Effect of Tenapanor on Global Endpoints in Patients with IBS-C: Results from a 12-Week, Double-Blind, Placebo-Controlled, Randomized Phase 2b Trial

William D Chey MD, FACG
University of Michigan Gastroenterology

William D Chey,[1] Anthony J Lembo,[2] David Rosenbaum[3]

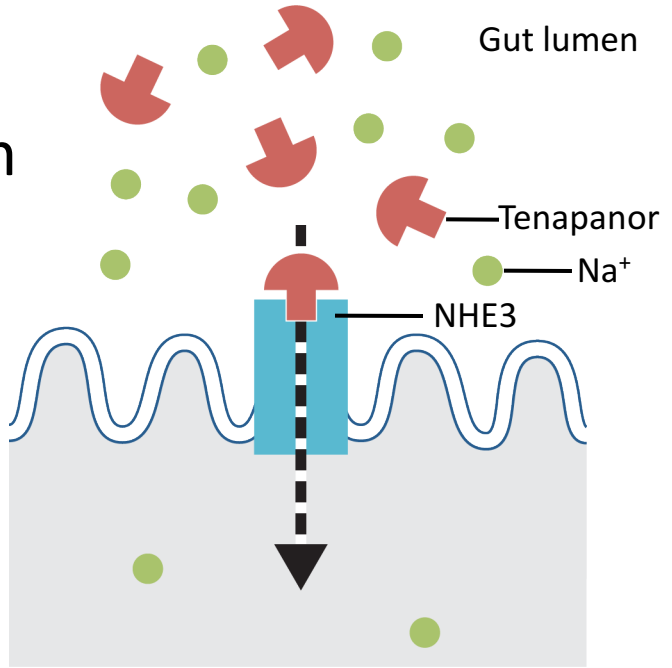
1. University of Michigan Gastroenterology, Ann Arbor, MI, USA; 2. Beth Israel Deaconess Medical Center & Harvard Medical School, Boston, MA, USA; 3. Ardelyx, Inc., Fremont, CA, USA

Role of NHE3 in the Intestine

- Na^+/H^+ exchangers are integral membrane transport proteins
- The Na^+/H^+ exchanger isoform 3 (NHE3) is the major absorptive Na^+/H^+ exchanger in the gut
  - Dominant role in sodium absorption[1]
  - Expression primarily in the stomach, duodenum, jejunum, ileum and proximal colon[2]

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

- Specific for NHE3
- Reduces absorption of dietary sodium and phosphate (via a downstream effect) in preclinical and clinical studies[1–3]
- Potential benefits for patients with IBS-C?



NHE3, sodium/hydrogen (Na^+/H^+) exchanger isoform 3

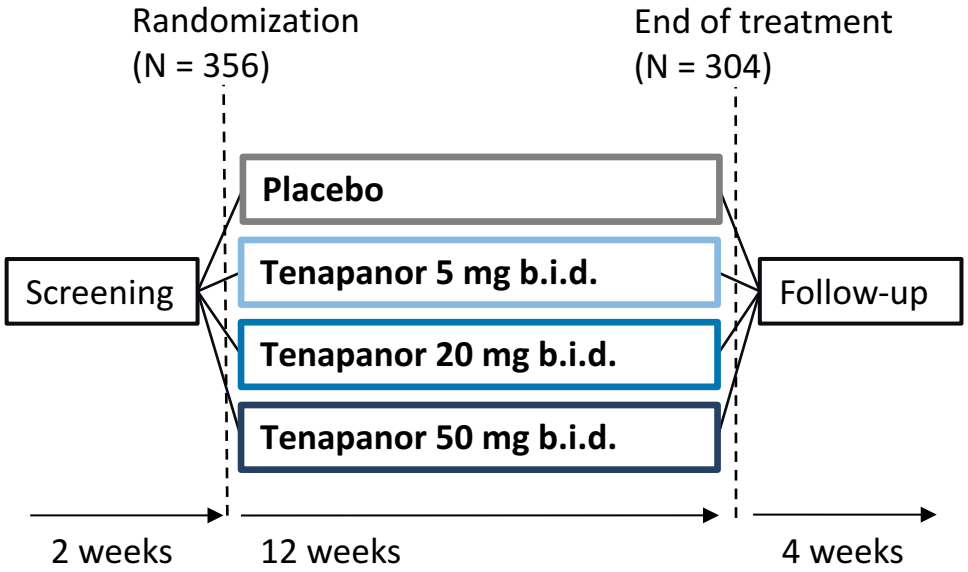
1. Spencer AG *et al. Sci Transl Med* 2014;6:227ra36; 2. Labonté ED *et al. J Am Soc Nephrol* 2015;26:1138–49; 3. Johansson S *et al. Clin Exp Nephrol* 2016; July 1 [Epub ahead of print]

Study Aim

- To assess the efficacy and safety of tenapanor for the treatment of patients with IBS-C when administered as oral b.i.d. doses for 12 consecutive weeks

Study Design

- Main eligibility criteria:
  - IBS-C diagnosis (Rome III criteria)
    - < 3 CSBMs and < 5 SBMs per week
    - Abdominal pain score ≥ 3 (0–10 Likert scale)



CSBM, complete spontaneous bowel movement; SBM, spontaneous bowel movement

ClinicalTrials.gov ID: NCT01923428. Available from: https://clinicaltrials.gov/ct2/show/NCT01923428 (Accessed August 2016)

Main Study Endpoints

Primary endpoint

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

Key secondary endpoints

- Abdominal pain responder rate
  - Proportion of patients with a decrease in abdominal pain of ≥ 30% from baseline for ≥ 6 of 12 treatment weeks
- Overall responder rate
  - Proportion of patients with CSBM response and abdominal pain response in the same week for ≥ 6 of 12 treatment weeks

Results: Patient Baseline Demographics and Disease Characteristics

- 356 patients with IBS-C were randomized, and 304 (85.4%) completed the study
  - 87% women; 93% aged < 65 years (mean 45.7 years); 76% Caucasian

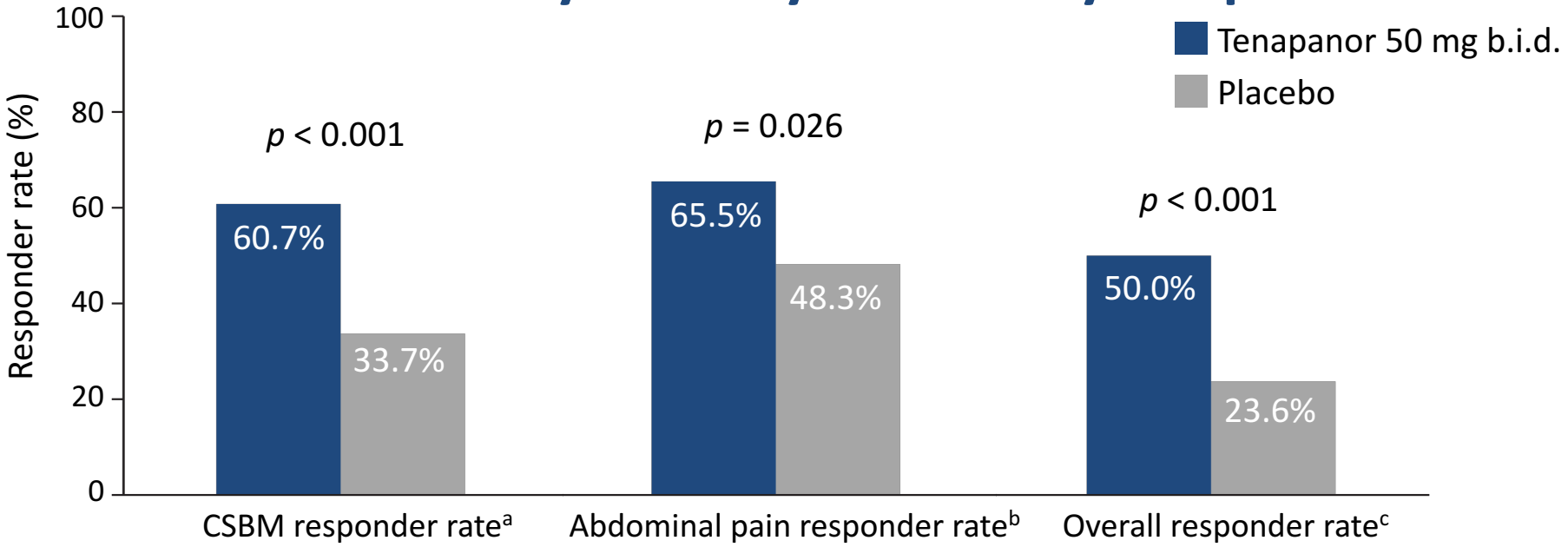
Baseline disease parameter	Tenapanor 5 mg b.i.d. (n = 87)	Tenapanor 20 mg b.i.d. (n = 87)	Tenapanor 50 mg b.i.d. (n = 84)	Placebo (n = 89)
Duration of symptoms (years)	14.7 (13.4)	12.5 (12.0)	13.3 (12.7)	14.1 (13.6)
Number of CSBMs per week	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)
Number of SBMs per week	1.9 (1.3)	1.9 (1.1)	2.0 (1.3)	2.0 (1.2)
IBS severity[a]	3.9 (0.7)	3.9 (0.8)	3.8 (0.7)	3.8 (0.7)
Constipation severity[a]	4.2 (0.6)	4.0 (0.7)	4.0 (0.8)	4.1 (0.7)
Abdominal pain[b]	6.1 (1.6)	6.3 (1.5)	6.0 (1.5)	6.1 (1.5)

Data are mean (standard deviation)

[a]Assessed weekly using a 5-point scale: 1 = none, 5 = very severe. [b]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

Chey *et al*. *Gastroenterology* 2015;148(Suppl. 1):S191–2

Results: Primary and Key Secondary Endpoints



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

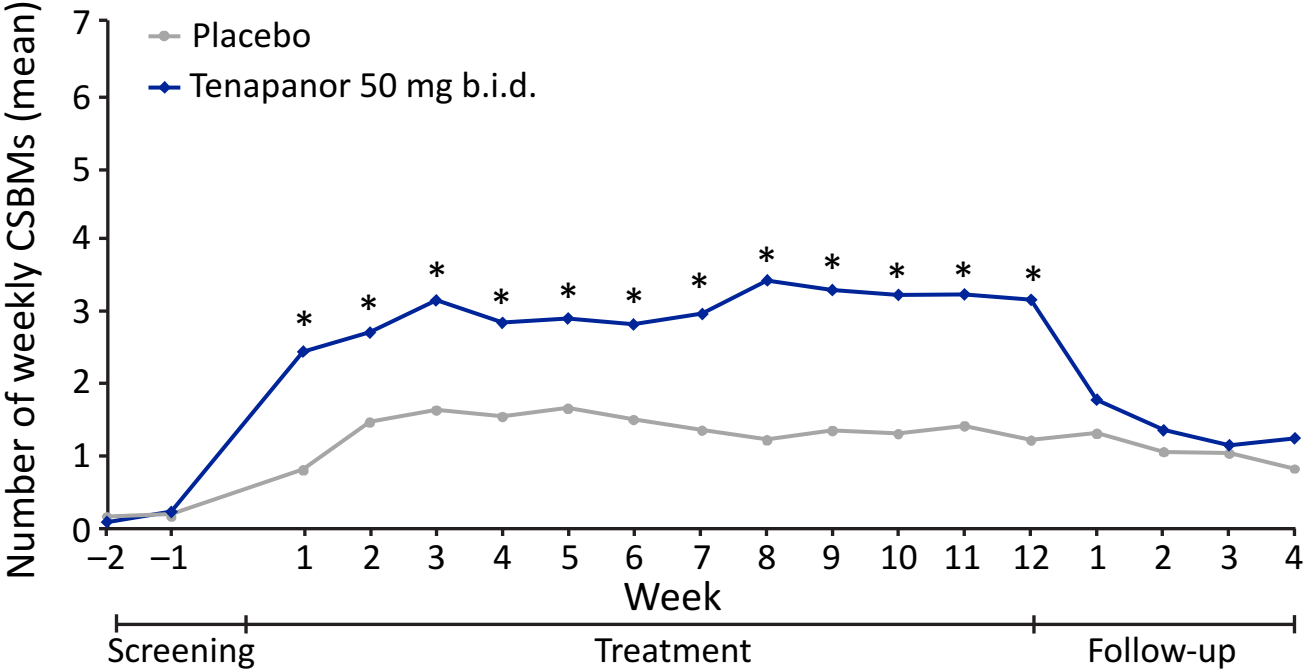
[a]Increase of at least 1 CSBM from baseline in a given week for at least 6 of 12 weeks

[b]Decrease of at least 30% mean worst abdominal pain from baseline in a given week for at least 6 of 12 weeks

[c]CSBM responder and abdominal pain responder in the same week for at least 6 of 12 weeks

Chey *et al*. *Gastroenterology* 2015;148(Suppl. 1):S191–2

Results: Weekly Rates of Complete Spontaneous Bowel Movements



Cochran–Mantel–Haenzel test, stratified by pooled investigator site

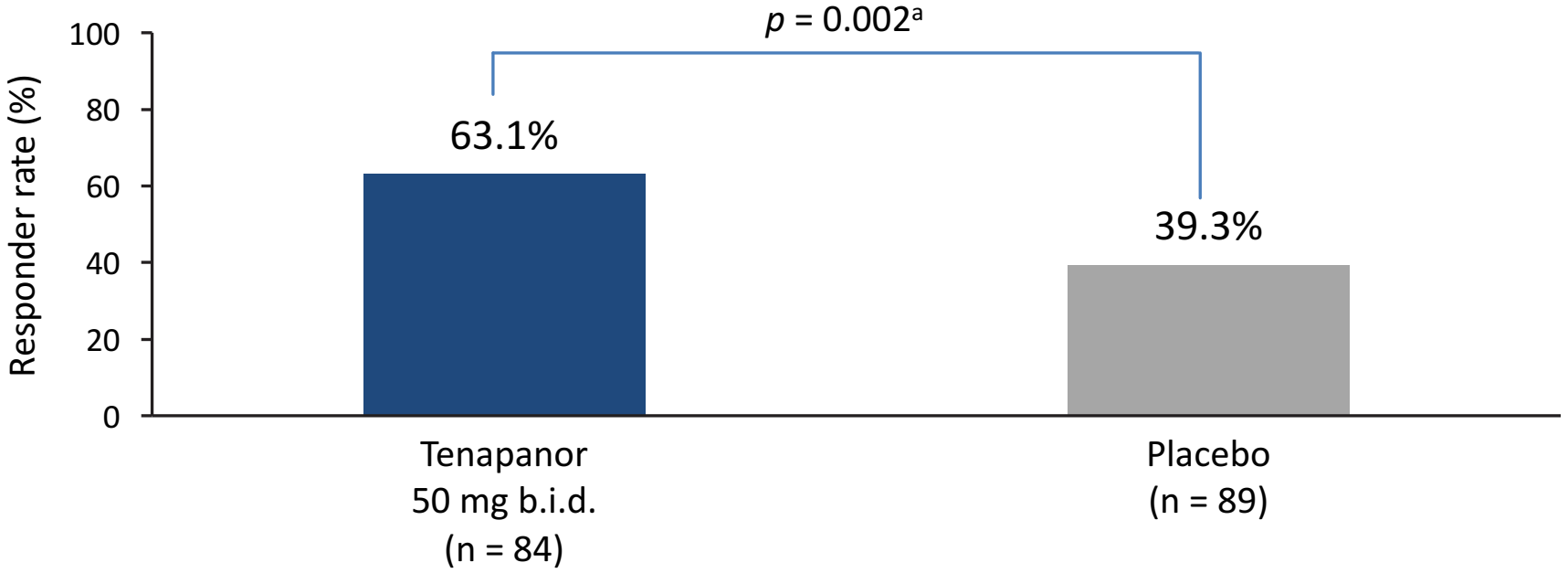
*$p < 0.05$, tenapanor 50 mg b.i.d. vs placebo

Chey *et al*. *Gastroenterology* 2015;148(Suppl. 1):S191–2

Global Efficacy Endpoints

- Adequate IBS symptom relief (yes/no)
- IBS severity (5-point scale)
- Constipation severity (5-point scale)
- Degree of IBS symptom relief (7-point scale)
- Treatment satisfaction (5-point scale)

Responder Rate for Adequate Relief of IBS Symptoms with Tenapanor after 12 Weeks



Adequate relief of IBS symptoms (yes/no) assessed weekly during the 12-week treatment period and the 4-week follow-up period

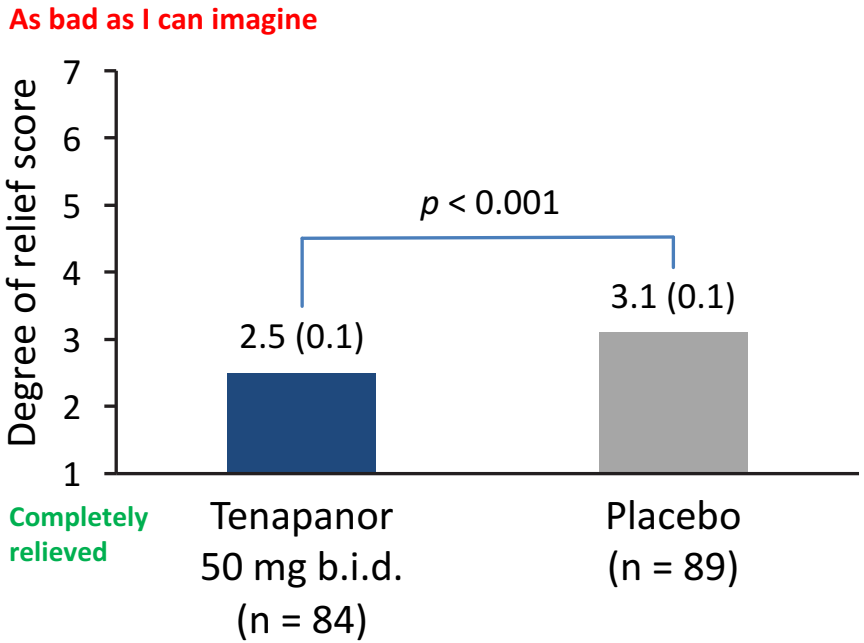
[a]Cochran–Mantel–Haenzel test, stratified by pooled investigator site

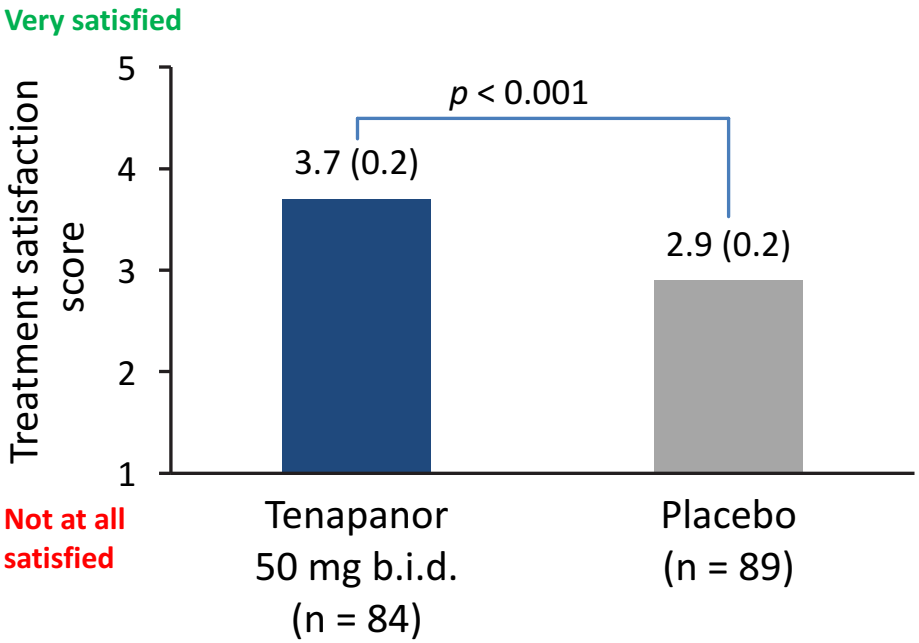
Improvements in IBS Severity and Constipation Severity Scores with Tenapanor after 12 Weeks

Endpoint (intention-to-treat analysis)	Tenapanor 50 mg b.i.d. (n = 84)	Placebo (n = 89)	*p* value
Baseline IBS severity	3.8 (0.7)	3.8 (0.7)	–
Change from baseline	−1.4 (1.2)	−1.0 (1.1)	0.024
Baseline constipation severity	4.0 (0.8)	4.1 (0.7)	–
Change from baseline	−1.6 (1.1)	−1.2 (1.1)	< 0.001

Analysis of covariance with terms for treatment group, pooled investigator site and baseline score as covariates
Data are mean (standard deviation)
IBS severity and constipation severity were assessed weekly using an interactive voice-response system diary
Both assessed using a 5-point scale: 1 = none, 5 = very severe

Degree of Relief and Treatment Satisfaction Scores were Better with Tenapanor than Placebo after 12 Weeks





Analysis of variance with terms for treatment group and pooled investigator site
Data are shown as least-squares means (standard error)
Degree of relief score assessed at week 12 using a 7-point scale
Treatment satisfaction score assessed at week 12 using a 5-point scale

Take-Home Points

- In patients with IBS-C, treatment with tenapanor 50 mg b.i.d. produced statistically and clinically significant improvements in:
  - responder rates (number of CSBMs per week, abdominal pain, overall response)
  - important global efficacy endpoints
    - adequate relief of IBS symptoms
    - IBS and constipation severity
    - degree of relief of IBS symptoms and treatment satisfaction
- Results from this phase 2b trial justify phase 3 trials with tenapanor 50 mg b.i.d. in patients with IBS-C
  - T3MPO-1 (12 weeks)[1] and T3MPO-2 (6 months)[2]

1. ClinicalTrials.gov ID: NCT02621892. Available from: https://clinicaltrials.gov/ct2/show/NCT02621892 (Accessed August 2016);
2. ClinicalTrials.gov ID: NCT02686138 Available from: https://clinicaltrials.gov/ct2/show/NCT02686138 (Accessed August 2016)

Acknowledgments

- We would like to thank the patients and their physicians who participated in the study
- We also thank Ardelyx, Inc. for supporting the study
- PharmaGenesis London, London, UK provided editorial assistance with this presentation, which was funded by Ardelyx