Plecanatide for Patients with Chronic Idiopathic Constipation and Irritable Bowel Syndrome–Constipation: Analysis of Symptoms' Responses by Baseline Bloating Severity from Four Randomized Phase 3 Clinical Trials

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Sa1720
Presented at the Digestive Disease Week 2020; May 2-5, 2020; Chicago, IL

BACKGROUND

- Patients with chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C) often report bloating as a predominant symptom.[1]
- Abdominal bloating is associated with reduced physical and mental quality of life; patients with bloating have higher healthcare costs than do patients without bloating.[2]
- Many treatments for CIC and IBS-C have limited efficacy in relieving bloating symptoms.[3]
- Plecanatide is an analogue of human uroguanylin that acts as a guanylyl cyclase-C (GC-C) agonist. The 3 mg dose is approved for the treatment of CIC and IBS-C.[4,5]
- Plecanatide has previously demonstrated efficacy and safety in two large-scale phase 3 studies enrolling patients with CIC[6,7] and in two large-scale phase 3 IBS-C studies,[5] including improvements in stool frequency and consistency, the completeness of evacuation, and reductions in straining and bloating.
  - In the IBS-C studies, significant improvements in bloating severity were evident in patients treated with plecanatide by the end of week 1; improvements versus placebo were maintained throughout all 12 treatment weeks.[5] Significant improvements over the 12-week period were also observed in patients with CIC.[6,7]

OBJECTIVE

- The objective of this post hoc analysis is to determine the efficacy of plecanatide on bloating and the impact of treatment on other gastrointestinal symptoms in patients with more severe bloating at baseline.

METHODS

- All four trials were multicenter, double-blind, randomized, placebo-controlled phase 3 studies (CIC, NCT01982240 and NCT02122471; IBS-C, NCT02387359 and NCT02493452).
- Patients meeting modified Rome III criteria for CIC and IBS-C were randomized to once-daily placebo, plecanatide 3 mg, or plecanatide 6 mg for 12 weeks. Participants utilized a daily electronic diary throughout pretreatment, treatment (12 weeks), and posttreatment (2 weeks) periods.
- The primary endpoints for the two CIC and two IBS-C studies were consistent with current FDA-recommended guidance standards.
- Electronic diaries were used to record daily bloating in CIC (Likert Scale; 0=none to 4=very severe) and IBS-C (Numeric Rating Scale [NRS]; 0=none to 10=worst possible).
- For this analysis, patients with CIC were stratified by those who experienced bloating at baseline and those who did not, defined as minimal (<1) or more severe bloating (≥1). For the IBS-C population, patients were stratified by severity defined as minimal (≤5) or more severe bloating (>5) at baseline.
- The pooled population analyses are based on unique patients who were randomized to receive study drug (intention-to-treat [ITT]–efficacy population, excluding duplicates) during the treatment period of the phase 3 studies.

RESULTS

Table 1. Demographics and Clinical Characteristics of CIC and IBS-C Patients With More Severe Abdominal Bloating at Baseline

	CIC (≥1 (0-4 Likert Scale))			IBS-C (>5 (0-10 Numeric Rating Scale))		
	Placebo (n = 761)	Plecanatide 3 mg (n = 739)	Plecanatide 6 mg (n = 761)	Placebo (n = 541)	Plecanatide 3 mg (n = 559)	Plecanatide 6 mg (n = 533)
Age (years), mean (SD)	45.7 (14.0)	45.4 (14.3)	45.5 (13.9)	43.2 (14.2)	43.7 (13.7)	42.8 (13.5)
Female, n (%)	601 (79.0)	593 (80.2)	626 (82.3)	410 (75.8)	417 (74.6)	406 (76.2)
Race, n (%)						
White/Caucasian	553 (72.7)	531 (71.9)	550 (72.3)	405 (74.9)	421 (75.3)	392 (73.5)
Black/African American	171 (22.5)	178 (24.1)	176 (23.1)	121 (22.4)	117 (20.9)	126 (23.6)
Asian	21 (2.8)	17 (2.3)	18 (2.4)	9 (1.7)	14 (2.5)	11 (2.5)
Other	15 (2.1)	13 (1.8)	17 (2.2)	6 (1.2)	7 (1.3)	4 (0.8)
Ethnicity, n (%)						
Hispanic or Latino	319 (41.9)	290 (39.2)	310 (40.7)	289 (53.4)	293 (52.4)	283 (53.1)
Non-Hispanic or Latino	442 (58.1)	449 (60.8)	451 (59.3)	252 (46.6)	266 (47.6)	250 (46.9)
Body mass index (kg/m^2), mean (SD)	28.1 (5.22)	28.4 (4.99)	28.2 (5.05)	28.1 (4.79)	28.5 (4.68)	28.3 (5.02)

- A total of N = 2639 patients with CIC and N = 2176 patients with IBS-C met modified Rome III criteria and were included in the ITT population excluding duplicates.
- At baseline, 86.1% and 76.1% of individuals in the CIC and IBS-C populations, respectively, reported bloating. Demographics and baseline characteristics for patients reporting bloating at baseline are presented in Table 1.

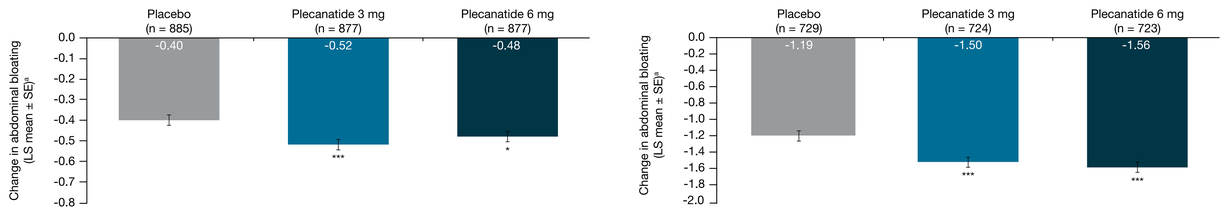
Table 2. Impact of Treatment on Gastrointestinal Symptoms in CIC and IBS-C With More Severe Abdominal Bloating at Baseline

	CIC (≥1 (0-4 Likert Scale) N=2261)			IBS-C (>5 (0-10 Numeric Rating Scale) N=1633)		
	Placebo (n = 761)	Plecanatide 3 mg (n = 739)	Plecanatide 6 mg (n = 761)	Placebo (n = 541)	Plecanatide 3 mg (n = 559)	Plecanatide 6 mg (n = 533)
Responders[a], n (%)	85 (11.1)	146 (19.7)	140 (18.4)	85 (15.6)	136 (24.3)	136 (25.5)
P value vs PB		<0.001	<0.001		<0.001	<0.001
Straining Baseline, mean (SD)	2.44 (0.80)	2.52 (0.77)	2.50 (0.83)	7.20 (1.68)	7.16 (1.64)	7.34 (1.60)
LS Mean Change (Wk 12)	–0.76	–1.04	–1.02	–1.85	–2.54	–2.66
Change from PB		–0.28	–0.26		–0.68	–0.81
P value vs PB		<0.001	<0.001		<0.001	<0.001
Abdominal Pain Baseline, mean (SD)	1.81 (0.99)	1.82 (0.96)	1.89 (1.02)	6.88 (1.45)	6.80 (1.47)	6.91 (1.45)
LS Mean Change (Wk 12)	–0.58 (0.03)	–0.70 (0.03)	–0.69 (0.03)	–1.70	–2.09	–2.27
Change from PB	n/a	–0.11	–0.11		–0.40	–0.57
P value vs PB		0.005	0.008		0.002	<0.001

[a]For CIC the percentage of durable overall CSBM responders was defined as patients experiencing ≥3 CSBMs/week and an increase from baseline of ≥1 CSBM during the same week for ≥9 of 12 treatment weeks inclusive of at least 3 of the last 4 weeks of the study. For IBS-C the overall responder rate was defined as a patient who was a weekly responder (≥1 CSBM/week increase from baseline plus ≥30% improvement in abdominal pain) for at least 6 of the 12 treatment weeks. CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement; IBS-C, irritable bowel syndrome with constipation; LS, least squares; PB, placebo; SD, standard deviation; Wk, week.

- Pooled efficacy analyses for CIC demonstrated a significantly greater percentage of CSBM responders in each of the plecanatide groups when compared to the placebo group in patients reporting more severe bloating at baseline (Table 2).
- Similarly, both plecanatide 3 mg and 6 mg resulted in a significantly greater percentage of overall responders than did placebo in the IBS-C studies irrespective of baseline bloating score (bloating ≤5, $P \leq 0.009$; bloating >5, $P < 0.001$).
- Significant improvements in straining and abdominal pain were observed in both doses of plecanatide-treated patients with CIC and IBS-C and more severe bloating at baseline (Table 2).
- In the minimal bloating CIC and IBS-C groups, significant improvements from baseline compared to placebo were reported in all plecanatide groups for overall CSBM responder rate (CIC) and overall responder rate (IBS-C). Decreases in straining and abdominal pain trended towards significance.

Figure 1. Change in Bloating Score in Patients with (A) CIC and (B) IBS-C Receiving Placebo or Plecanatide (full ITT population excluding duplicates)



*P <0.05, ***P <0.001 vs placebo. CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; LS, least squares; SE, standard error. [a]Change from baseline is the overall average estimate across the 12-week treatment period. Outcomes were compared using pairwise comparisons of least squares means between the specified treatment group and the placebo group using a linear mixed-effects model with fixed effects for gender (stratification variable), baseline value, treatment, week, the interaction of treatment and week, and a random intercept for patient.

- Significantly greater reductions in weekly mean abdominal bloating scores were identified in favor of plecanatide 3 mg and 6 mg compared to placebo in both the CIC (difference from placebo –0.12, –0.08; P <0.001, P = 0.012, respectively, Figure 1A) and IBS-C cohorts (difference from placebo, –0.31, –0.37; P <0.001 for both, respectively, Figure 1B) over the 12-week treatment period.

DISCUSSION

- Plecanatide (3 mg and 6 mg) significantly reduced abdominal bloating across the 12-week treatment period in both CIC and IBS-C.
- Plecanatide (3 mg and 6 mg) significantly improved the percentage of overall CSBM responders (CIC) and overall responders (IBS-C) compared to placebo, irrespective of bloating severity at baseline.
- Abdominal pain and straining significantly improved with plecanatide treatment in CIC and IBS-C patients reporting more severe bloating at baseline.

References

1. Shah ED, Almario CV, Spiegel BMR, Chey WD. *J Neurogastroenterol Motil*. 2018;24(2):299-306.
2. Ringel Y, Williams RE, Kalilani L, Cook SF. *Clin Gastroenterol Hepatol*. 2009;7(1):68-72; quiz 63.
3. Furnari M, de Bortoli N, Martinucci I, et al. *Ther Clin Risk Manag*. 2015;11:691-703.
4. Rao SSC. *Therap Adv Gastroenterol*. 2018;11:1756284818777945.
5. Brenner DM, Fogel R, Dorn SD, et al. *Am J Gastroenterol*. 2018;113(5):735-745.
6. DeMicco M, Barrow L, Hickey B, Shailubhai K, Griffin P. *Therap Adv Gastroenterol*. 2017;10(11):837–851.
7. Miner Jr PB, Koltun WD, Wiener GJ, et al. *Am J Gastroenterol*. 2017;112(4):613–621.

Disclosures: D. Brenner is a consultant and speaker for Salix Pharmaceuticals, Inc. and is supported in research by a gift from the IDP Foundation. A. Sharma served on Advisory Boards for Ironwood & Salix Pharmaceuticals, Inc. R. Patel is an employee and stockholder at Bausch Health. G.S. Sayuk is a consultant and speaker for Salix Pharmaceuticals, Inc., and for Allergan/Ironwood Pharmaceuticals, and is a consultant for the GI Health Foundation.

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

This poster was funded by Salix Pharmaceuticals.