Plecanatide for Treating Chronic Idiopathic Constipation: A Pooled Analysis of Efficacy and Safety

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Background

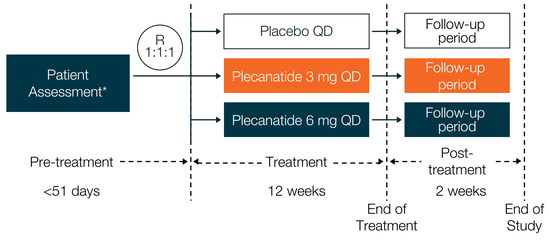
- Chronic idiopathic constipation (CIC) is a common gastrointestinal (GI) disorder, affecting ~14% of the population.[1,2]
- CIC is characterized by infrequent stools and straining and can be accompanied by abdominal symptoms such as bloating and discomfort,[3] which can drive patients' experience with disease and treatment.[4]
- Treatment of constipation may be challenging as many CIC patients cite dissatisfaction with their treatments.[5,6]
  - From the BURDEN-CIC Study, >80% of CIC patients reported a wide variety of residual symptoms despite using a prescription CIC treatment.[6]
- Plecanatide is an analog of the human GI peptide uroguanylin, and preclinical evidence indicates that plecanatide replicates the pH-sensitive binding of uroguanylin to guanylate cyclase-C receptors in the small intestine, inducing fluid secretion and contributing to normal bowel function.[7]
- Plecanatide has demonstrated clinical efficacy with a benign safety and tolerability profile in 2 large, double-blind, placebo-controlled, phase 3 clinical trials in patients with CIC[8,9] and has been approved for the treatment of adults with CIC and adults with constipation-predominant irritable bowel syndrome (IBS-C) in the United States.[10]

Aim

- To evaluate the efficacy and safety of plecanatide in patients with CIC in two identically designed phase 3 trials, including the impact on patient-reported secondary outcomes.

Methods

Figure 1. Study Design Schematic for the Phase 3 Studies



*Electronic diary assessment for eligibility, compliance, and baseline parameters was completed during the last 2 weeks of the pre-treatment period. R=randomization; QD=once daily.

- Two 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical studies were conducted to assess oral plecanatide for treatment of adults with CIC.[8,9]

Inclusion Criteria

- Eligible patients for the study included:
  - Males or females (not pregnant or lactating), aged 18–80 years (inclusive)
  - Patient met the Rome III functional constipation criteria as modified for this study (eg, excluded patients using manual maneuvers to facilitate defecations)
  - Patients who met the modified Rome III criteria based on history must also have demonstrated the following during the 2-week electronic diary assessment:
    - <3 complete spontaneous bowel movements (CSBMs) each week
    - Bristol Stool Form Scale (BSFS) of 6 or 7 in <25% of spontaneous bowel movements
    - ≥1 of the following:
      - BSFS of 1 or 2 in ≥25% of defecations
      - A straining value recorded on ≥25% of days when a BM was reported
      - ≥25% of BMs resulted in a sense of incomplete evacuation

Efficacy Measures

Population

- Efficacy analyses were based on the intention-to-treat (ITT) efficacy population

Primary Efficacy Endpoint

- Percentage of patients who were durable overall CSBM responders (Efficacy Responders)
  - 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

Secondary Efficacy Endpoints

- Change from baseline in straining severity
  - Rated at its worst when the patient had a BM on a scale of 0–4, where 0=none and 4=very severe
- Change from baseline in abdominal bloating and abdominal discomfort severity
  - Rated at its worst on a 5-point Likert scale, where 0=none and 4=very severe

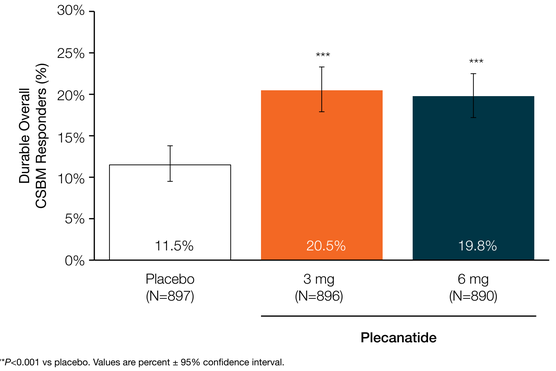
Results

Table 1. Demographics and Baseline Characteristics

	Placebo (N=897)	Plecanatide 3 mg (N=896)	Plecanatide 6 mg (N=890)
Age, years, mean (range)	45.5 (18–80)	45.2 (18–80)	45.2 (18–80)
Females	78.8%	79.6%	80.3%
Males	21.2%	20.4%	19.7%
Race			
White	72.9%	71.8%	70.3%
Black	22.2%	24.2%	23.6%
Other	4.9%	3.9%	6.1%
Weight, kg, mean (range)	76.7 (40.9–135.6)	77.6 (41.3–147.0)	77.7 (45.0–126.6)
BMI, kg/m^2, mean (range)	28.02 (17.8–41.7)	28.35 (18.2–39.9)	28.27 (18.1–40.0)

- There were 2683 patients in the combined ITT population, of which 798 placebo-treated and 1567 plecanatide-treated patients (3 mg, n=784; 6 mg, n=783) completed treatment (**Table 1**).

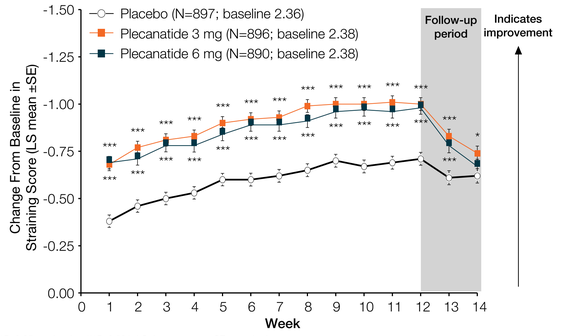
Figure 2. Plecanatide Treatment Resulted in a Significantly Greater Percentage of Durable Overall CSBM Responders Compared to Placebo



***P<0.001 vs placebo. Values are percent ± 95% confidence interval.

- A significantly greater percentage of patients in each plecanatide group were durable overall CSBM responders compared with with placebo (**Figure 2**).

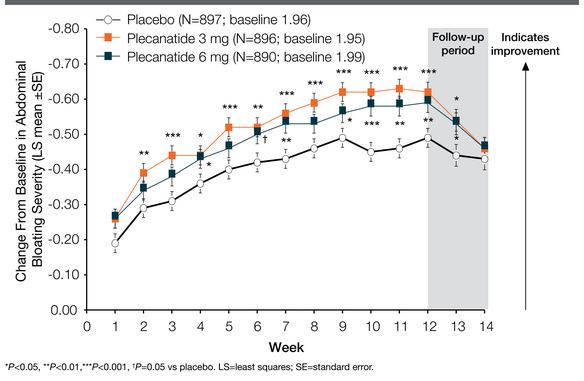
Figure 3. Plecanatide Significantly Reduced (Improved) Straining Severity



*P<0.05 vs placebo, ***P<0.001. LS=least squares; SE=standard error.

- Statistically significant improvements in straining severity were demonstrated with plecanatide 3 mg and 6 mg compared with placebo, beginning after the first week of treatment and maintained through week 12 (3 mg, Δ=−0.31; 6 mg, Δ=−0.27; P<0.001 vs placebo both doses) (**Figure 3**).

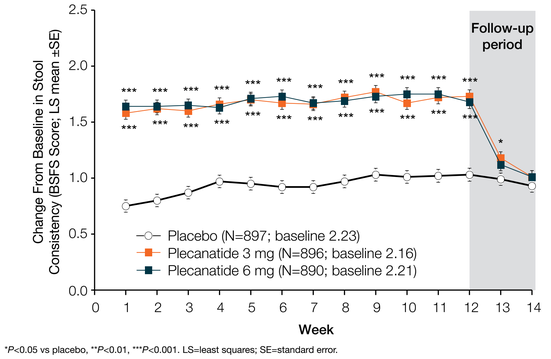
Figure 4. Plecanatide Significantly Reduced Abdominal Bloating Severity



*P<0.05, **P<0.01,***P<0.001, †P=0.05 vs placebo. LS=least squares; SE=standard error.

- Significant improvements in abdominal bloating severity were demonstrated for plecanatide 3 mg and 6 mg compared with placebo, with significant differences for plecanatide 3 mg observed after week 2 and maintained through week 12 (3 mg, Δ=−0.12; P<0.001 vs placebo; 6 mg, Δ=−0.08; P=0.009 vs placebo) (**Figure 4**).

Figure 5. Plecanatide Significantly Reduced Abdominal Discomfort Severity



*P<0.05 vs placebo, **P<0.01, ***P<0.001. LS=least squares; SE=standard error.

- Significant improvements in abdominal discomfort severity were demonstrated for plecanatide 3 mg and 6 mg compared with placebo, with significant differences for plecanatide 3 mg observed beginning at week 2 and maintained through week 12 (3 mg, Δ=−0.11; P<0.001 vs placebo; 6 mg, Δ=−0.07; P=0.027 vs placebo) (**Figure 5**).

Safety and Tolerability

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%

AE=adverse event; CIC=chronic idiopathic constipation.

- The most common AE was diarrhea. There was a slight increase in severe diarrhea in the 6-mg dose group compared with the 3-mg dose group.
- Discontinuation rates due to AEs, including diarrhea, were similar (**Table 2**).

Summary

- Pooled results from the two largest double-blind studies in patients with CIC demonstrated that plecanatide treatment resulted in significantly greater percentages of durable overall CSBM responders (Efficacy Responders) relative to placebo.
- Both plecanatide doses significantly decreased the severity of constipation-related symptoms, including straining, abdominal bloating, and abdominal discomfort.
- In the follow-up period, the pharmacological effect of plecanatide diminished, and the symptom assessments merged with those of the placebo group.
- 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.

Conclusion

Plecanatide is efficacious, safe, and well-tolerated in patients with CIC. Compared with placebo, plecanatide 3 mg and 6 mg demonstrated durable improvements in key clinical outcomes for patients with CIC, including improvements in stool frequency, straining, and perceptive abdominal symptoms.

References

1. Higgins PD, Johanson JF. *Am J Gastroenterol*. 2004;99:750–759.
2. Suares NC, Ford AC. *Am J Gastroenterol*. 2011;106:1582–1591.
3. Lacy BE, Mearin F, Chang L, et al. *Gastroenterology*. 2016;150:1393–1407.e5.
4. Heidelbaugh JJ, Stelwagon M, Miller SA, et al. *Am J Gastroenterol*. 2015; 110:580–587.
5. Johanson JF, Kralstein J. *Aliment Pharmacol Ther*. 2007;25:599–608.
6. Harris LA, Horn J, Kissous-Hunt M, et al. *Adv Ther*. 2017 Dec;34(12):2661-2673.
7. Boulete IM, Thadi A, Beaufrand C, et al. *World J Gastroenterol*. 2018;24(17): 1888-1900.
8. DeMicco M, Barrow L, Hickey B, et al. *Therap Adv Gastroenterol*. 2017;10(11): 837-851.
9. Miner PB Jr, Koltun WD, Wiener GJ, et al. *Am J Gastroenterol*. 2017;112(4): 613-621.
10. Trulance (plecanatide) [package insert]. Bridgewater, NJ: Salix Pharmaceuticals Inc.; 2019.

Disclosures

H. Franklin is an employee and stockholder at Salix Pharmaceuticals Inc.; G.S. 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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