Plecanatide for the Treatment of Chronic Idiopathic Constipation: An Analysis of Patient-Reported Symptoms Associated With Constipation

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Background

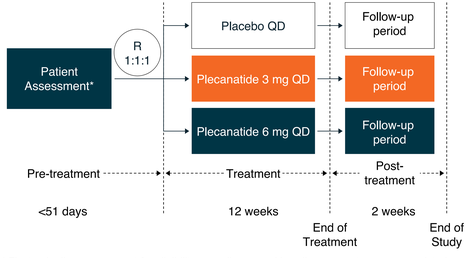
- Chronic idiopathic constipation (CIC) is a common gastrointestinal (GI) disorder, affecting ~14% of the population.[1,2]
- CIC is characterized by infrequent stools and straining and can be accompanied by abdominal symptoms such as bloating and discomfort,[3] which can drive patients' experience with 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 (ClinicalTrials.gov identifiers: NCT01982240 [Study -00]; NCT0212247 [Study -03]), which have been reported previously, and has been approved for the treatment of adults with CIC in the United States.

Objective

- To evaluate the impact of plecanatide on the secondary endpoints of straining severity, abdominal bloating severity, abdominal discomfort severity, and stool consistency in 2 plecanatide CIC registration trials.

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.

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
- Change from baseline in stool consistency
  - Assessed with the 7-point BSFS

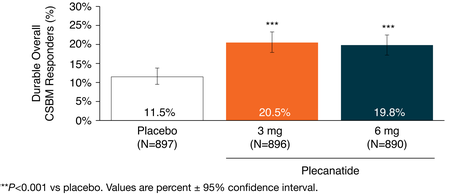
Results

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/m², 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.

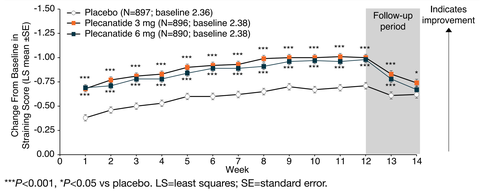
Figure 2. Plecanatide Treatment Resulted in a Significantly Greater Percentage of Durable Overall CSBM Responders Compared to Placebo



***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 placebo.

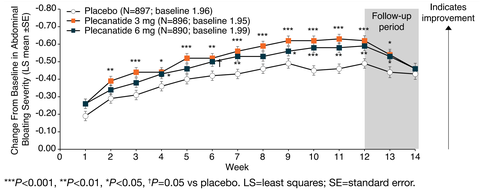
Figure 3. Plecanatide Significantly Reduced (Improved) Straining Severity



***P<0.001, *P<0.05 vs placebo. 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.

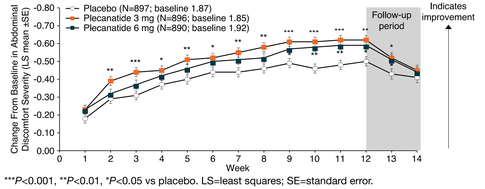
Figure 4. Plecanatide Significantly Reduced Abdominal Bloating Severity



***P<0.001, **P<0.01, *P<0.05, †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.

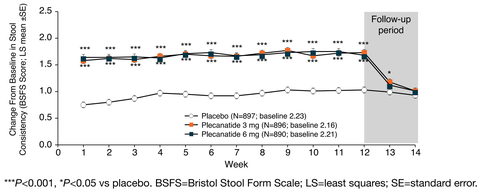
Figure 5. Plecanatide Significantly Reduced Abdominal Discomfort Severity



***P<0.001, **P<0.01, *P<0.05 vs placebo. 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.

Figure 6. Plecanatide Significantly Improved Stool Consistency



***P<0.001, *P<0.05 vs placebo. BSFS=Bristol Stool Form Scale; LS=least squares; SE=standard error.

- Both doses of plecanatide demonstrated statistically significant improvements in stool consistency beginning at the first week of treatment and maintained through week 12.

Summary

- Pooled results from the 2 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.
- Plecanatide improved stool consistency beginning at week 1 and this improvement was sustained through the end of treatment.
- In the follow-up period, the pharmacological effect of plecanatide diminished, and the symptom assessments merged with those of the placebo group.

Conclusion

In studies showing the therapeutic benefit of plecanatide on stool frequency in CIC patients, plecanatide also demonstrated improvements in symptoms commonly associated with CIC, including straining, abdominal bloating, and abdominal discomfort.

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Disclosures

Miner PB was a study investigator paid for his participation in this clinical trial and has received funding for advisory board meetings. Shailubhai K is an employee of Synergy Pharmaceuticals and one of the inventors of the drug plecanatide. At the time of the studies, Barrow L was an employee of Synergy Pharmaceuticals.