Plecanatide Improves Abdominal Symptoms in Individuals With Irritable Bowel Syndrome With Constipation and Chronic Idiopathic Constipation, Including Those Experiencing Severe Bloating, Pain, and Discomfort

P2482

Gregory S. Sayuk, MD, MPH[1,2,3]; Amy Kassebaum-Ladewski, PA-C[4]; Sarah M. Lorenzen, PhD[5]*; Darren M. Brenner, MD[6]

[1]Division of Gastroenterology, Washington University School of Medicine, St. Louis, MO, USA; [2]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA; [3]Gastroenterology Section, John Cochran Veterans Affairs Medical Center, St. Louis, MO, USA; [4]Digestive Health Center, Northwestern Memorial Hospital, Chicago, IL, USA; [5]Salix Pharmaceuticals, Inc., Bridgewater, NJ, USA; [6]Internal Medicine–Gastroenterology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; *Former employee.

INTRODUCTION

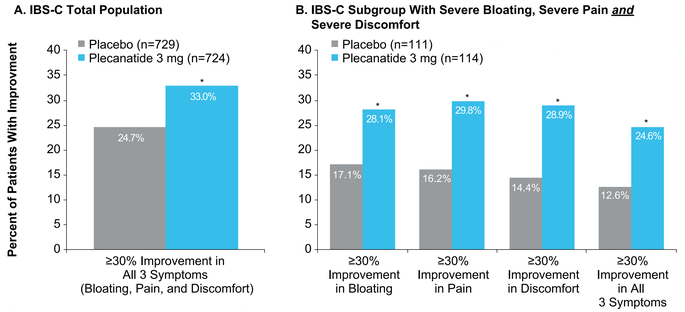
- Irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) are bothersome disorders of gut-brain interaction commonly associated with varying degrees of abdominal symptoms.[1]
  - The estimated prevalence of Rome IV-defined IBS in the U.S. is 4.7%, with approximately one-third being IBS-C; 6.9% of the U.S. population is affected with CIC.[2]
- Abdominal pain, discomfort, and bloating are bothersome symptoms commonly experienced by patients with IBS-C and CIC.[3-5]
  - IBS-C and CIC are regarded by some to be constipation disorders along an abdominal pain continuum, rather than distinct conditions.[2]
- Plecanatide is a U.S. Food and Drug Administration approved locally acting structural analogue of human uroguanylin for the treatment of adults with IBS-C and CIC.[6,7]
- Plecanatide activates guanylate cyclase-C (GC-C) receptors, leading to cyclic guanosine monophosphate (cGMP) production.
  - The resulting increase in intracellular levels of cGMP promote fluid secretion into the intestinal lumen, which increases stool water content and bowel movement frequency, potentially alleviating bowel symptoms.[6]
  - Preclinical trials have also indicated that GC-C receptor activation with plecanatide may reduce the activity of visceral nociceptive neurons,[8] thereby reducing visceral pain.
- This post hoc analysis evaluates the impact of plecanatide on the combination of pain, discomfort, and bloating in patients with IBS-C and CIC including those with severe abdominal symptoms at baseline.

METHODS

- Data from four multicenter, double-blind, placebo-controlled phase 3 trials in IBS-C (NCT02387359, NCT02493452) and CIC (NCT01982240, NCT02122471)[9-11] were pooled (separately for each indication).
  - In the original studies, adults meeting Rome III criteria for IBS-C or CIC were randomized to once-daily plecanatide 3 mg or 6 mg (data not shown), or placebo.
- Patients recorded the number of bowel movements and their characteristics daily in electronic diaries throughout the 12-week treatment period.
  - Abdominal symptoms (bloating, pain, and discomfort) were rated using an 11-point numeric rating scale (0=none; 10=worst possible) in IBS-C studies and a 5-point Likert scale (0=none; 4=very severe) in CIC studies.
- Outcomes across all studies included changes from baseline to Week 12 in abdominal bloating, pain, and discomfort.
  - A post hoc analysis was conducted calculating the percent of abdominal symptom responders, defined as patients with ≥30% improvement in all three abdominal symptoms at Week 12, consistent with the threshold used for the FDA-recommended co-primary endpoint related to pain.
  - Covariance of changes from baseline to Week 12 in bloating, pain, and discomfort were calculated using Pearson correlation coefficients.
  - The strength of the correlation was interpreted using the following criteria[12]: ±0.00–0.09, negligible; ±0.10–0.39, weak; ±0.40–0.69, moderate; ±0.70–0.89, strong; ±0.90–1.00, very strong.
- A separate subgroup analysis was conducted in those patients reporting severe bloating, pain, and discomfort at baseline. Severe abdominal symptoms were defined as a baseline score of ≥8 (IBS-C) and ≥3 (CIC) for each symptom.
- 1453 patients with IBS-C and 1762 patients with CIC comprised the pooled intention-to-treat population, including 225 (plecanatide, n=114; placebo, n=111) and 179 (plecanatide, n=80; placebo, n=99), respectively, with severe abdominal symptoms.

RESULTS

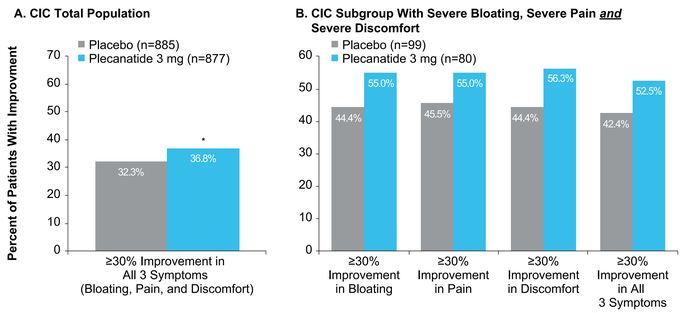
Figure 1. Patients With IBS-C Experiencing a ≥30% Improvement at Week 12 in Abdominal Symptoms (Bloating, Pain, and Discomfort) in (A) Total Population and (B) Severe Subgroup



*P<0.05 vs placebo. Analyses in Panel B conducted in patients with IBS-C reporting all three symptoms (i.e., bloating, pain, and discomfort) as severe (i.e., score ≥8) at baseline. IBS-C, irritable bowel syndrome with constipation.

- Significantly more plecanatide-treated patients in the total IBS-C population were abdominal symptom responders (Figure 1A).
- Significantly more IBS-C plecanatide-treated patients in the subgroup with severe baseline abdominal symptoms experienced ≥30% improvement at Week 12 in bloating, pain, discomfort (both individually and in combination; Figure 1B).

Figure 2. Patients With CIC Experiencing a ≥30% Improvement at Week 12 in Abdominal Symptoms (Bloating, Pain, and Discomfort) in (A) Total Population and (B) Severe Subgroup



*P<0.05 vs placebo (x^2 test). Analyses in Panel B conducted in patients with CIC reporting all three symptoms (i.e., bloating, pain, and discomfort) as severe (i.e., score ≥3) at baseline. CIC, chronic idiopathic constipation.

- Significantly more plecanatide-treated patients in the total CIC population were abdominal symptom responders (Figure 2A).
- Over half of plecanatide-treated CIC patients in the subgroup with severe baseline abdominal symptoms experienced ≥30% improvement at Week 12 in bloating, pain, discomfort, and all three symptoms simultaneously (Figure 2B).
  - Rates of improvement were numerically but not statistically significantly greater with plecanatide compared with placebo.

Table 1. Relationships Between Changes in Pain, Bloating, and Discomfort at Week 12 in Patients With IBS-C

Variables		Pearson Correlation Coefficient: Total Population	Pearson Correlation Coefficient: Subgroup Population
Pain	Bloating	0.853	0.917
Discomfort	Bloating	0.891	0.929
Discomfort	Pain	0.924	0.955

All treatment arms pooled for analysis. Subgroup analyses were conducted in patients with IBS-C reporting all three symptoms (i.e., bloating, pain, and discomfort) as severe (i.e., score ≥8) at baseline. IBS-C, irritable bowel syndrome with constipation.

- Week 12 changes from baseline in pain, bloating, and discomfort were very strongly correlated with each other in both the total IBS-C population and subgroup of IBS-C patients with severe abdominal symptoms at baseline (Table 1).

Table 2. Relationships Between Changes in Pain, Bloating, and Discomfort at Week 12 in Patients With CIC

Variables		Pearson Correlation Coefficient: Total Population	Pearson Correlation Coefficient: Subgroup Population
Pain	Bloating	0.853	0.948
Discomfort	Bloating	0.883	0.968
Discomfort	Pain	0.819	0.958

All treatment arms pooled for analysis. Subgroup analyses were conducted in patients with CIC reporting all three symptoms (i.e., bloating, pain, and discomfort) as severe (i.e., score ≥3) at baseline. CIC, chronic idiopathic constipation.

- For patients with CIC, Week 12 changes from baseline in pain, bloating, and discomfort were strongly correlated with each other in both the total population and subgroup of patients with severe abdominal symptoms at baseline (Table 2).

KEY FINDINGS

- This post hoc analysis of four clinical studies in IBS-C and CIC revealed that significantly greater percentages of plecanatide-treated patients in the total populations experienced a ≥30% improvement in a composite responder endpoint of abdominal pain, bloating, and discomfort compared with placebo after 12 weeks of treatment.
- In patients with IBS-C who rated their baseline abdominal pain, bloating, and discomfort as severe, plecanatide treatment resulted in significantly greater percentages of patients experiencing ≥30% improvement in each individual symptom and all three symptoms combined compared with placebo.
- For patients with CIC and severe baseline abdominal symptoms, responder rates for individual and combined abdominal symptoms were numerically larger than placebo.
  - The studies included were not powered to analyze the cohorts of patients with severe abdominal symptoms. While the proportion of responders and differences in response between those receiving plecanatide or placebo in the CIC studies were comparable to previous findings, the lack of statistical significance may have been a result of type II error.
- Changes in each abdominal symptom highly correlated with the others, suggesting that generalized visceral hypersensitivity (central or peripheral), or perhaps patient symptom reporting are important factors underlying severity of abdominal symptoms.

References

1. Heidelbaugh JJ, Stelwagon M, Miller SA, Shea EP, Chey WD. *Am J Gastroenterol.* 2015;110(4):580-587.
2. Palsson OS, Whitehead W, Törnblom H, Sperber AD, Simren M. *Gastroenterology.* 2020;158(5):1262-1273.e1263.
3. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology.* 2016;150(6):1393-1407.e1395.
4. Higgins PD, Johanson JF. *Am J Gastroenterol.* 2004;99(4):750-759.
5. Hungin AP, Chang L, Locke GR, Dennis EH, Barghout V. *Aliment Pharmacol Ther.* 2005;21(11):1365-1375.
6. Sharma A, Herekar AA, Bhagatwala J, Rao SS. *Clin Exp Gastroenterol.* 2019;12:31-36.
7. Menees SB, Franklin H, Chey WD. *Clin Ther.* 2020 Jul;42(7):1406-1414.e4.
8. Boulete IM, Thadi A, Beaufrand C, et al. *World J Gastroenterol.* 2018;24(17):1888-1900.
9. Brenner DM, Fogel R, Dorn SD, et al. *Am J Gastroenterol.* 2018;113(5):735-745.
10. Miner Jr PB, Koltun WD, Wiener GJ, et al. *Am J Gastroenterol.* 2017;112(4):613-621.
11. DeMicco M, Barrow L, Hickey B, Shailubhai K, Griffin P. *Therap Adv Gastroenterol.* 2017;10(11):837-851.
12. Schober P, Boer C, Schwarte LA. *Anesth Analg.* 2018;126(5):1763-1768.

Disclosures

Gregory S. Sayuk is a consultant and speaker for AbbVie/Ironwood Pharmaceuticals, Alnylam, and Salix Pharmaceuticals, and a consultant for the GI Health Foundation. Amy Kassebaum-Ladewski is a consultant for Salix Pharmaceuticals and AbbVie/Ironwood Pharmaceuticals, and a speaker for Takeda Pharmaceuticals. Sarah M. Lorenzen was an employee at Salix Pharmaceuticals at the time of analysis. Darren M. Brenner is a consultant and speaker for Salix Pharmaceuticals and for AbbVie/Ironwood Pharmaceuticals.

Acknowledgements

Funding for this study and poster support was provided by Salix Pharmaceuticals, Inc. (Bridgewater, NJ, USA). Medical writing and editorial support were provided by The Medicine Group, LLC (New Hope, PA, USA), in accordance with Good Publication Practice guidelines.

This poster was funded by Salix Pharmaceuticals.