3 = a moderate amount, 4 = a great deal, 5 = an extreme amount; mean weekly score calculated from scores for all SBMs during the week

[c]Assessed weekly using a 5-point scale: 1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe

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

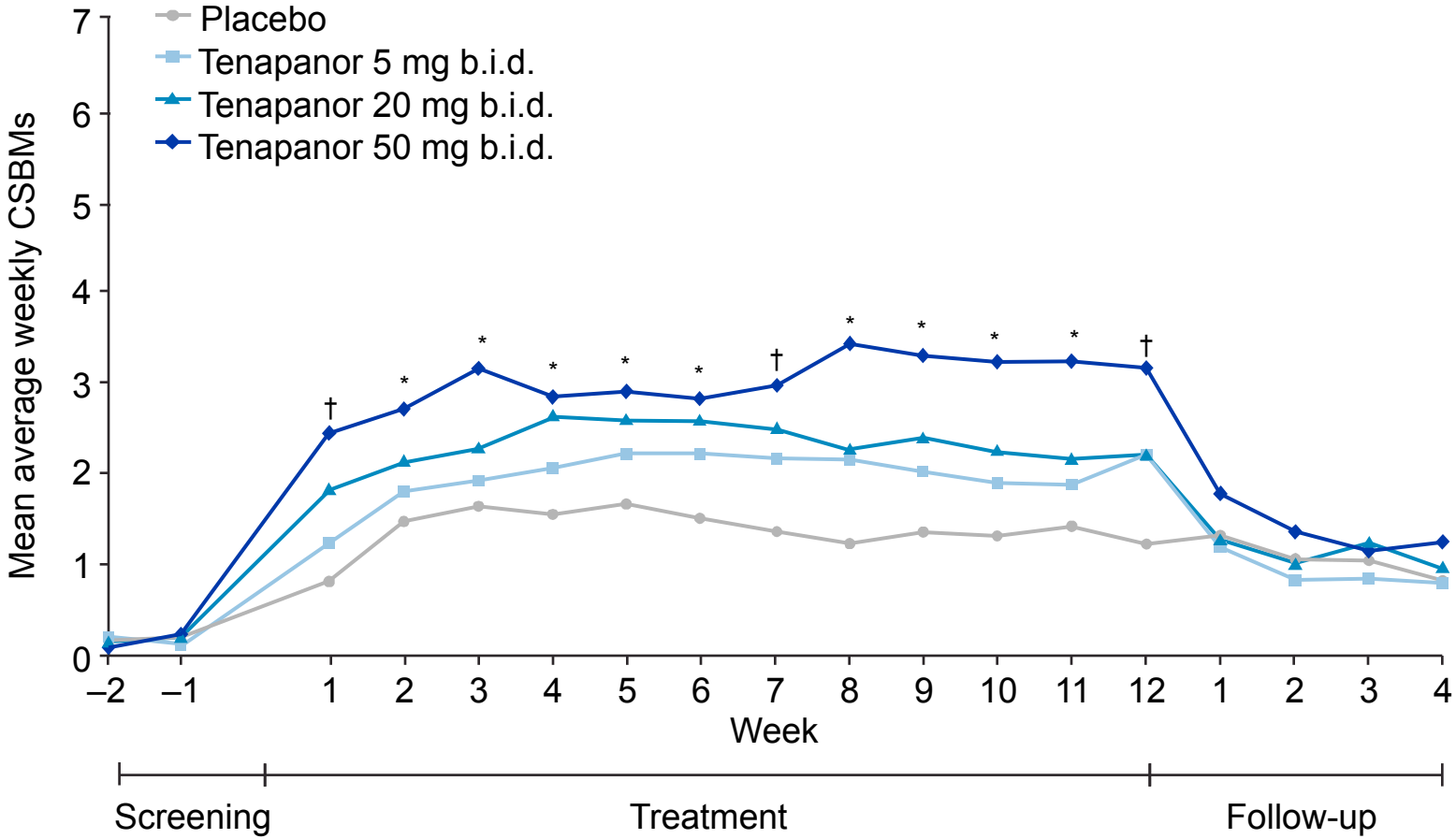
Tenapanor 50 mg b.i.d. resulted in a significantly higher CSBM responder rate than placebo

- Primary endpoint (CSBM responder rate): proportion of patients with an increase of ≥ 1 CSBM per week from baseline for ≥ 6/12 treatment weeks (ITT analysis)



CSBM, complete spontaneous bowel movement

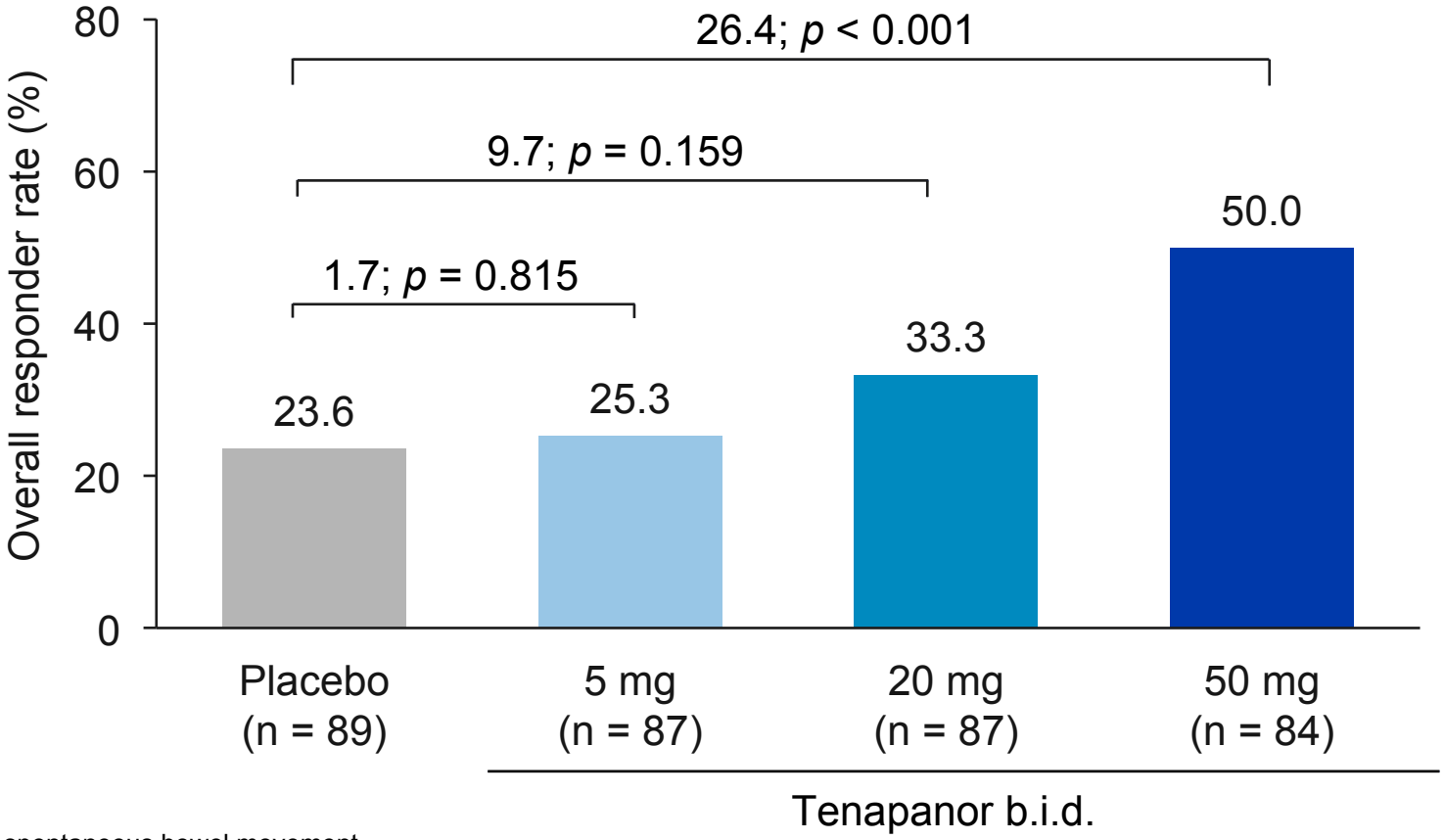
CSBM improvements were maintained over the 12 weeks in a dose-dependent manner



CSBM, complete spontaneous bowel movement
*$p < 0.05$, tenapanor 50 mg b.i.d. versus placebo
†$p < 0.05$, tenapanor 20 mg b.i.d. and 50 mg b.i.d. versus placebo

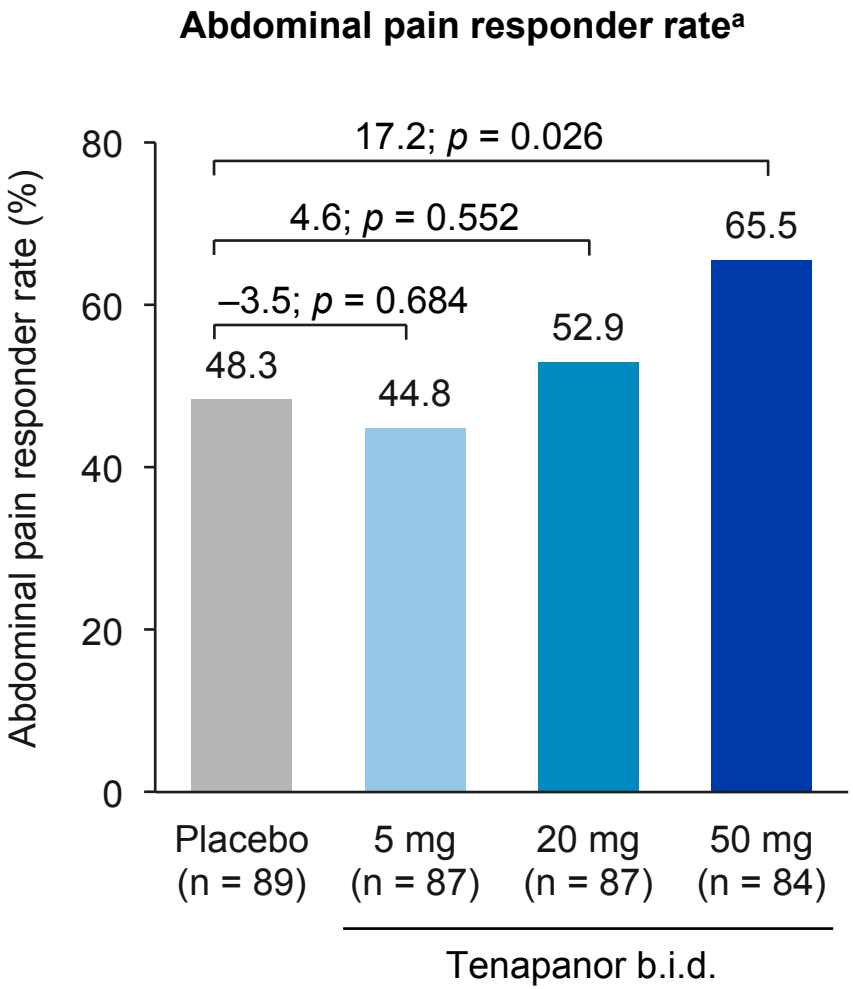
Tenapanor 50 mg b.i.d. resulted in a significantly higher overall responder rate than placebo

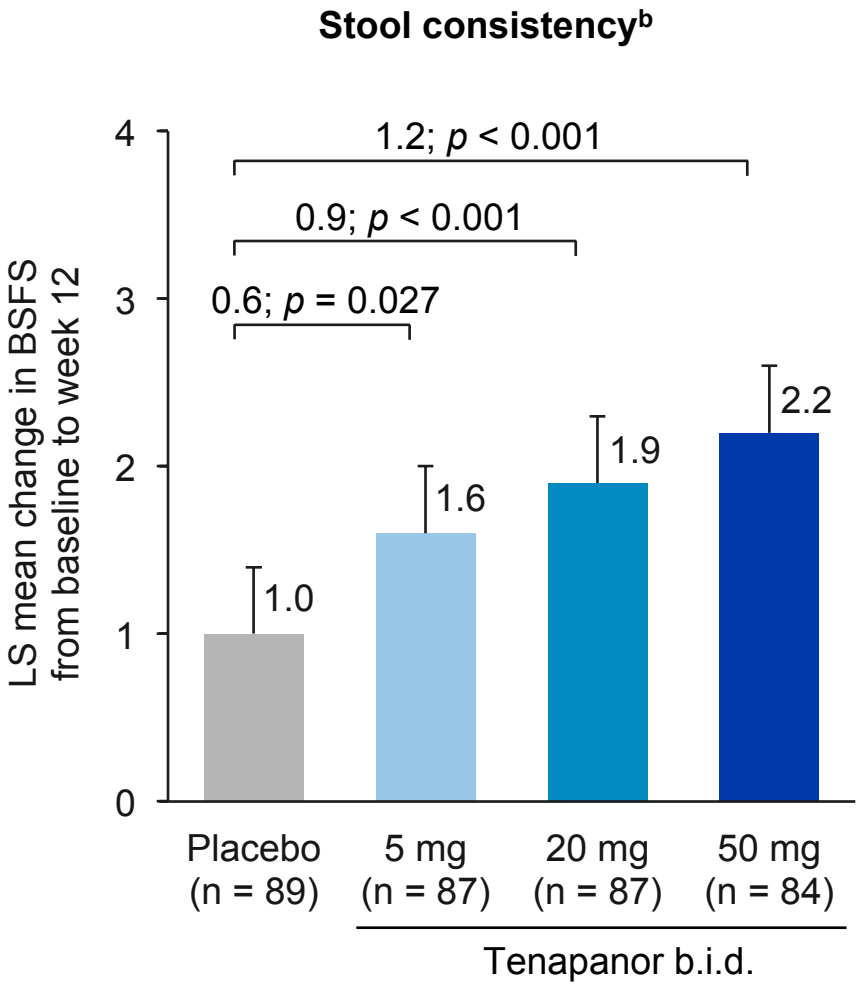
- Overall responder rate: proportion of patients with a ≥ 30% decrease in abdominal pain and an increase of ≥ 1 CSBM per week versus baseline for ≥ 6/12 treatment weeks



CSBM, complete spontaneous bowel movement

Improvements in other key secondary endpoints with tenapanor



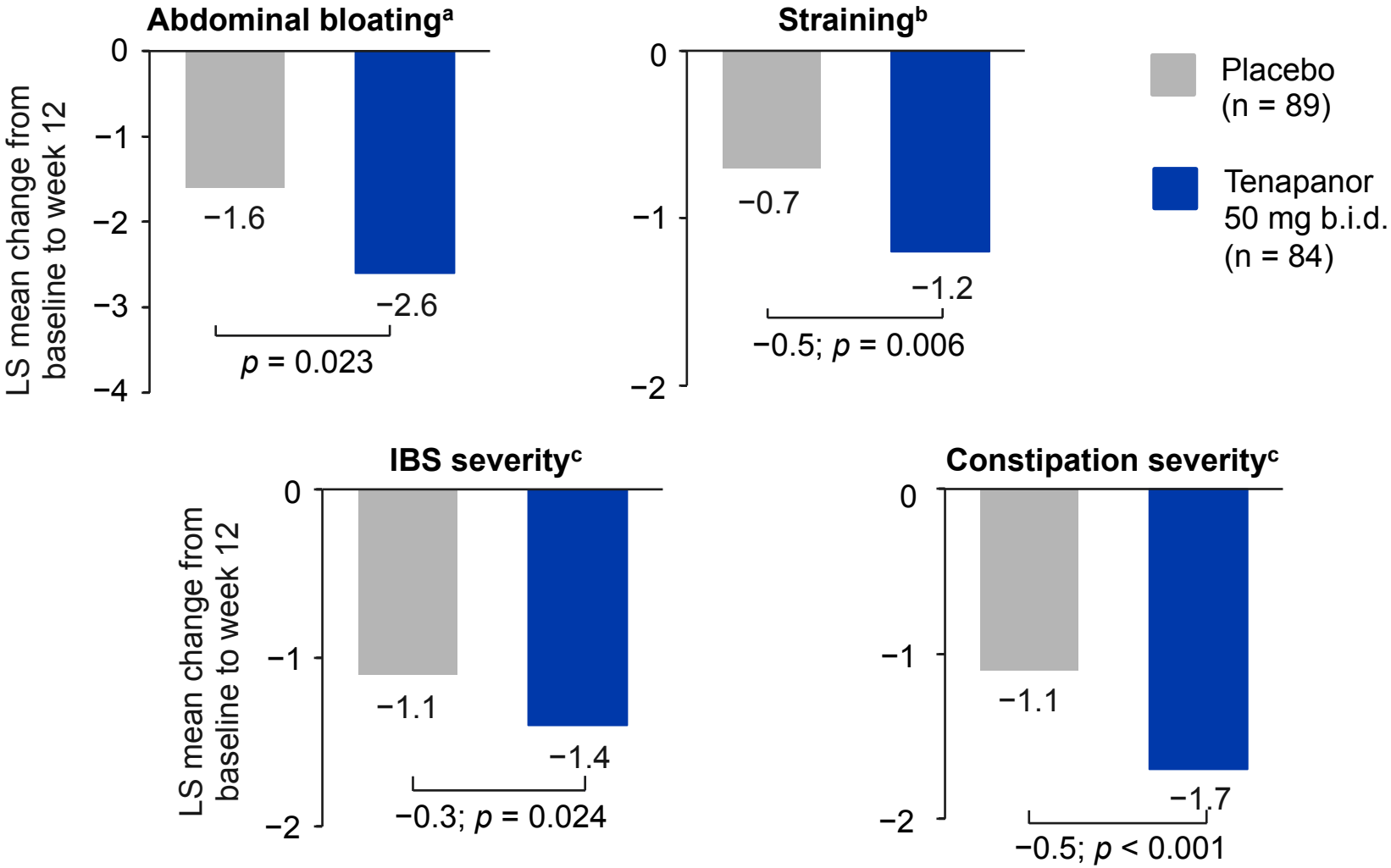


BSFS, Bristol Stool Form Scale; LS, least-squares

[a]Proportion of patients with a ≥ 30% decrease in abdominal pain from baseline for ≥ 6/12 treatment weeks; treatment comparisons versus placebo represent the risk difference

[b]Error bars represent upper limit of 95% confidence interval

Improvements in exploratory endpoints with tenapanor 50 mg b.i.d.



[a]Assessed daily using a 10-point scale: 0 = none to 10 = very severe; average weekly score was calculated from scores for all days during a week
[b]Assessed for each SBM using a 5-point scale: 1 = not at all to 5 = an extreme amount; average weekly straining score calculated from scores for all SBMs during the week
[c]Assessed weekly using a 5-point scale: 1 = none to 5 = very severe

Tenapanor was generally well tolerated and had minimal systemic availability

AE summary, n (%)	Placebo (n = 90)	Tenapanor 5 mg b.i.d. (n = 88)	Tenapanor 20 mg b.i.d. (n = 89)	Tenapanor 50 mg b.i.d. (n = 89)
Any AE	38 (42.2)	43 (48.9)	32 (36.0)	45 (50.6)
Treatment-related AEs	13 (14.4)	22 (25.0)	15 (16.9)	17 (19.1)
Serious AEs	1 (1.1)	2 (2.3)	1 (1.1)	0 (0.0)
AEs leading to discontinuation[a]	3 (3.3)	9 (10.2)	6 (6.7)	4 (4.5)

- Most AEs were mild to moderate in severity and none of the three serious AEs in patients receiving tenapanor were judged to be treatment-related
- No clinically meaningful changes from baseline were reported for clinical laboratory parameters, vital signs, electrocardiographic parameters or physical examination findings
- Tenapanor had minimal to no systemic availability
  - Tenapanor concentrations were below the lower limit of quantification (0.5 ng/mL) in > 97% (283/291) samples (highest concentration measured: 1.03 ng/mL)

AE, adverse event

[a]Most common AEs leading to discontinuation: diarrhea (3 [3.4%] patients each in 5 mg, 20 mg and 50 mg b.i.d. groups), abdominal distension (3 [3.4%] patients in 5 mg b.i.d. group); no other specific AE led to discontinuation in > 2 patients in any treatment group

AEs occurring in ≥ 3% of patients in any tenapanor group and more frequently than in the placebo group

Individual event, n (%)	Placebo (n = 90)	Tenapanor 5 mg b.i.d. (n = 88)	Tenapanor 20 mg b.i.d. (n = 89)	Tenapanor 50 mg b.i.d. (n = 89)
Diarrhea	0 (0.0)	7 (8.0)	11 (12.4)	10 (11.2)
Nausea	1 (1.1)	6 (6.8)	4 (4.5)	3 (3.4)
Abdominal pain	2 (2.2)	7 (8.0)	0 (0.0)	4 (4.5)
Vomiting	0 (0.0)	4 (4.5)	1 (1.1)	2 (2.2)
GERD	1 (1.1)	3 (3.4)	0 (0.0)	1 (1.1)
Abdominal distension	0 (0.0)	3 (3.4)	1 (1.1)	0 (0.0)
Urinary tract infection	4 (4.4)	3 (3.4)	2 (2.2)	5 (5.6)
Influenza	0 (0.0)	2 (2.3)	1 (1.1)	3 (3.4)
Headache	5 (5.6)	6 (6.8)	1 (1.1)	3 (3.4)

GERD, gastroesophageal reflux disease

Conclusions

- Tenapanor 50 mg b.i.d. significantly improved CSBM responder rate (primary endpoint) compared with placebo in patients with IBS-C
- Tenapanor 50 mg b.i.d. also improved key secondary endpoints compared with placebo, including overall responder rate, abdominal pain responder rate and stool frequency
- In addition, improvements were observed in several exploratory endpoints addressing a range of symptoms in patients with IBS-C
- Tenapanor was generally well tolerated and had minimal systemic availability
- Tenapanor shows promise as a future treatment option for patients with IBS-C

Acknowledgments

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