Plecanatide Improved Stool Consistency in Patients With Chronic Idiopathic Constipation Regardless of Baseline BSFS: A Post Hoc Analysis

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Lucinda A. Harris, MD[1]; Jennifer Winters, CRNP[1]; Andrew Herman, MD[2]; Sarah Lorenzen, PhD[3]*; Brooks Cash, MD[2]

[1]Mayo Clinic, Scottsdale, AZ, USA; [2]University of Texas Health Science Center at Houston, Houston, TX, USA; [3]Salix Pharmaceuticals, Inc., Bridgewater, NJ, USA; *Former employee

INTRODUCTION

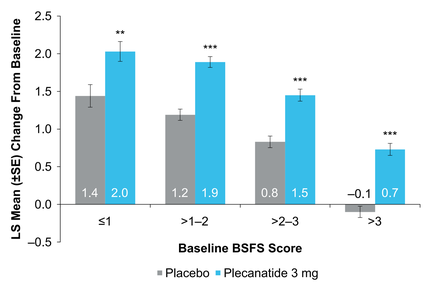
- Chronic idiopathic constipation (CIC) is a bothersome functional gastrointestinal disorder; it is estimated between 7% and 14% of the US population is affected by CIC.[1,2]
  - CIC is often accompanied by decreased health-related quality of life, reduced work/school productivity and attendance, and significant direct and indirect costs.[3-6]
- Plecanatide, a pH-sensitive analog of human uroguanylin, has demonstrated clinical efficacy and tolerability in patients with CIC in two phase 3 clinical trials, and is FDA approved in the United States for the treatment of CIC.[7-9]
  - Plecanatide acts as a guanylate cyclase-C receptor agonist primarily in the small intestine to produce cyclic guanosine monophosphate (cGMP).[7]
  - The production of cGMP increases both water content and bowel movement frequency, thus alleviating abdominal symptoms.[7]
- Because CIC complaints are variable among patients, it is important to assess the effects of therapies across a range of patient reported symptoms.
  - One of the primary symptoms of CIC is abnormal stool form according to the Bristol Stool Form Scale (BSFS).[1,3]
- This post hoc analysis evaluated the impact of plecanatide in patients classified by their BSFS score at baseline.

METHODS

- Data were pooled from two multicenter, double-blind, phase 3 studies in CIC (NCT01982240, NCT02122471).[8,9]
  - Adults who met Rome III criteria for CIC were randomized (1:1:1) to plecanatide 3 mg, 6 mg (data not shown), or placebo once daily for 12 treatment weeks.
- Patients recorded bowel movement frequencies and characteristics daily in electronic diaries throughout the 12-week treatment period.
- Outcomes included changes from baseline in stool consistency, straining severity, and complete spontaneous bowel movements (CSBMs) per week, as well as durable overall responder rate and treatment satisfaction score.
  - Stool consistency was measured using the BSFS,[10,11] which has the following classifications:
    - Type 1: Separate hard lumps, like nuts [associated with constipation]
    - Type 2: Sausage-shaped but lumpy [associated with constipation]
    - Type 3: Like a sausage but with cracks on its surface
    - Type 4: Like a sausage or snake, smooth and soft
    - Type 5: Soft blobs with clear-cut edges
    - Type 6: Fluffy pieces with ragged edges, a mushy stool [associated with diarrhea]
    - Type 7: Watery, no solid pieces, entirely liquid [associated with diarrhea]
  - Straining severity was rated using a 5-point Likert scale (0=none; 4=very severe).
  - Durable overall responders were patients who reported ≥3 CSBMs and a mean change from baseline of ≥1 CSBM in the same week for ≥9 of 12 treatment weeks, including ≥3 of the last 4 weeks.
  - Treatment satisfaction was measured using a 5-point Likert scale (0=not at all; 4=extremely).
- For these analyses, patients were classified by their average baseline BSFS score into four subgroups: ≤1, >1–2, >2–3, and >3.
  - A total of 208, 611, 455, and 412 patients had baseline BSFS scores of ≤1, >1–2, >2–3, and >3, respectively.
  - A separate analysis of BSFS was conducted in the subgroup of patients indicating "hard stools" as their most bothersome symptom on the Patient Constipation Experience questionnaire that was captured at baseline.

RESULTS

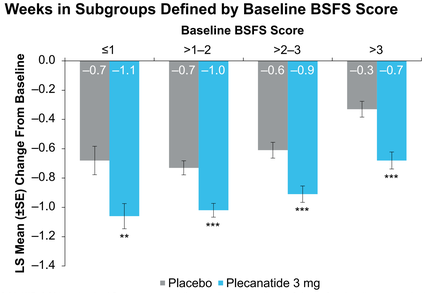
Figure 1. Stool Consistency (BSFS Score): Change From Baseline Over 12 Weeks in Subgroups Defined by Baseline BSFS Score



***P<0.01, ***P<0.001 vs placebo. LS means represent the overall average estimate of change from baseline over weeks 1–12. P-value vs placebo is from the pairwise comparison of LS means between the specified treatment group and the placebo group using a linear mixed-effects model with fixed effects for gender (stratification variable), treatment, week, the interaction of treatment and week, and a random intercept for patient. The model considers the repeated measurements for each patient. BSFS, Bristol Stool Form Scale; LS, least squares; SE, standard error.*

- The average change from baseline in stool consistency was greatest in patients with BSFS scores ≤1 at baseline, with incrementally smaller effects seen in subgroups closer to normal-type[12] BSFS scores (ie, 3–4; Figure 1).
- Across BSFS subgroups, plecanatide treatment resulted in statistically significantly greater improvements in stool consistency compared with placebo.

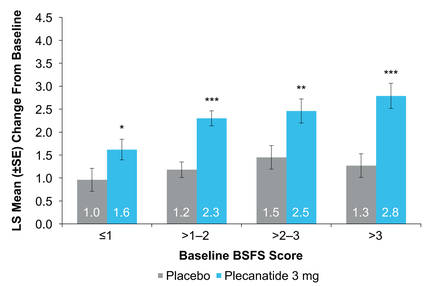
Figure 2. Straining Severity: Change From Baseline Over 12 Weeks in Subgroups Defined by Baseline BSFS Score



***P<0.01, ***P<0.001 vs placebo. LS means represent the overall average estimate of change from baseline over weeks 1–12. P-value vs placebo is from the pairwise comparison of LS means between the specified treatment group and the placebo group using a linear mixed-effects model with fixed effects for gender (stratification variable), treatment, week, the interaction of treatment and week, and a random intercept for patient. The model considers the repeated measurements for each patient. BSFS, Bristol Stool Form Scale; LS, least squares; SE, standard error.*

- At baseline, mean (SD) straining severity scores in the placebo and plecanatide arms were, respectively:
  - 2.78 (0.990) and 2.90 (0.890) in the BSFS ≤1 subgroup,
  - 2.57 (0.831) and 2.57 (0.759) in the BSFS >1–2 subgroup,
  - 2.29 (0.696) and 2.28 (0.717) in the BSFS >2–3 subgroup, and
  - 1.91 (0.749) and 1.88 (0.788) in the BSFS >3 subgroup.
- Plecanatide-treated patients experienced greater improvements in straining severity compared to placebo across BSFS subgroups, with the greatest improvement noted in patients with lowest baseline BSFS scores (Figure 2).

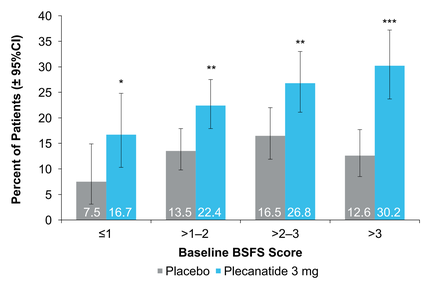
Figure 3. CSBMs/Week: Change From Baseline Over 12 Weeks in Subgroups Defined by Baseline BSFS Score



**P<0.05, **P<0.01, ***P<0.001 vs placebo. LS means represent the overall average estimate of change from baseline over weeks 1–12. P-value vs placebo is from the pairwise comparison of LS means between the specified treatment group and the placebo group using a linear mixed-effects model with fixed effects for gender (stratification variable), treatment, week, the interaction of treatment and week, and a random intercept for patient. The model considers the repeated measurements for each patient. BSFS, Bristol Stool Form Scale; LS, least squares; SE, standard error.*

- Mean (SD) CSBMs/week at baseline in the placebo and plecanatide arms were, respectively:
  - 0.12 (0.339) and 0.15 (0.333) in the BSFS ≤1 subgroup,
  - 0.31 (0.533) and 0.18 (0.372) in the BSFS >1–2 subgroup,
  - 0.48 (0.564) and 0.47 (0.541) in the BSFS >2–3 subgroup, and
  - 0.43 (0.553) and 0.47 (0.807) in the BSFS >3 subgroup.
- Compared with placebo, plecanatide treatment resulted in statistically significant improvements in mean CSBMs/week over 12 weeks (**Figure 3**).
- Incrementally smaller improvements were noted in subgroups with stool consistency closer to normal-type12 BSFS scores.

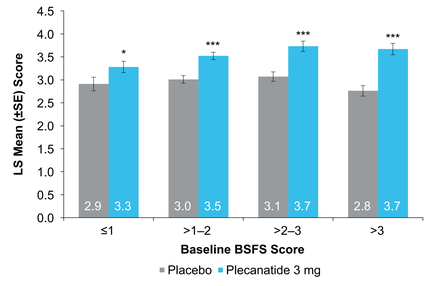
Figure 4. Durable Overall CSBM Responder Rates in Subgroups Defined by Baseline BSFS Score



**P<0.05, **P<0.01, ***P<0.001 vs placebo. P-value vs placebo is from Cochran–Mantel–Haenszel test, stratified by gender. BSFS, Bristol Stool Form Scale; CI, confidence interval; CSBM, complete spontaneous bowel movement.*

- More plecanatide-treated patients were durable overall CSBM responders compared with placebo (Figure 4).

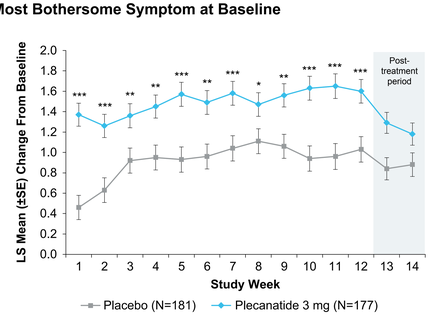
Figure 5. Treatment Satisfaction Scores at Week 12 in Subgroups Defined by Baseline BSFS Score



**P<0.05, **P<0.01, ***P<0.001 vs placebo. P-value is from the pairwise comparison of LS means between the placebo group and the specified treatment group using an analysis of covariance model with fixed effect for treatment and covariates of gender and corresponding baseline. BSFS, Bristol Stool Form Scale; LS, least squares; SE, standard error.*

- Mean treatment satisfaction scores at Week 12 were statistically significantly greater with plecanatide across all BSFS subgroups (Figure 5).
- In patients who received placebo, mean scores indicated moderately to quite satisfied (2–3); patients who received plecanatide indicated quite to extremely satisfied (3–4).

Figure 6. Stool Consistency (BSFS Score): Change From Baseline by Week in Patients Reporting "Hard Stools" as Their Most Bothersome Symptom at Baseline



**P<0.05, **P<0.01, ***P<0.001 vs placebo. P-value is from the pairwise comparison of LS means between the placebo group and the specified treatment group using an analysis of covariance model with fixed effect for treatment and covariates of gender and corresponding baseline.*

- In patients who reported "hard stools" as their most bothersome symptom at baseline, mean (SD) baseline BSFS scores were 2.10 (0.884) and 2.11 (1.028) in the placebo (N=181) and plecanatide (N=177) arms, respectively.
- Patients in this subgroup treated with plecanatide experienced statistically significant improvement in stool consistency across 12 weeks of treatment compared with placebo (Figure 6).
- The overall average estimate of change from baseline in stool consistency across 12 weeks was 1.48 with plecanatide and 0.89 with placebo (*P*<0.001).

KEY FINDINGS

- In this post hoc analysis of patients with CIC, plecanatide treatment showed significantly greater improvements in stool consistency, straining severity, and weekly CSBM frequency – as well as greater durable overall responder rate and treatment satisfaction score – across all subgroups defined by baseline BSFS score.
- For patients indicating "hard stools" as their most bothersome symptom at baseline, plecanatide resulted in significant improvement in stool consistency across 12 weeks of treatment compared with placebo.
- Results of this analysis show that plecanatide is an efficacious treatment option for the management of stool consistency, particularly in patients reporting "hard stools" as their most bothersome symptom.

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Disclosures

Lucinda A. Harris is a consultant for Allergan Pharmaceuticals, Alnylam, Gemelli Biotech, Ironwood Pharmaceuticals, the Rome Foundation, Salix Pharmaceuticals, and Takeda (Shire). Jennifer Winter, Andrew Herman, and Brooks Cash have nothing to disclose. Sarah M. Lorenzen was an employee at Salix Pharmaceuticals at the time of analysis.

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