The Impact of Plecanatide on Quality of Life for Patients With Chronic Idiopathic Constipation (CIC): Results From Two Phase 3 Clinical Studies

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Introduction

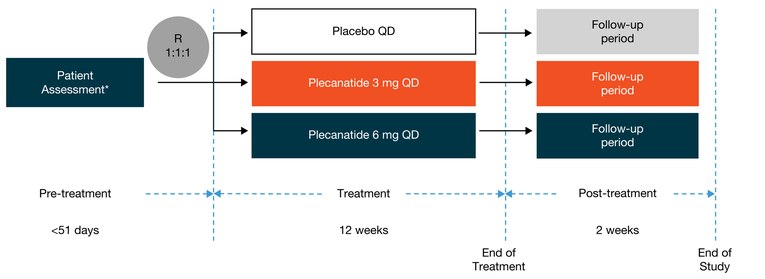
- Chronic idiopathic constipation (CIC) is a common gastrointestinal disorder, affecting ~14% of the population.[1,2]
- Treatment of constipation may be challenging as many patients cited dissatisfaction with their treatments.[3]
- CIC can negatively impact health-related quality of life, productivity, and healthcare costs.[3-7]
  - Over half of individuals report that CIC impacts their quality of life,[3] with one-fourth indicating poor quality of life.[4,6]
  - Over one-third of individuals report that CIC impacts their productivity at work, school, or home situations,[3] with an average of 1-3 days a month impacted.[5]
  - The direct costs of CIC range from $1,912 to $7,522 per year.[7]
- Based on this data, additional treatment options for CIC would benefit patients. Plecanatide has been studied in the two largest phase 3 clinical trials conducted to date.
- With the exception of a single amino acid substitution, plecanatide is structurally identical to human uroguanylin and is the only treatment that is thought to replicate the pH-sensitive activity of human uroguanylin.
- Uroguanylin, a GC-C agonist, is a naturally occurring, endogenous GI peptide that modulates its activity within the changing pH environment of the intestine.
- Based on preclinical studies, plecanatide appears to act primarily in the small intestine coinciding with physiological areas of fluid secretion.
- Plecanatide was recently approved as a once daily oral tablet in the United States for the treatment of adults with CIC.

Objective

- To investigate whether plecanatide improved health-related quality of life in patients with CIC, through an analysis of two phase 3 clinical 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 two 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 (Study –00 and Study –03) were conducted to assess oral plecanatide for treatment of adults with CIC (**Figure 1**).

Inclusion / Exclusion Criteria

- Eligible patients for the study included:
  - Males or females between 18 and 80 years of age (inclusive). Females must not have been pregnant or lactating.
  - Patient met the Rome III functional constipation criteria as modified for this study for ≥3 months prior to the screening visit with symptom onset ≥6 months prior to the diagnosis.
  - 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 (SBMs)
    - ≥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

Primary Efficacy Endpoint

- The percentage of patients who were durable overall CSBM responders (efficacy responders) during the 12-week treatment period
  - An overall CSBM responder was defined as a patient who was a weekly CSBM responder for ≥9 of the 12 treatment weeks, including ≥3 of the last 4 weeks of treatment.
  - A weekly CSBM responder was defined as a patient who had ≥3 CSBMs per week and an increase from baseline of ≥1 CSBM for that week.

Additional Efficacy Endpoints

- Patient Assessment of Constipation–Symptoms (PAC-SYM)
  - Questionnaire composed of 12 questions addressing specific symptoms of constipation (ie, abdominal symptoms, rectal symptoms, and stool symptoms).
  - Patients responded using a 5-point Likert scale of 0 (“absent”) to 4 (“very severe”).
- Patient Assessment of Constipation–Quality of Life (PAC-QOL)
  - Questionnaire composed of 28 questions assessing how the patient has been impacted by constipation (ie, worries and concerns, physical discomfort, psychosocial discomfort, satisfaction, and overall effects on the quality of life).
  - Patients responded using a 5-point Likert scale of 0 (“not at all” or “none of the time”) to 4 (“extremely” or “all of the time”).
- Both PAC-SYM and PAC-QOL are validated instruments.
- Treatment satisfaction at weeks 4, 8, and 12
  - Captured using a 5-point Likert scale (1 to 5), where increases indicate greater satisfaction.

Statistical Analyses

Populations

- Efficacy analyses were based on the intention-to-treat efficacy (ITT-E) population, which included all randomized patients whose first experience in any plecanatide study was either of these phase 3 clinical studies.

Results

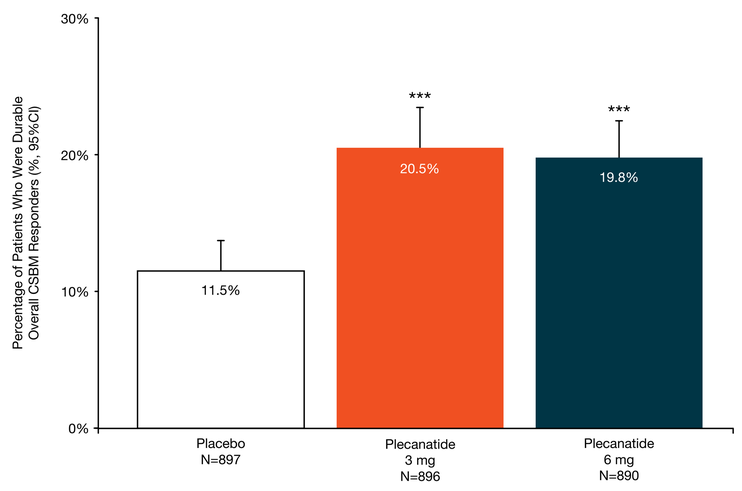
- The integrated intention-to-treat efficacy population (ITT-E) was composed of 2683 patients.

Table 1. Demographic and Baseline Characteristics

	Placebo N=897	Plecanatide 3 mg N=896	Plecanatide 6 mg N=890	Plecanatide Combined N=1786
Mean age, years (range)	45.5 (18–80)	45.2 (18–80)	45.2 (18–80)	45.2 (18–80)
Female, %	78.8	79.6	80.3	80.0
Male, %	21.2	20.4	19.7	20.0
Race, %				
White	72.9	71.8	70.3	71.1
Black	22.2	24.2	23.6	23.9
Other	4.9	3.9	6.1	5.0
Weight, kg (range)	76.7 (40.9–135.6)	77.6 (41.3–147.0)	77.7 (45.0–126.6)	76.2 (41.3–147.0)
BMI, kg/m^2 (range)	28.02 (17.8–41.7)	28.35 (18.2–39.9)	28.37 (18.1–40.0)	28.31 (18.1–40.0)

- Demographic and baseline characteristics were similar across the 3 treatment groups (**Table 1**).
- Of the ITT-E population, 798 placebo-treated patients and 1567 plecanatide-treated patients (3 mg, n=784; 6 mg, n=783) completed treatment.

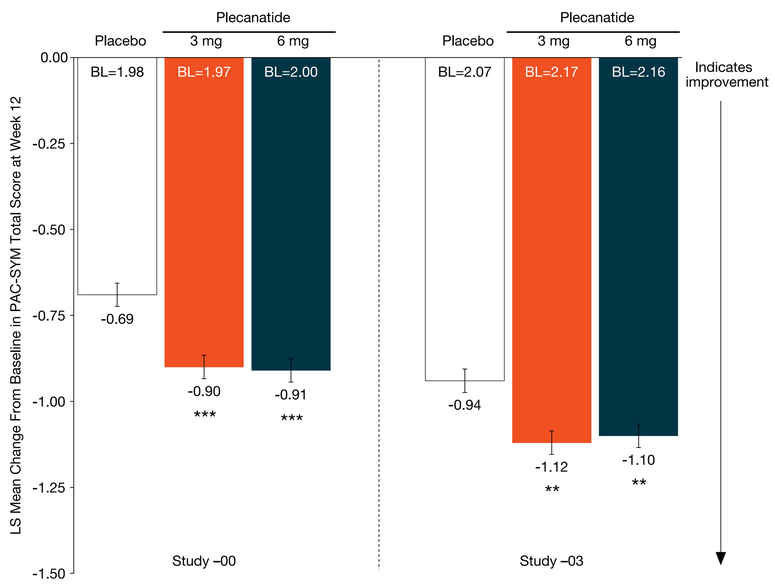
Figure 2. Primary Efficacy Endpoint



***P<0.001 vs placebo (Cochran-Mantel-Haenszel test). CI=confidence interval.

- Over the 12-week period, a significantly greater percentage of patients in each plecanatide group were durable overall CSBM responders compared with placebo (**Figure 2**).

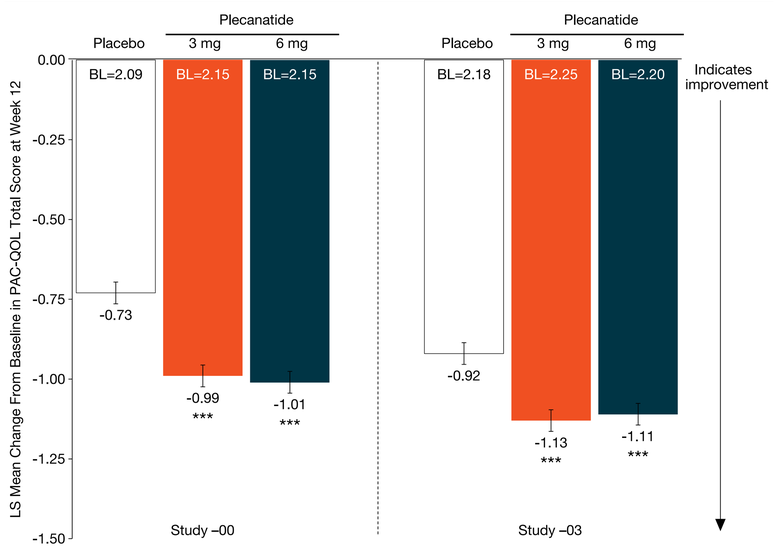
Figure 3. Effect of Treatment on Symptoms of CIC



***P<0.001, **P<0.01 vs placebo. BL=baseline; LS=least squares.

- Both plecanatide doses demonstrated a statistically significant change from baseline compared to placebo in PAC-SYM total score at week 12 (**Figure 3**).

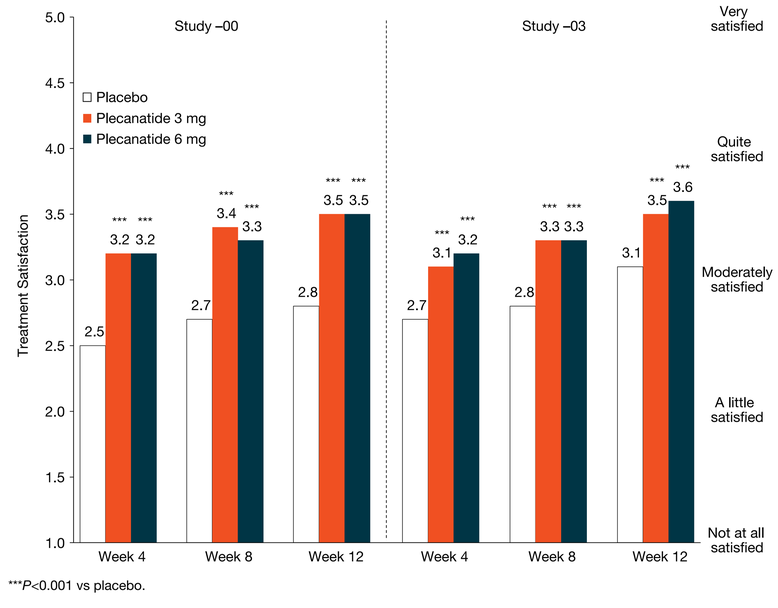
Figure 4. Effect of Treatment on Quality of Life



***P<0.001 vs placebo. BL=baseline; LS=least squares.

- Both plecanatide doses demonstrated a statistically significant change from baseline compared to placebo in PAC-QOL total score at week 12 (**Figure 4**).

Figure 5. Treatment Satisfaction



***P<0.001 vs placebo.

- Across studies and at each assessment point, both plecanatide doses yielded higher LS mean treatment satisfaction scores (**Figure 5**).
- Plecanatide 3 mg and 6 mg reported similar treatment satisfaction scores across time points, with treatment satisfaction increasing over time.

Safety and Tolerability

- Of the ITT-S population, 841 patients experienced ≥1 TEAE, with the incidence being similar across groups and the majority being mild or moderate in severity.
- The most frequently reported TEAE was diarrhea (placebo, 1.3%; 3 mg, 4.6%; 6 mg, 5.1%), with the incidences of all other TEAEs similar between placebo and plecanatide.
- Discontinuations due to TEAEs were low (placebo, 2.2%; 3 mg, 4.1%; 6 mg, 4.5%), with few due to diarrhea (placebo, 0.4%; 3 mg, 1.9%; 6 mg; 1.8%).

Conclusions

- **Results from two identically-designed pivotal phase 3 studies of plecanatide 3 mg and 6 mg demonstrated a significant improvement in health-related quality of life, as measured by the PAC-QOL and PAC-SYM.**
- **Patient-reported constipation-related quality of life (PAC-QOL) and patient-reported severity of abdominal, rectal, and stool symptoms (PAC-SYM) were improved at all time points for patients who were treated with plecanatide, with a clinically meaningful improvement at week 12 (~1-point improvement) for both measures.**
  - **No significant differences between plecanatide 3 mg and 6 mg were observed in PAC-SYM or PAC-QOL.**
- **Treatment satisfaction scores with plecanatide increased over time and were significantly higher for each plecanatide dose compared to placebo, and by week 12 patients were moderately/quite satisfied with plecanatide treatment.**
- **There was a low incidence of diarrhea, a commonly reported side effect of CIC treatments, with plecanatide treatment.**
- **These results demonstrate that plecanatide is a promising and viable new treatment option for patients with CIC and may help to alleviate the burden of CIC symptoms and reduced quality of life that patients with CIC experience.**

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ClinicalTrials.gov identifiers for the studies included in this analysis: NCT01982240 (Study –00), NCT02122471 (Study –03).

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