Efficacy of Plecanatide for Patients with Chronic Idiopathic Constipation and Irritable Bowel Syndrome–Constipation with Abdominal Bloating: Analysis from Four Randomized Phase 3 Clinical Trials

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Background

- Abdominal bloating is a key symptom of functional constipation disorders and is associated with reduced physical and mental quality of life,[1,2] and increased healthcare use compared to patients without bloating.[1]
- Bloating is common in patients with irritable bowel syndrome with constipation (IBS-C) and with chronic idiopathic constipation (CIC), although it is more prevalent and more severe in patients with IBS-C.[3]
- Bloating is also the second most commonly bothersome symptom of IBS-C, following abdominal cramping.[1]
- Plecanatide – approved for CIC and IBS-C – is a guanylate cyclase-C (GC-C) receptor agonist.[4] It is a structural analog of the naturally occurring human gastrointestinal (GI) peptide uroguanylin and replicates its pH-sensitive activity in preclinical studies.[5]
- Two CIC[6,7] and 2 IBS-C[8] trials with plecanatide have been completed and represent the largest phase 3 trials to date in each of these disorders.

Aim

- To provide an integrated analysis of the efficacy results obtained during the clinical development program for plecanatide for the treatment of CIC and IBS-C
- Pooled results from four phase three studies with a focus on abdominal bloating symptoms are presented herein

Methods

- Each phase 3 trial was a 12-week, multicenter, randomized, double-blind, placebo-controlled clinical study.
- Safety populations from the 4 trials (2 CIC, 2 IBS-C) were combined for this post hoc analysis.
- Patients enrolled in these trials were adults (aged ≥18 years) who met modified Rome III criteria for either CIC or IBS-C.
- Upon completion of the 2-week baseline/screening period, patients were randomized to receive plecanatide 3 mg, plecanatide 6 mg, or placebo.
  - Medication was taken once daily with or without food.
- Efficacy assessments were made from the combined intent-to-treat (ITT) populations and were limited to endpoints that were common between the CIC and IBS-C trials.
- The primary endpoints for each study were:
  - The percentage of durable overall complete spontaneous bowel movement (CSBM) responders in the two studies performed in patients with CIC
    - Weekly CSBM responder: a patient who had ≥3 CSBMs/week and an increase from baseline of ≥1 CSBM for that week
    - Durable overall CSBM responder: a patient who was a weekly CSBM responder for ≥9 of the 12 treatment weeks, and at least 3 of the last 4 weeks of treatment
  - Overall responder, defined as a patient who was a weekly responder (CSBM + ≥30% improvement in abdominal pain) for ≥6 of the 12 treatment weeks, as defined previously for IBS-C
- Abdominal bloating was a secondary patient-reported endpoint in all studies.
  - In the CIC studies, abdominal bloating was reported on a 5-point Likert scale of 0 to 4 (0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe).
  - In the IBS-C studies, abdominal bloating was reported on an 11-point Numeric Rating Scale from 0 (no abdominal bloating) to 10 (worst possible abdominal bloating).
- Daily bowel movements and symptoms were recorded in an electronic diary.
- Bloating outcomes were compared using pairwise comparisons of least-square means between the specified treatment group and the placebo group using a linear mixed-effects model with fixed effects for sex (stratification variable), baseline value, treatment, week, the interaction of treatment and week, and a random intercept for patient.
- Safety assessments were conducted using the collection of spontaneously reported adverse events (AEs) and responses to open-ended nonspecific questions.

Results

Patients

- 2683 participants who met modified Rome III criteria for CIC and 2189 participants who met the criteria for IBS-C were included in combined phase 3 ITT–efficacy populations for each condition. Participants were predominantly female, white, and aged <65 years (**Table 1**).

Table 1. Patient Demographics and Baseline Characteristics (ITT Population)

	CIC			IBS-C		
		Plecanatide			Plecanatide	
N	Placebo 897	3 mg 896	6 mg 890	Placebo 733	3 mg 728	6 mg 728
Age, years, mean (SD)	45.5 (14.3)	45.2 (14.5)	45.2 (14.1)	43.9 (14.2)	43.5 (14.2)	43.5 (14.2)
Sex, n (%)						
Male	190 (21.2)	183 (20.8)	175 (19.7)	189 (25.4)	191 (26.2)	189 (26.0)
Female	707 (78.8)	713 (79.6)	715 (80.3)	544 (74.2)	537 (73.8)	539 (74.0)
BMI, mean kg/m^2 (SD)	28.0 (5.2)	28.4 (5.0)	28.3 (5.1)	28.0 (4.8)	28.2 (4.8)	28.0 (4.9)
Ethnicity*, n (%)						
White	654 (72.9)	643 (71.8)	626 (70.3)	538 (73.4)	529 (72.7)	518 (71.2)
Black or African American	199 (22.2)	217 (24.2)	210 (23.6)	162 (22.1)	156 (21.4)	179 (24.6)
Asian	27 (3.0)	20 (2.2)	29 (3.3)	25 (3.4)	34 (4.7)	25 (3.4)
American Indian or Alaskan Native	0 (0)	2 (0.2)	7 (0.8)	1 (0.1)	3 (0.4)	2 (0.3)
Native Hawaiian or Other Pacific Islander	3 (0.2)	2 (0.2)	2 (0.2)	4 (0.5)	0 (0)	2 (0.3)
Other	14 (1.6)	12 (1.3)	16 (1.8)	–	–	–
Multiple	–	–	–	3 (0.4)	6 (0.8)	2 (0.3)
Weekly baseline values, mean (SD)						
CSBMs	0.35 (0.53)	0.31 (0.55)	0.28 (0.48)	0.23 (0.45)	0.24 (0.50)	0.27 (0.53)
SBMs	1.86 (1.85)	1.89 (1.92)	1.71 (1.74)	1.42 (1.09)	1.48 (1.08)	1.48 (1.14)
Stool consistency[a]	2.23 (0.98)	2.16 (0.93)	2.21 (0.98)	2.03 (1.02)	1.97 (0.91)	1.92 (0.91)
Straining score[b]	2.36 (0.84)	2.38 (0.85)	2.38 (0.89)	6.58 (1.93)	6.66 (1.85)	6.69 (1.88)
Abdominal pain[b]	1.61 (1.07)	1.58 (1.06)	1.67 (1.10)	6.26 (1.71)	6.26 (1.70)	6.22 (1.76)
Abdominal bloating[b]	1.96 (0.91)	1.95 (0.92)	1.99 (0.94)	6.47 (1.77)	6.48 (1.70)	6.40 (1.78)
Abdominal discomfort[b]	1.87 (0.94)	1.85 (0.93)	1.92 (0.95)	6.37 (1.61)	6.44 (1.61)	6.35 (1.73)
Abdominal fullness[b]	–	–	–	6.50 (1.74)	6.48 (1.71)	6.43 (1.76)
Patient global rating – IBS disease severity	–	–	–	3.6 (0.72)	3.6 (0.74)	3.5 (0.74)

*Ethnicity was self-reported. Percentages may not add up to 100% due to rounding.
[a]Stool consistency was assessed using the 7-point Bristol Stool Form Scale.
[b]For CIC studies, abdominal bloating was assessed on a 5-point Likert scale where 0=none and 4=very severe; for IBS-C studies, abdominal bloating was assessed on an 11-point Numeric Rating Scale from 0 (no abdominal bloating) to 10 (worst possible abdominal bloating).
BMI, body mass index; CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement; IBS-C, irritable bowel syndrome with constipation-predominant symptoms; SBM, spontaneous bowel movement; SD, standard deviation.

Clinical Efficacy

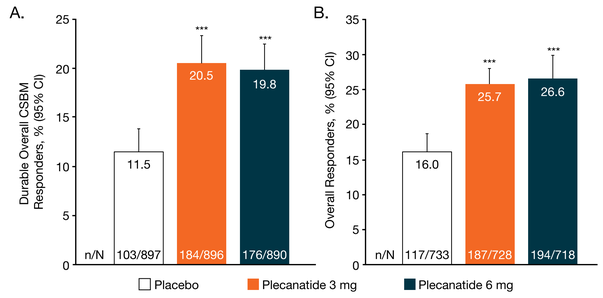
Participants with CIC

- A significantly greater proportion of patients treated with plecanatide (3 or 6 mg) were classified as overall responders compared with those receiving placebo (**Figure 1A**).
- Plecanatide 3 and 6 mg significantly improved abdominal bloating scores by –0.12 points (95% CI, –0.18 to –0.06; P<0.001) and –0.08 points (95% CI, –0.14 to –0.02; P=0.009), respectively, after 12 weeks of treatment (**Figure 2**).
- Two weeks after ceasing treatment, no significant difference in abdominal bloating was observed between placebo and either treatment group.
- No worsening, compared with baseline, was reported at any timepoint.

Participants with IBS-C

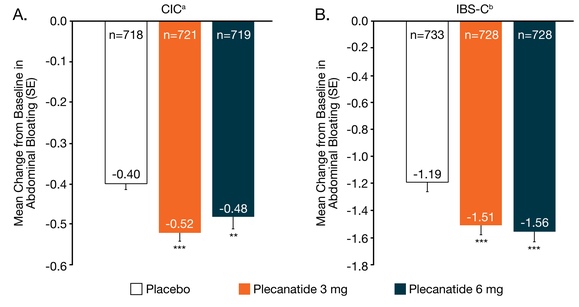
- A significantly greater proportion of patients treated with plecanatide (3 or 6 mg) were classified as overall responders compared with those receiving placebo (**Figure 1B**).
- Plecanatide 3 and 6 mg significantly improved abdominal bloating scores by –0.31 points (95% CI, –0.49 to –0.13; P<0.001) and –0.37 points (95% CI, –0.55 to –0.19; P<0.001), respectively, after 12 weeks of treatment (**Figure 2**).
  - Significant improvement in abdominal bloating from baseline, compared with placebo, was observed in both the 3- and 6-mg plecanatide groups after 1 week and persisted throughout 12 weeks of treatment.
  - Change in abdominal bloating scores remained significantly lower 2 weeks after ceasing treatment when compared with placebo.
- No worsening, compared with baseline, was reported at any timepoint, including 2 weeks after ceasing treatment.

Figure 1. Primary Endpoints at Week 12 for the Pooled CIC (A) and Pooled IBS-C (B) Populations Administered Placebo or Plecanatide (ITT Efficacy Population)



***P<0.001 versus placebo.
CI, confidence interval; CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement; IBS-C, irritable bowel syndrome with constipation-predominant symptoms; ITT, intent-to-treat.

Figure 2. Change in Abdominal Bloating Score in Patients With CIC (A) and IBS-C (B) Administered Placebo or Plecanatide (ITT Efficacy Population)



**P=0.009 versus placebo; ***P<0.001 versus placebo.
[a]For CIC studies, abdominal bloating was assessed on a 5-point Likert scale where 0=none and 4=very severe.
[b]For IBS-C studies, abdominal bloating was assessed on an 11-point Numeric Rating Scale from 0 (no abdominal bloating) to 10 (worst possible abdominal bloating).
CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation-predominant symptoms; ITT, intent-to-treat; SE, standard error of the mean.

Safety and Tolerability

- The most common AE across all studies was diarrhea.
- The AE profiles for the 3-mg and 6-mg plecanatide dose groups were generally similar, except for a slight increase in severe diarrhea in the 6-mg dose group compared with the 3-mg dose group in patients with CIC.
- Discontinuation rates due to AEs, including diarrhea, were similar across studies and indications (**Table 2**).

Table 2. Summary of Adverse Events (Safety Population)

Patients, %		Placebo	Plecanatide 3 mg	Plecanatide 6 mg
CIC N=2791	Diarrhea	1.3%	4.6%	5.1%
	Discontinuation due to AEs	2.2%	4.1%	4.5%
	Discontinuation due to diarrhea	0.4%	1.9%	1.8%
IBS-C N=2182	Diarrhea	1.0%	4.3%	4.0%
	Discontinuation due to AEs	0.4%	2.5%	2.2%
	Discontinuation due to diarrhea	0	1.2%	1.4%

AE, adverse event; CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation-predominant symptoms.

Conclusions

- **The efficacy of plecanatide for patients with both CIC and IBS-C is consistent with the concept of these disorders existing on a spectrum of functional constipation disorders.**
- **This integrated analysis of data from phase 3 studies confirms the efficacy of plecanatide for patients with CIC and IBS-C, including significantly improved bloating symptoms compared with placebo.**
- **Future research is needed as to whether the efficacy of plecanatide in significantly reducing the severity of abdominal bloating in patients with CIC and IBS-C may improve patient quality of life and reduce healthcare resource utilization.**
- **Plecanatide-treated patients experienced low rates of AEs, including diarrhea, and low rates of treatment discontinuation due to diarrhea, indicating a benign safety and tolerability profile.**

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Disclosures

D. Brenner is a consultant and speaker for Allergan/Ironwood Pharmaceuticals, for Salix Pharmaceuticals Inc, and a consultant for Shire Pharmaceuticals; H. Franklin is an employee and stockholder at Salix Pharmaceuticals Inc; G. Sayuk is a consultant and speaker for Salix Pharmaceuticals Inc, and for Allergan/Ironwood Pharmaceuticals, and a consultant for the GI Health Foundation.

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