Efficacy of Plecanatide in Bloated Patients With Chronic Idiopathic Constipation and Moderate to Severely Bloated Patients With Irritable Bowel Syndrome With Constipation

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BACKGROUND

- Abdominal bloating is a common and bothersome symptom of chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C).[1-3]
- Clinicians recognize CIC and IBS-C patients with bloating as particularly challenging to treat, and 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 guanylate cyclase-C (GC-C) agonist. GC-C receptor activation by plecanatide may modulate pain and decrease hypersensitivity in the gut.[4] The 3 mg dose is approved for the treatment of CIC and IBS-C.[5,6]
- Plecanatide has demonstrated efficacy and safety in four large-scale phase 3 studies (two in CIC[7,8] and two in IBS-C[6]), including improvements in stool frequency and consistency, the completeness of evacuation, and reductions in 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.[6] Significant improvements over the 12-week period were also observed in patients with CIC.[7,8]

OBJECTIVE

- The objective of this post hoc analysis is to examine treatment outcomes in patient populations with any bloating (CIC) and moderate to severe bloating (IBS-C) 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.
- Daily bloating and pain scores were recorded electronically using a Likert scale in CIC (0=none to 4=very severe) and numeric rating scale in IBS-C (0=none to 10=worst possible).
- Patients with any bloating (CIC, ≥1) and moderate to severe baseline bloating (IBS-C, >5) were evaluated.

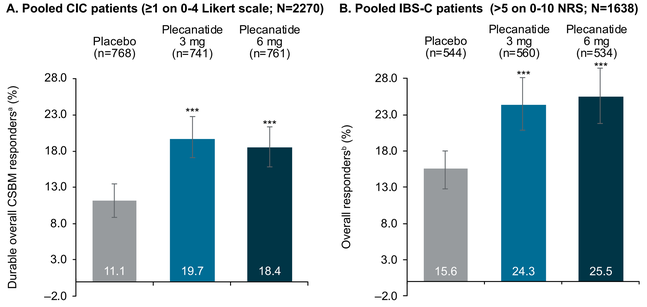
RESULTS

Table 1. Demographics and Clinical Characteristics of CIC Patients With Any Bloating and IBS-C Patients With Moderate to Severe Abdominal Bloating at Baseline (Safety)

	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)

- Demographics and baseline characteristics for patients in the safety population are presented in Table 1.
- A total of 2639 patients with CIC and 2176 patients with IBS-C met modified Rome III criteria and were included in the ITT population excluding duplicates.
- **At baseline, 86% (n=2270) of patients with CIC reported bloating and 75% (n=1638) of patients with IBS-C met criteria for moderate to severe bloating.**

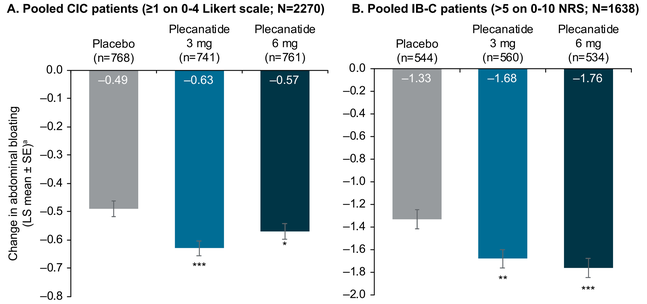
Figure 1. Impact of Plecanatide on (A) Percentage of Overall Durable CSBM Responders (CIC With Any Baseline Bloating) and (B) Overall Responder Rate (IBS-C With Moderate to Severe Baseline Bloating) (ITT)



***P<0.001 vs placebo. [a]Defined as ≥3 CSBMs/week and ≥1 CSBM increase from baseline for at least 9/12 weeks including 3 of the last 4 weeks. [b]Defined as ≥1 CSBM/week increase from baseline plus ≥30% improvement in abdominal pain for at least 6/12 weeks. CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement; IBS-C, irritable bowel syndrome with constipation; NRS, numeric rating scale. Error bars indicate 95% confidence intervals.

- Plecanatide-treated patients demonstrated significant improvements in primary efficacy endpoints compared to placebo (ie, percentage of CSBM responders in CIC and percentage of overall responders in IBS-C; Figure 1).

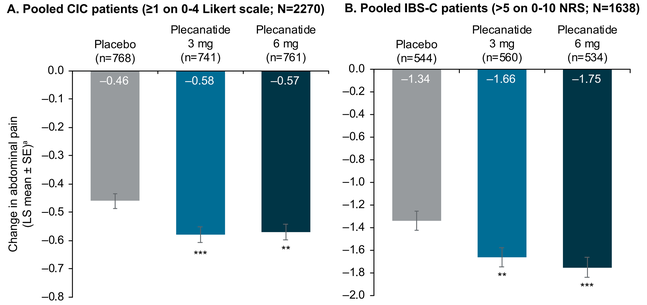
Figure 2. Change in Abdominal Bloating Score in Patients With (A) CIC With Any Baseline Bloating and (B) IBS-C With Moderate to Severe Baseline Bloating (ITT)



*P<0.05, **P<0.01, ***P<0.001 vs placebo. CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; LS, least squares; NRS, numeric rating scale; SE, standard error.
[a]Change from baseline is the overall average estimate across the 12-week treatment period.

- 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 and IBS-C cohorts over the 12-week treatment period (Figure 2).

Figure 3. Change in Abdominal Pain Score in Patients With (A) CIC With Any Baseline Bloating and (B) IBS-C With Moderate to Severe Baseline Bloating (ITT)



**P<0.01; ***P<0.001 vs placebo. CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; LS, least squares; NRS, numeric rating scale; SE, standard error.
[a]Change from baseline is the overall average estimate across the 12-week treatment period.

- Significant improvements in abdominal pain were reported across the 12 treatment weeks in CIC patients with any bloating and IBS-C patients with moderate to severe baseline bloating (Figure 3).

DISCUSSION

- A majority of CIC and IBS-C patients experienced abdominal bloating.
- In CIC patients with any baseline bloating (≥1 on a 0-4 Likert scale), both plecanatide doses (3 mg and 6 mg) yielded significant improvements in the percentage of durable overall CSBM responders.
- In patients with IBS-C with moderate to severe baseline bloating (>5 on a 0-10 numeric rating scale), the overall responder rate was significantly improved in both plecanatide-treated groups.
- Abdominal bloating and abdominal pain significantly improved over 12 weeks in CIC patients with any baseline bloating and in IBS-C patients with moderate to severe baseline bloating.

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