# Efficacy and Safety of Plecanatide in Patients With Chronic Idiopathic Constipation: An Analysis of Patients With Moderate to Very Severe Bloating

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## Background

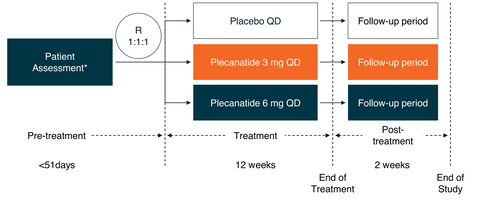
- Chronic idiopathic constipation (CIC) has been reported to affect ~14% of the population.[1,2]
- CIC is characterized by altered stool frequency and consistency and by abdominal symptoms such as bloating and discomfort.[3]
- Patients with abdominal bloating, distension, and discomfort tend to be less satisfied with their constipation care than those without.[4]
- Plecanatide is a pH-sensitive analog of the human GI peptide uroguanylin that preferentially activates guanylate cyclase-C receptors in the small intestine, the site of natural physiological fluid secretion, and induces fluid release.[5]
- The efficacy and safety profile of plecanatide was established in 2 large, double-blind, placebo-controlled, phase 3 clinical trials (ClinicalTrials.gov identifiers: NCT01982240; NCT0212247). Plecanatide is now approved in the United States for the treatment of adults with CIC.

## Objective

To examine the efficacy and safety of plecanatide in the subset of CIC patients with moderate, severe, or very severe abdominal bloating at baseline.

## 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. QD=once daily; R=randomization.

- 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)
  - Patients who 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 pretreatment 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*

- The analyses herein focused on patients whose baseline abdominal bloating score was moderate to very severe (ie, score ≥2).
  - Abdominal bloating was reported in the daily symptom diary and was rated on a scale of 0 to 4, where 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe.
- Efficacy analyses were based on the intention-to-treat (ITT) efficacy population.

*Primary Efficacy Endpoint*

- Percentage of patients who were durable overall CSBM 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, including ≥3 of the last 4 weeks of treatment

*Secondary Efficacy Endpoints*

- Percent change from baseline in abdominal bloating severity

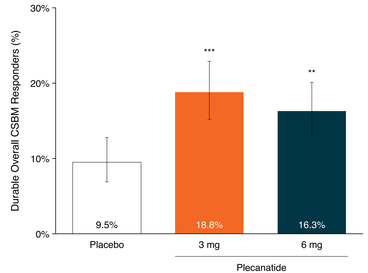
## Results

**Table 1. Demographics and Baseline Characteristics of Patients With Moderate, Severe, or Very Severe Abdominal Bloating**

| | Placebo (N=419) | Plecanatide 3 mg (N=414) | Plecanatide 6 mg (N=441) |
|---|---|---|---|
| Age, years, mean (range) | 45.1 (18–78) | 45.4 (18–79) | 44.8 (18–78) |
| Females, % | 79.0% | 78.5% | 80.5% |
| Race, % | | | |
| White | 69.9% | 73.4% | 73.5% |
| Black | 26.3% | 24.4% | 22.7% |
| Asian | 2.1% | 1.2% | 1.6% |
| Other | 1.7% | 1.0% | 2.2% |
| Hispanic or Latino, % | 46.8% | 47.3% | 47.6% |
| BMI, kg/m$^2$, mean (range) | 28.5 (17.8–41.7) | 28.4 (18.2–39.9) | 28.3 (18.4–40.0) |
| CSBMs/week, mean (range) | 0.25 (0–2) | 0.20 (0–2) | 0.20 (0–2) |
| Abdominal bloating score, mean (SD) | 2.70 (0.52) | 2.71 (0.49) | 2.72 (0.52) |

- There were a combined 2683 patients in the ITT population, with 1274 (47.5%) categorized as having moderate, severe, or very severe abdominal bloating at baseline.

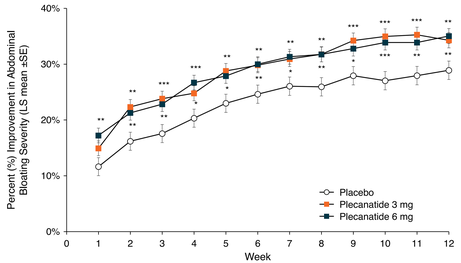
**Figure 2. Plecanatide Resulted in a Significantly Greater Percentage of Durable Overall CSBM Responders Compared With Placebo in Patients With Moderate to Very Severe Abdominal Bloating**




***$P$<0.001, **$P$<0.01 vs placebo. Values are percent ± 95% confidence interval.

- Both plecanatide doses resulted in a significantly greater percentage of durable overall CSBM responders (Efficacy Responders) as compared to placebo in CIC patients with moderate to very severe bloating (3 mg, $P$<0.001; 6 mg, $P$=0.003).

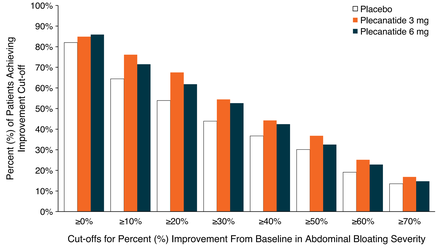
**Figure 3. Plecanatide Significantly Improved Abdominal Bloating Severity Scores Compared With Placebo in Patients With Moderate to Very Severe Abdominal Bloating**




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

- Both plecanatide doses demonstrated statistically significant improvements in the percent change from baseline in abdominal bloating scores.
- Improvements in abdominal bloating scores were statistically significant after one week and continued throughout the 12-week treatment period.

**Figure 4. More Plecanatide-Treated Patients Reported Improvements in Abdominal Bloating Than Placebo-Treated Patients With Moderate to Very Severe Abdominal Bloating**




- At week 12, a higher percentage of plecanatide-treated patients reported improvements in abdominal bloating severity than did placebo-treated patients at each of the percentage cut-off points.

**Table 2. Summary of Treatment-Emergent Adverse Events in Patients With Moderate to Very Severe Abdominal Bloating**

| Patients, n (%) | Placebo (N=415) | Plecanatide 3 mg (N=418) | Plecanatide 6 mg (N=441) |
|---|---|---|---|
| ≥1 TEAE | 112 (27.0%) | 124 (29.7%) | 113 (25.6%) |
| Mild | 66 (15.9%) | 75 (17.9%) | 61 (13.8%) |
| Moderate | 39 (9.4%) | 39 (9.3%) | 42 (9.5%) |
| Severe | 6 (1.4%) | 10 (2.4%) | 10 (2.3%) |
| Missing | 1 (0.2%) | 0 | 0 |
| TEAEs reported by ≥2% of patients in any plecanatide group | | | |
| Diarrhea | 3 (0.7%) | 17 (4.1%) | 20 (4.5%) |
| Headache | 8 (1.9%) | 10 (2.4%) | 8 (1.8%) |
| ≥1 SAE* | 7 (1.7%) | 9 (2.2%) | 3 (0.7%) |
| ≥1 TEAE leading to discontinuation | 10 (2.4%) | 15 (3.6%) | 15 (3.4%) |
| Diarrhea | 1 (0.2%) | 4 (1.0%) | 7 (1.6%) |

*Includes pregnancies: 2 with placebo group and 1 with plecanatide 3 mg.
SAE=serious adverse event; TEAE=treatment-emergent adverse event.

- Rates of TEAEs were similar across treatment groups, with the majority rated as mild or moderate.
- The rate of diarrhea was low and occurred in <5% of plecanatide-treated patients.
  - The incidence of diarrhea with plecanatide treatment was slightly lower than that reported in the full clinical study population (3 mg, 4.6%; 6 mg, 5.1%).
- Discontinuations due to TEAEs were low, with diarrhea as the most common TEAE leading to study withdrawal.

## Summary

- Plecanatide treatment resulted in a significantly greater percentage of durable overall CSBM responders (Efficacy Responders) relative to placebo in CIC patients with moderate to very severe bloating.
- Plecanatide demonstrated significant improvements in abdominal bloating scores, with improvements beginning at week 1 and sustained throughout the 12-week treatment period.
- Diarrhea occurred in a small number of patients with moderate to very severe bloating at baseline, and few events led to treatment discontinuation, with rates similar to those of the full clinical study population.

## Conclusion

**In patients with CIC who have moderate to very severe abdominal bloating, plecanatide demonstrated sustained efficacy and significantly improved bloating severity.**

**These data add to the previous results[6] that plecanatide, a uroguanylin analog, is an effective treatment option in adult CIC patients with or without abdominal symptoms.**

## References

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## Acknowledgements

Funding for these trials and editorial support were provided by Synergy Pharmaceuticals Inc., who also provided the plecanatide and placebo used for these studies. Writing and editorial support were provided by The Medicine Group.

## Disclosures

Rao SSC has been paid for teaching, research, and consultation at Synergy Pharmaceuticals. Griffin PH and Magnus L are employees and stockholders of Synergy Pharmaceuticals.