Impact of Plecanatide on Quality of Life for Patients with Chronic Idiopathic Constipation: Analysis of PAC-SYM and PAC-QOL from Two Randomized Phase 3 Clinical Trials

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Background

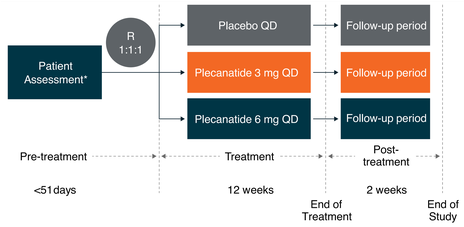
- Chronic idiopathic constipation (CIC) is a common gastrointestinal (GI) disorder, affecting ~14% of the population.[1,2]
- CIC is characterized by infrequent stools and straining and can be accompanied by abdominal symptoms such as bloating and discomfort,[3] which can further impact patients' experience with disease and treatment.[4]
- Treatment of constipation can be difficult and many CIC patients cite dissatisfaction with their treatments.[5,6]
  - In 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 suggests that plecanatide replicates the pH-sensitive binding of uroguanylin to guanylate cyclase-C receptors, acting primarily in the small intestine to induce fluid secretion and contribute to normal bowel function.
- Plecanatide has demonstrated clinical efficacy with a benign safety and tolerability profile in two 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.[7,8] Plecanatide has been approved for the treatment of adults with CIC in the United States.

Objective

- To evaluate the impact of plecanatide on health-related quality of life (HRQOL) in patients with CIC, using the Patient Assessment of Constipation Symptoms (PAC-SYM®) and Patient Assessment of Quality of Life (PAC-QOL®) Questionnaires, as well as their respective domain scores.

Methods

Figure 1. Study Design 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 identically-designed 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical studies were conducted to assess once-daily 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
  - 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 each week
    - Bristol Stool Form Scale (BSFS) score of 6 or 7 in <25% of spontaneous bowel movements
    - ≥1 of the following:
      - BSFS score of 1 or 2 in ≥25% of defecations
      - A straining value recorded on ≥25% of days when a bowel movement was reported
      - ≥25% of bowel movements resulted in a sense of incomplete evacuation

Efficacy Measures

Population

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

PAC-SYM Questionnaire

- The PAC-SYM is a validated questionnaire made up of 12 questions measuring the severity of specific abdominal, rectal, and stool symptoms of CIC.[9,10]
- Patients were asked to rate each symptom on a 5-point Likert scale of 0 ("absent") to 4 ("very severe").

PAC-QOL Questionnaire

- The PAC-QOL is a validated questionnaire made up of 28 questions assessing how the patient has been affected by constipation over the specified period.[11]
- The questions measure worries and concerns, physical discomfort, psychosocial discomfort, satisfaction, and overall effects on the patient's quality of life.
- Patients were asked to give their response on a 5-point Likert scale of 0 ("not at all" or "none of the time") to 4 ("extremely" or "all of the time").

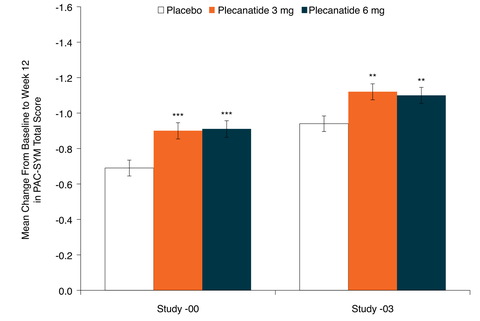
Results

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, %	78.80%	79.60%	80.30%
Race, %			
White	72.90%	71.80%	70.30%
Black	22.20%	24.20%	23.60%
Other	4.90%	3.90%	6.10%
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)	28.37 (18.1–40.0)

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

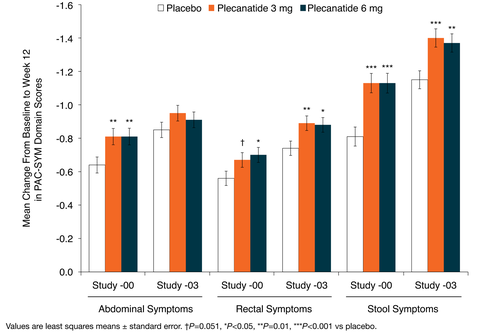
Figure 2. Effect of Plecanatide Treatment on Overall CIC Symptomatology



Values are least squares means ± standard error. **P<0.01, ***P<0.001 vs placebo.

- A significant improvement in PAC-QOL Total Score was observed for plecanatide 3 mg and 6 mg vs placebo at week 12 in both studies.
  - Similar results were observed at weeks 4 and 8.

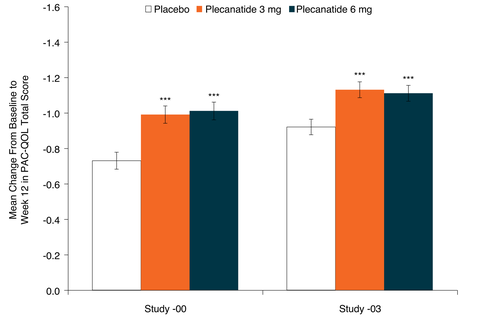
Figure 3. Effect of Plecanatide Treatment on PAC-SYM Domain Scores



Values are least squares means ± standard error. †P=0.051, *P<0.05, **P=0.01, ***P<0.001 vs placebo.

- Plecanatide-treated patients reported significant improvements in abdominal, rectal, and stool symptoms compared with placebo.
- The largest improvements were observed with stool symptoms.

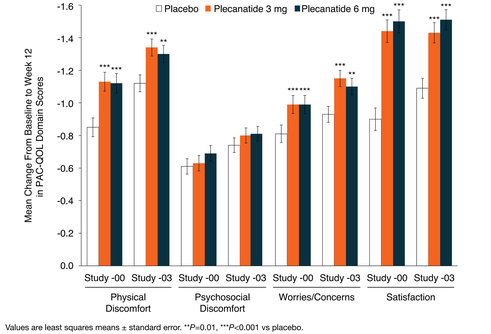
Figure 4. Assessment of Plecanatide Treatment on Overall HRQOL



Values are least squares means ± standard error. ***P≤0.001 vs placebo.

- A significant improvement in PAC-SYM Total Score was observed for plecanatide 3 mg and 6 mg vs placebo at week 12 in both studies.
  - Similar results were observed at weeks 4 and 8.

Figure 5. Effect of Plecanatide Treatment on PAC-QOL Domain Scores



Values are least squares means ± standard error. **P=0.01, ***P<0.001 vs placebo.

- Plecanatide-treated patients (3 mg and 6 mg) reported significant improvements in physical discomfort, worries/concerns, and satisfaction PAC-QOL Domain Scores compared with placebo.
- The largest improvements were observed with satisfaction related to bowel habits and physical discomfort.

Table 2. Summary of Treatment-Emergent Adverse Events

	Placebo (N=924)	Plecanatide 3 mg (N=941)	Plecanatide 6 mg (N=926)
Patients with ≥1 TEAE	265 (28.7%)	288 (30.6%)	288 (31.1%)
Diarrhea	12 (1.3%)	43 (4.6%)	47 (5.1%)
Patients with ≥1 TEAE leading to study discontinuation	20 (2.2%)	39 (4.1%)	42 (4.5%)
Diarrhea	4 (0.4%)	18 (1.9%)	17 (1.8%)

TEAE=treatment-emergent adverse event.

Discussion

- Plecanatide treatment resulted in significant improvements in CIC symptomatology and HRQOL in two large clinical trials in patients with CIC.
- After 12 weeks of treatment, plecanatide-treated patients reported significant improvements in abdominal, rectal, and stool symptoms compared with placebo.
- Additionally, patients reported significant improvements in physical discomfort, worries/concerns related to constipation, and satisfaction with constipation (eg, frequency, regularity).
- These results add to the growing evidence that plecanatide is a promising new treatment option for patients with CIC that helps to alleviate the burden of CIC symptoms.

References

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Disclosures

Hixson, M. and Cavallo, J.S. are employees and stockholders of Synergy Pharmaceuticals Inc.