*Original Research*

# The Effect of Acid Suppression Therapy on the Safety and Efficacy of Plecanatide: Analysis of Randomized Phase III Trials

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## ABSTRACT

**Purpose:** Plecanatide, an approved therapy for chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation, is an analogue of uroguanylin that replicates its pH-sensitive activity and binds to guanylate cyclase-C receptors expressed on intestinal epithelium, stimulating fluid secretion. This analysis explores concomitant acid suppression therapy's effect on the efficacy and safety of plecanatide in adults with CIC.

**Methods:** Data from 2 placebo-controlled, 12-week Phase III trials of plecanatide in CIC were pooled. Patients were randomized to receive placebo, plecanatide 3 mg, or plecanatide 6 mg. The primary endpoint was the durable, overall complete spontaneous bowel movement (CSBM) response rate (defined as ≥3 CSBMs in a given week and ≥1 CSBM increase from baseline within a week for ≥9 of 12 weeks, including ≥3 of the last 4 treatment weeks). Safety was also evaluated. Results were stratified by concomitant use or nonuse of acid suppression therapy.

**Findings:** Of the pooled intent-to-treat population, 338 of 2639 patients (12.8%) received concomitant acid suppression medication. Efficacy response rates in patients using acid suppressors were 23.6% with plecanatide 3 mg ($P = 0.001$ vs placebo), 22.1% with plecanatide 6 mg ($P = 0.002$), and 7.6% with placebo. Responses were similar in patients not using acid suppressors: 20.4% (plecanatide 3 mg, $P < 0.001$), 19.6% (plecanatide 6 mg, $P < 0.001$), and 12.1% (placebo). Serious adverse events were experienced by 3.3% of patients who used concomitant acid suppression and 1.0% of those who did not.

**Implications:** Plecanatide treatment is safe and efficacious for patients with CIC when administered with concomitant acid suppression medication. ClinicalTrials.gov identifiers: NCT02122471 and NCT01982240. (*Clin Ther.* 2022;44:98–110.)


**Key words:** constipation, functional gastrointestinal diseases, irritable bowel syndrome, plecanatide.

## INTRODUCTION

Chronic idiopathic constipation (CIC) is a bothersome condition characterized by decreased stool frequency (<3 defecations per week) and/or associated symp-

AE, adverse event; BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement; GC-C, guanylate cyclase-C; GERD, gastroesophageal reflux disease; $H_2$ blockers, histamine $H_2$ receptor antagonists; IBS-C, irritable bowel syndrome with constipation; ITT, intention-to-treat; ITT-E, intention-to-treat efficacy; PGA, Patient Global Assessment; PPI, proton pump inhibitor; SBM, spontaneous bowel movement; TEAE, treatment-emergent adverse event.

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toms, including straining, lumpy or hard stools, incomplete evacuation, and/or the sensation of anorectal obstruction.[1–3] CIC affects approximately 14% of the North American population,[4] frequently interfering with daily activities (including work and/or school attendance) and reducing quality of life.[2] Less than half of individuals with CIC seeking symptom relief consult their physicians, and few are completely satisfied with subsequent care.[1]

Uroguanylin, predominantly expressed by epithelial cells in the gastrointestinal tract,[5] contributes to normal bowel homeostasis by activating the guanylate cyclase-C (GC-C) receptor, stimulating intracellular cyclic guanosine monophosphate synthesis and subsequently deactivating the Na-H channels and activating the cystic fibrosis transmembrane conductance regulator (CFTR).[6] Activation of CFTR facilitates the secretion of chloride, bicarbonate, and then water into the intestinal lumen. This efflux of fluid leads to improved bowel movements by softening the stool and facilitating peristalsis.[6] Plecanatide is an analogue of the human endogenous peptide uroguanylin and is indicated for the treatment of CIC and irritable bowel syndrome with constipation (IBS-C) in adults.[7] It is structurally identical to uroguanylin, with the exception of a single amino acid substitution, and replicates the activity of uroguanylin on GC-C receptors in the gastrointestinal tract.[6]

Similar to uroguanylin, the binding of plecanatide to GC-C receptors is pH-sensitive and optimal in the slightly acidic environment (pH 5–7) of the proximal small intestine.[8–11] Research suggests that proton pump inhibitors (PPIs) or histamine $H_2$ receptor antagonists ($H_2$ blockers) do not change the pH of the duodenum.[12,13] Because many individuals with CIC also experience gastroesophageal reflux disease (GERD),[14] concomitant acid suppression therapy (e.g., PPIs and $H_2$ blockers) is not uncommon in these patient populations.[15] Understanding the potential impact of these agents on the clinical effects of plecanatide is important.

The efficacy and safety of plecanatide 3 mg and 6 mg for the treatment of CIC were previously established in two 12-week, randomized, double-blind, placebo-controlled clinical trials (NCT02122471 and NCT01982240).[16,17] Currently, only the 3 mg dose is approved by the US Food and Drug Administration; however, results of treatment with the 6 mg dose are also included in this analysis.

Because CIC presents as a continuum of multiple symptoms (e.g., abdominal pain, bloating, and discomfort) and common comorbidities (e.g., GERD), concomitant medication, such as acid suppression therapy, may be necessary and can vary from patient to patient. This study aims to support the use of plecanatide treatment of patients with CIC regardless of concomitant acid suppressor use. In addition, because plecanatide acts through a pH-dependent mechanism, the objective of this *post hoc* analysis was to explore the impact of concomitant acid suppressor use on the efficacy and safety of plecanatide in adults with CIC.

## METHODS

### Study Design and Protocol

Data were extracted from two 12-week, randomized, double-blind, placebo-controlled clinical trials that enrolled adults (aged ≥18 years) who met modified Rome III criteria for CIC.[16,17] Study materials were reviewed and approved by institutional review boards before study initiation. Studies were conducted in accordance with the International Conference on Harmonisation E6 Consolidated Guidance for Good Clinical Practice and the Declaration of Helsinki; informed consent was obtained. Patients were stratified by concomitant acid suppressor use (yes vs no). In both studies, patients were randomly assigned (1:1:1) to receive plecanatide 3 mg, plecanatide 6 mg, or placebo once daily.[16,17] Sample size determinations and randomization procedures were previously reported.[16,17]

For the current analysis, acid suppression medication was defined as PPIs and/or $H_2$ blockers; prescription and over-the-counter options were allowed. An exploratory subgroup analysis was performed separately in a PPI-only group, and this subgroup was compared to the subgroup with concomitant PPI and/or $H_2$ blocker therapy. Medication use was reported by patients, but dosages were not captured. Eligibility criteria permitted patients receiving concomitant therapy with PPIs and/or $H_2$ blockers to enroll if the dosing of the acid suppressor was not stopped or changed during the study. By pooling data from the 2 Phase III studies, there was a sufficiently large sample size to determine the efficacy of plecanatide in patients with CIC using concomitant acid suppression medication.

### Outcomes

The primary efficacy endpoint in these studies was the durable, overall complete spontaneous bowel movement (CSBM) response rate (the percentage of patients who had ≥3 CSBMs in a given week and an increase of ≥1 CSBMs from baseline in the same week for ≥9 of the 12 treatment weeks and ≥3 of the last 4 weeks of study treatment).[16,17] Secondary and additional outcome measures included changes from baseline in CSBM and spontaneous bowel movement (SBM) frequency, time to first CSBM or SBM from start of study medication use, and the percentages of patients experiencing an SBM or a CSBM within 24 hours of the first dose of study medication. Stool consistency was measured by the Bristol Stool Form Scale.[18] Daily CIC symptom scores were assessed using a 5-point Likert scale (with 0 indicating none to 4 indicating very severe). Patient Global Assessment (PGA) questionnaire scores for constipation severity, constipation symptoms, and treatment satisfaction were also evaluated. Standard safety evaluations were conducted in both studies.[16,17] Adverse events (AEs) were derived from unsolicited reports from patients, observation, and routine open questions; assessed for frequency and severity; and classified for relatedness to the study medication. In both trials, reports of "diarrhea" were recorded in the standard case report form, whereas reports of "an increased number of stools" were assessed to differentiate the potentially desirable therapeutic effect from an unexpected or unwanted AE.[19]

### Statistical Analysis

In both studies, efficacy was analyzed in the intention-to-treat efficacy (ITT-E) population (i.e., all unique patients who were randomized into the studies). To maintain clinical study database integrity, duplicate patients were excluded to ensure that patients were only counted once in the ITT-E population. Patients were considered duplicates if they registered multiple times across and within studies at different sites, potentially misrepresenting themselves as plecanatide-naive patients. Safety was analyzed in all patients in the safety population who received ≥1 dose of study medication, excluding duplicates. Descriptive statistics assessing the incidence, nature, and severity of AEs occurring during the treatment period were used to characterize safety (safety population). Because dose interruptions were not permitted, patients could discontinue treatment if they could not tolerate the medication and had an adverse event, such as diarrhea.[20]

The primary endpoint (overall response rate) was analyzed using the Cochran-Mantel-Haenszel hypothesis test. The secondary endpoints (CSBM and SBM frequency, stool consistency, CIC symptom scores, and PGA scores) were assessed using linear mixed-effect models that incorporated treatment, sex, and week as fixed or repeated effects and including other factors of interest and their treatment interaction as additional terms. Time to first CSBM and SBM was measured using nonparametric Kaplan-Meier survival methods. For all statistical testing, a 2-sided $\alpha = 0.05$ was used, with $P < 0.05$ indicating statistical significance.

Comparisons between the placebo group and each plecanatide group (3 and 6 mg) were assessed separately for the acid suppression cohort and the no acid suppression cohort. In this *post hoc* analysis, the primary endpoint was the efficacy responder rate (i.e., durable overall CSBM response rate). For the responder analysis, patients with ≤4 complete diary days were considered "non-responders" for that week; calculations for patients with 4 to 6 assessments in a week were based on a mean replacement approach method. Patients with no assessments in a week were categorized as missing in the linear mixed model. For change from baseline endpoints, mean weekly scores during a given week were calculated as the mean of the nonmissing scores in that week.

## RESULTS

### Patient Disposition and Demographic Characteristics

The pooled ITT population for the current analysis comprised 2639 patients, of whom 338 (12.8%) received concomitant acid suppression medication (plecanatide 3 mg, n = 106/877; plecanatide 6 mg, n = 113/877; placebo, n = 119/885). The pooled safety population comprised 2627 patients (plecanatide 3 mg, n = 875; plecanatide 6 mg, n = 877; placebo, n = 875). Overall, 337 patients (12.8%) included in the safety analysis were using concomitant acid suppression medication (plecanatide 3 mg, n = 107; plecanatide 6 mg, n = 112; placebo, n = 118).

Sex, race, and body mass index distributions were broadly similar across the treatment groups (Table I). Most patients (74.8%–86.6% across groups) were female. However, patients taking acid suppression

Table I. Demographic and baseline characteristics of patients receiving and not receiving concomitant acid suppression therapy (intention-to-treat population).

| Characteristic | Receiving Concomitant Acid Suppression Therapy | | | Not Receiving Concomitant Acid Suppression Therapy | | |
|---|---|---|---|---|---|---|
| | Placebo (n = 119) | Plecanatide 3 mg (n = 106) | Plecanatide 6 mg (n = 113) | Placebo (n = 766) | Plecanatide 3 mg (n = 771) | Plecanatide 6 mg (n = 765) |
| Age, y | | | | | | |
| Mean (SD) | 54.8 (12.2) | 56.5 (12.5) | 53.1 (12.2) | 44.0 (14.0) | 43.7 (14.2) | 43.9 (14.0) |
| Median (range) | 56 (27–78) | 59 (24–79) | 53 (18–78) | 44 (18–80) | 43 (18–80) | 44 (18–80) |
| Sex, No. (%) | | | | | | |
| Female | 101 (85.7) | 79 (74.5) | 97 (86.7) | 595 (77.7) | 619 (80.3) | 610 (79.8) |
| Male | 17 (14.3) | 27 (25.5) | 15 (13.3) | 171 (22.3) | 152 (19.7) | 154 (20.2) |
| Race, No. (%) | | | | | | |
| White | 95 (79.8) | 83 (78.3) | 86 (76.1) | 552 (72.1) | 549 (71.2) | 531 (69.5) |
| Black | 24 (20.2) | 20 (18.9) | 21 (18.6) | 170 (22.2) | 191 (24.8) | 185 (24.2) |
| Asian | 0 (0) | 2 (1.9) | 2 (1.8) | 27 (3.5) | 18 (2.3) | 27 (3.5) |
| Other | 0 (0) | 1 (0.9) | 4 (3.6) | 17 (2.2) | 13 (1.7) | 21 (2.8) |
| BMI, kg/m$^2$ | | | | | | |
| Mean (SD) | 29.5 (5.2) | 30.1 (4.9) | 28.9 (5.1) | 27.8 (5.1) | 28.1 (5.0) | 28.2 (5.1) |
| Median (range) | 28.6 (18.6–39.8) | 28.8 (20.3–39.9) | 28.1 (18.9–39.9) | 27.3 (17.8–41.7) | 27.7 (18.2–39.9) | 27.8 (18.1–40.0) |
| Concomitant GERD, No. (%) | 97 (81.5) | 88 (83.0) | 96 (85.0) | 41 (5.4) | 41 (5.3) | 59 (7.7) |

BMI = body mass index; GERD = gastroesophageal reflux disease; ITT = intention-to-treat; SD = standard deviation.

medication were approximately 10 years older than those not taking acid suppressors (acid suppression cohort: plecanatide groups: mean [SD] age, 54.8 [12.4] years; placebo: mean [SD] age, 54.8 [12.2] years; no acid suppression cohort: plecanatide groups: mean [SD] age, 43.9 [14.1] years; placebo: 44.0 [14.0] years) (Table I). A total of 281 patients (83.1%) taking acid suppression medication had GERD compared with 141 (6.1%) of those not taking acid suppression medication. Other gastrointestinal disorders in patients taking acid suppression medication included dyspepsia (10.7%), Barrett esophagus (1.2%), and peptic ulcer disease (0.9%).

Among patients using acid suppression medication, PPIs were used by 86.3% in the plecanatide groups and 86.4% in the placebo group; $H_2$ blockers were used by 18.3% in the plecanatide groups and 16.9% in the placebo group (Table II). Percentages for PPIs and $H_2$ blockers are presented per the total population for each treatment arm; percentages do not total 100 because of a small subset of patients who used both treatments. If a patient used ≥1 medications in a drug class, the patient was counted once in the respective drug class. The most used PPI was omeprazole, and the most common $H_2$ blocker was ranitidine (Table II).

## Primary Efficacy Endpoint

Among patients using acid suppression medication, durable overall CSBM responses during the 12-week treatment period were found in 25 of 106 patients (23.6%; 95% CI, 15.9%–32.8%) taking plecanatide 3 mg ($P = 0.001$ vs placebo) and 25 of 113 (22.1%; 95% CI, 14.9%–30.9%) of those taking plecanatide 6 mg ($P = 0.002$ vs placebo) compared with 9 of 119 (7.6%; 95% CI, 3.5%–13.9%) of those taking placebo (Figure 1). The relative difference between the treatment and placebo groups (adjusted for sex) in the proportion of responders was 15.6% (95%

Table II. Baseline PPI and $H_2$ blocker use in patients with concomitant acid suppression therapy (safety population)*.

| Agent | No. (%) of Patients | | |
|---|---|---|---|
| | Placebo (n = 118) | Plecanatide 3 mg (n = 107) | Plecanatide 6 mg (n = 112) |
| PPIs | 102 (86.4) | 92 (86.0) | 97 (86.6) |
| Omeprazole | 63 (53.4) | 40 (37.4) | 49 (43.8) |
| Esomeprazole magnesium | 15 (12.7) | 19 (17.8) | 14 (12.5) |
| Pantoprazole | 7 (5.9) | 6 (5.6) | 12 (10.7) |
| Lansoprazole | 8 (6.8) | 8 (7.5) | 8 (7.1) |
| Pantoprazole sodium sesquihydrate | 3 (2.5) | 12 (11.2) | 8 (7.1) |
| Dexlansoprazole | 3 (2.5) | 4 (3.7) | 5 (4.5) |
| Esomeprazole | 4 (3.4) | 1 (0.9) | 0 |
| Omeprazole magnesium | 0 | 2 (1.9) | 1 (0.9) |
| Rabeprazole sodium | 0 | 2 (1.9) | 0 |
| Omeprazole sodium bicarbonate | 0 | 0 | 2 (1.8) |
| Rabeprazole | 0 | 1 (0.9) | 0 |
| $H_2$ blockers | 20 (16.9) | 20 (18.7) | 20 (17.9) |
| Ranitidine | 14 (11.9) | 9 (8.4) | 10 (8.9) |
| Ranitidine hydrochloride | 4 (3.4) | 7 (6.5) | 6 (5.4) |
| Famotidine | 3 (2.5) | 4 (3.7) | 3 (2.7) |
| Ranitidine hydrochloride, sodium hydrochloride | 0 | 0 | 1 (0.9) |
| Cimetidine | 0 | 1 (0.9) | 0 |

$H_2$ = histamine$_2$; PPI = proton pump inhibitor.

* Percentages for PPIs and $H_2$ blockers are presented per the total population for each treatment arm; percentages do not total 100 because of a small subset of patient who used both. If a patient had ≥1 medication in a drug class or preferred term, the patient is counted once in the respective drug class or preferred term.

CI, 6.1%–25.1%) for those taking plecanatide 3 mg and 14.6% (95% CI, 5.6%–23.6%) for those taking plecanatide 6 mg. In patients not using acid suppression medication, durable overall CSBM responses during the 12-week treatment period were found in 157 of 771 patients (20.4%; 95% CI, 17.6–23.4) taking plecanatide 3 mg, 150 of 764 patients (19.6%; 95% CI, 16.9–22.6) taking plecanatide 6 mg, and 93 of 766 patients (12.1%; 95% CI, 9.9–14.7) taking placebo ($P < 0.001$ for both comparisons) (Figure 1). The relative difference between the treatment and placebo groups (adjusted for sex) in the proportion of responders was 8.2% (95% CI, 4.5%–11.8%) for plecanatide 3 mg and 7.5% (95% CI, 3.9%–11.2%) for plecanatide 6 mg. The proportion of plecanatide-treated patients using acid suppressors who were durable overall CSBM responders was not significantly different from those not using acid suppressors (3 mg: 23.6% vs 20.4%, $P = 0.443$; 6 mg: 22.1% vs 19.6%, $P = 0.536$). In both the evaluation of the primary endpoint in plecanatide arms compared with placebo and with acid suppression therapy use vs without, results for plecanatide 3 mg and 6 mg were similar. In the exploratory analysis of the subgroup defined by PPI use only, primary endpoint results appear similar to those in the subgroup with concomitant PPI and/or $H_2$ blocker use; significantly higher rates of responders were observed in the plecanatide 3 mg and 6 mg cohorts compared with placebo in both patients with concomitant PPI use and those without PPI use (Supplemental Table I).

### Secondary and Additional Efficacy Endpoints

Plecanatide 3 mg and 6 mg with or without concomitant acid suppression therapy significantly

increased the mean weekly CSBM and SBM frequencies from baseline during the 12-week treatment period compared with placebo ($P < 0.001$ vs placebo for all comparisons) (Table III). Results observed with plecanatide 3 mg and 6 mg were similar in patients with and those without concomitant acid suppression therapy ($P \geq 0.11$ for all comparisons). Improvements in weekly CSBM and SBM frequencies were similar in the exploratory subgroup analysis defined by PPI use only (Supplemental Table I).

Among patients using acid suppression therapy, times to first CSBM from start of plecanatide therapy were significantly shorter in the plecanatide 3 mg and 6 mg groups than in the placebo group ($P \leq 0.002$ vs placebo for all comparisons) (Figure 2A). For those not using acid suppression therapy, time to first CSBM was significantly shorter in patients treated with plecanatide 3 mg compared with placebo ($P < 0.001$) (Figure 2B). Times to first SBM were significantly shorter for all plecanatide groups (both 3 mg and 6 mg groups in the patients using acid suppression therapy and those not, $P \leq 0.002$ vs placebo for all comparisons) (Figures 3A and 3B). A significantly greater proportion of patients using acid suppressors experienced a CSBM (plecanatide 3 mg, 30.2%; plecanatide 6 mg, 28.3%; vs placebo, 12.6%; $P \leq 0.003$ vs placebo for both comparisons) or an SBM (plecanatide 3 mg, 63.2%; plecanatide 6 mg, 60.2%; vs placebo, 44.5%; $P \leq 0.016$ vs placebo for both comparisons) within 24 hours after starting plecanatide therapy compared with the corresponding placebo group. Patients not using acid suppression therapy experienced similarly significant results: CSBM was experienced within 24 hours for 24.5% of plecanatide 3 mg, 22.1% of plecanatide 6 mg, and 12.8% of placebo groups ($P < 0.001$ both doses), and an SBM was experienced within 24 hours in 49.9% of plecanatide 3 mg, 50.5% of plecanatide 6 mg, and 37.2% of placebo groups.

Across all 4 plecanatide treatment groups, statistically significant improvements were found in stool consistency from baseline during the 12-week treatment period compared with placebo ($P < 0.001$ for all comparisons vs placebo) (Table III). Plecanatide treatment had statistically significantly greater efficacy across secondary endpoints, including straining, abdominal pain, and abdominal discomfort from baseline during the 12-week treatment period, compared with placebo ($P$ ranging from $< 0.001$ to 0.05 vs placebo for the different comparisons) (Table III). Abdominal bloating improved with plecanatide 3 mg over placebo regardless of acid suppression use ($P$ ranging from 0.013 to $< 0.001$); plecanatide 6 mg significantly improved bloating among patients not using acid suppressors ($P = 0.049$) and trended toward improvement in the acid suppression group. For all

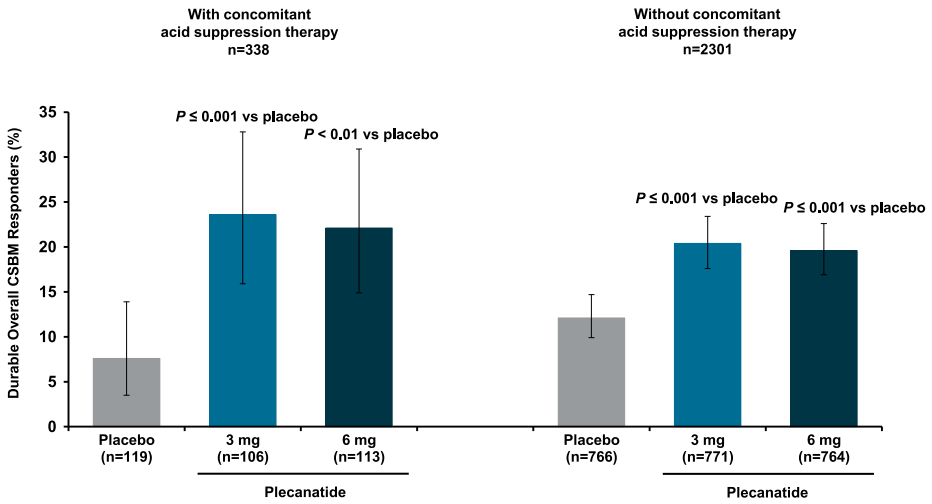


Figure 1. Percentage of patients with durable overall complete spontaneous bowel movement (CSBM) response (primary efficacy endpoint), stratified by concomitant acid suppression therapy use. Error bars indicate 95% CIs.

Table III. Change from baseline in bowel movement frequency, stool consistency, and CIC symptoms in patients with and without concomitant acid suppression therapy (intention-to-treat population).

| Variable | Receiving Concomitant Acid Suppression Therapy | | | Not Receiving Concomitant Acid Suppression Therapy | | |
|---|---|---|---|---|---|---|
| | Placebo (n = 119) | Plecanatide 3 mg (n = 106) | Plecanatide 6 mg (n = 113) | Placebo (n = 766) | Plecanatide 3 mg (n = 771) | Plecanatide 6 mg (n = 764) |
| **Bowel movements** | | | | | | |
| CSBMs per week* | | | | | | |
| LS mean (SE) | 1.09 (0.25) | 2.58 (0.24) | 2.46 (0.25) | 1.32 (0.11) | 2.35 (0.11) | 2.15 (0.11) |
| Difference from placebo (95% CI) | | 1.49 (0.87 to 2.11) | 1.37 (0.77 to 1.97) | | 1.03 (0.75 to 1.31) | 0.82 (0.54 to 1.10) |
| *P* vs NO acid suppression† | 0.05 | 0.65 | 0.60 | | | |
| *P* vs placebo | | <0.001 | <0.001 | | <0.001 | <0.001 |
| SBMs per week* | | | | | | |
| LS mean (SE) | 1.34 (0.33) | 3.56 (0.32) | 3.49 (0.334) | 1.39 (0.14) | 2.82 (0.14) | 2.89 (0.14) |
| Difference from placebo (95% CI) | | 2.23 (1.41 to 3.05) | 2.15 (1.35 to 2.95) | | 1.43 (1.08 to 1.79) | 1.50 (1.14 to 1.85) |
| *P* vs NO acid suppression† | 0.50 | 0.11 | 0.29 | | | |
| *P* vs placebo | | <0.001 | <0.001 | | <0.001 | <0.001 |
| Stool consistency* | | | | | | |
| LS mean (SE) | 0.70 (0.16) | 1.52 (0.14) | 1.54 (0.11) | 0.84 (0.05) | 1.52 (0.05) | 1.50 (0.05) |
| Difference from placebo (95% CI) | | 0.82 (0.55 to 1.09) | 0.84 (0.58 to 1.10) | | 0.68 (0.57 to 0.80) | 0.66 (0.55 to 0.78) |
| *P* vs NO acid suppression† | 0.54 | 0.33 | 0.27 | | | |
| *P* vs placebo | | <0.001 | <0.001 | | <0.001 | <0.001 |
| **Daily symptom scores** | | | | | | |
| Straining* | | | | | | |
| LS mean (SE) | −0.41 (0.08) | −0.76 (0.08) | −0.80 (0.08) | −0.62 (0.03) | −0.93 (0.03) | −0.87 (0.03) |
| Difference from placebo (95% CI) | | −0.35 (−0.54 to −0.16) | −0.39 (−0.58 to −0.20) | | −0.31 (−0.39 to −0.23) | −0.25 (−0.33 to −0.18) |
| *P* vs NO acid suppression† | 0.09 | 0.31 | 0.81 | | | |
| *P* vs placebo | | <0.001 | <0.001 | | <0.001 | <0.001 |
| Abdominal pain severity* | | | | | | |
| LS mean (SE) | −0.31 (0.07) | −0.51 (0.06) | −0.48 (0.07) | −0.40 (0.03) | −0.48 (0.03) | −0.48 (0.03) |
| Difference from placebo (95% CI) | | −0.20 (−0.36 to −0.03) | −0.17 (−0.33 to −0.01) | | −0.08 (−0.14 to −0.01) | −0.08 (−0.14 to −0.01) |
| *P* vs NO acid suppression† | 0.12 | 0.74 | 0.96 | | | |
| *P* vs placebo | | 0.02 | 0.04 | | 0.02 | 0.02 |

(*continued on next page*)

Table III. (*continued*)

| Variable | Receiving Concomitant Acid Suppression Therapy | | | Not Receiving Concomitant Acid Suppression Therapy | | |
|---|---|---|---|---|---|---|
| | Placebo (n = 119) | Plecanatide 3 mg (n = 106) | Plecanatide 6 mg (n = 113) | Placebo (n = 766) | Plecanatide 3 mg (n = 771) | Plecanatide 6 mg (n = 764) |
| Abdominal bloating severity* | | | | | | |
| LS mean (SE) | −0.29 (0.07) | −0.50 (0.07) | −0.44 (0.07) | −0.44 (0.03) | −0.56 (0.03) | −0.51 (0.03) |
| Difference from placebo (95% CI) | | −0.21 (−0.38 to −0.05) | −0.14 (−0.31 to 0.02) | | −0.11 (−0.18 to −0.05) | −0.07 (−0.13 to −0.0) |
| *P* vs NO acid suppression† | 0.03 | 0.72 | 0.58 | | | |
| *P* vs placebo | | 0.013 | 0.08 | | <0.001 | 0.05 |
| Abdominal discomfort severity* | | | | | | |
| LS mean (SE) | −0.30 (0.07) | −0.54 (0.07) | −0.47 (0.07) | −0.47 (0.03) | −0.57 (0.03) | −0.54 (0.03) |
| Difference from placebo (95% CI) | | −0.24 (−0.40 to −0.07) | −0.17 (−0.33 to −0.0) | | −0.10 (−0.17 to −0.03) | −0.07 (−0.14 to −0.0) |
| *P* vs NO acid suppression† | 0.01 | 0.88 | 0.56 | | | |
| *P* vs placebo | | 0.006 | 0.045 | | 0.003 | 0.039 |
| **Patient Global Assessments** | | | | | | |
| Constipation severity‡ | | | | | | |
| LS mean (SE) | −0.7 (0.14) | −1.4 (0.13) | −1.4 (0.15) | −1.3 (0.05) | −1.5 (0.05) | −1.4 (0.05) |
| Difference from placebo (95% CI) | | −0.7 (−1.1 to −0.4) | −0.7 (−1.1 to −0.4) | | −0.3 (−0.4 to −0.1) | −0.2 (−0.3 to −0.0) |
| *P* vs NO acid suppression† | <0.001 | 0.417 | 0.814 | | | |
| *P* vs placebo | | <0.001 | <0.001 | | <0.001 | 0.007 |
| Change in constipation‡ | | | | | | |
| LS mean (SE) | 3.0 (0.12) | 2.4 (0.12) | 2.2 (0.12) | 2.7 (0.04) | 2.2 (0.04) | 2.3 (0.04) |
| Difference from placebo (95% CI) | | −0.6 (−0.9 to −0.3) | −0.8 (−1.1 to −0.5) | | −0.5 (−0.6 to −0.4) | −0.4 (−0.5 to −0.3) |
| *P* vs NO acid suppression† | 0.115 | 0.128 | 0.307 | | | |
| *P* vs placebo | | <0.001 | <0.001 | | <0.001 | <0.001 |
| Treatment satisfaction§ | | | | | | |
| LS mean (SE) | 2.6 (0.14) | 3.5 (0.14) | 3.6 (0.14) | 3.0 (0.05) | 3.5 (0.05) | 3.5 (0.05) |
| Difference from placebo (95% CI) | | 0.9 (0.6 to 1.3) | 1.0 (0.7 to 1.4) | | 0.5 (0.4 to 0.7) | 0.5 (0.4 to 0.7) |

(*continued on next page*)

Table III. (*continued*)

| Variable | Receiving Concomitant Acid Suppression Therapy | | | Not Receiving Concomitant Acid Suppression Therapy | | |
|---|---|---|---|---|---|---|
| | Placebo (n = 119) | Plecanatide 3 mg (n = 106) | Plecanatide 6 mg (n = 113) | Placebo (n = 766) | Plecanatide 3 mg (n = 771) | Plecanatide 6 mg (n = 764) |
| *P* vs NO acid suppression[†] | 0.009 | 0.916 | 0.750 | | | |
| *P* vs placebo | | <0.001 | <0.001 | | <0.001 | <0.001 |

CIC = chronic idiopathic constipation; CI = confidence interval; CSBM = complete spontaneous bowel movement; ITT = intention-to-treat; LS = least squares; SBM = spontaneous bowel movement; SE = standard error.

[*] Change from baseline (overall mean estimate across the 12-week treatment period).

[†] *P* value is from the pairwise comparison of LS means between concomitant use of proton pump inhibitor (PPI) or histamine$_2$ ($H_2$) blocker use (yes vs no) within a treatment group using a linear mixed-effects model with fixed effects for sex (stratification variable), concomitant use of PPI or $H_2$ blocker (yes vs no), week, the interaction of the medication use and week, and the corresponding baseline value and a random intercept for patient. The model accounts for the repeated measurements for each patient.

[‡] Change from baseline at week 12.

[§] Treatment satisfaction at week 12 (not a change from baseline score).

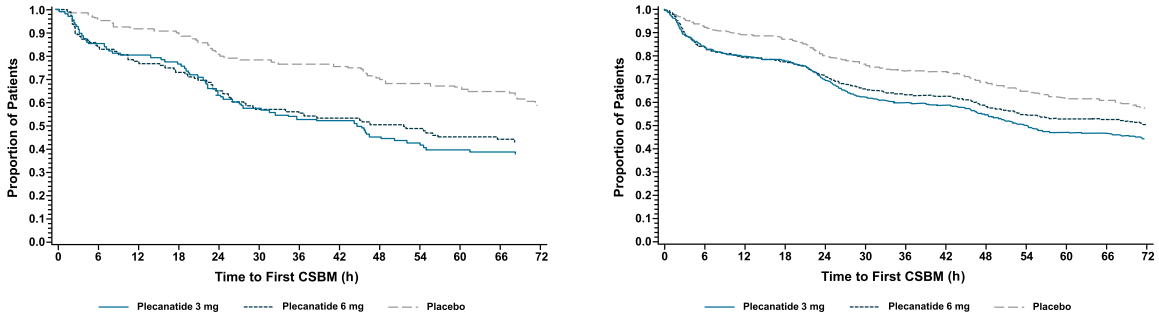


Figure 2. Time to first complete spontaneous bowel movement (CSBM) in (A) patients receiving concomitant acid suppression therapy and (B) those not receiving therapy.

endpoints, pairwise comparisons between concomitant use of acid suppression (yes vs no) within a treatment group did not have significant differences.

PGA questionnaire scores revealed that constipation severity and constipation symptoms were significantly reduced with plecanatide 3 mg or 6 mg compared with placebo among patients using and not using acid suppression medication ($P \leq 0.007$ for all comparisons vs placebo) (Table III). In addition, patient satisfaction with treatment was significantly greater with plecanatide 3 mg or 6 mg compared with placebo among patients using and not using acid suppression medication ($P < 0.001$ for all comparisons vs placebo) (Table III).

## Adverse Events

The treatment-emergent adverse event (TEAE) profile found no new safety signals among patients using concomitant acid suppression medication compared with the full study populations[16,17] or with patients not using acid suppression medication. Table IV provides a summary of TEAEs. The most common TEAE reported

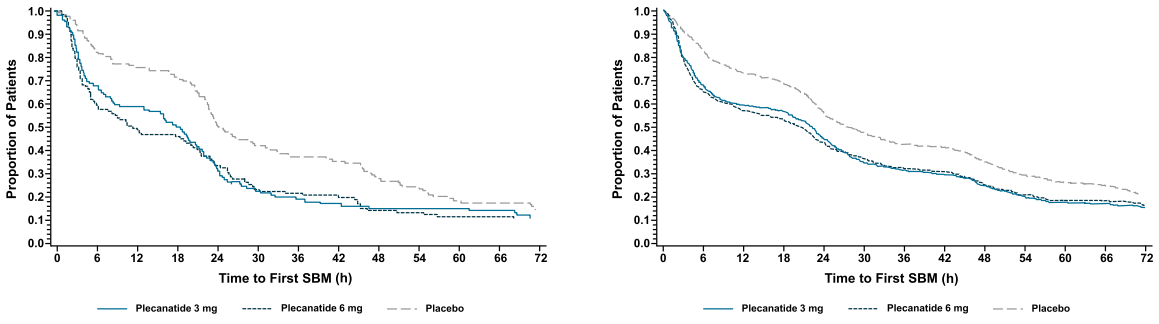


Figure 3. Time to first spontaneous bowel movement (SBM) in (A) patients receiving concomitant acid suppression therapy and (B) those not receiving therapy.

was diarrhea, with a rate of 6.4% in the plecanatide groups (vs 2.5% in the placebo group) among patients using acid suppression medication and of 5.0% (vs 1.1% in the placebo group) among patients not using acid suppression medication (Table IV). The rate of plecanatide treatment discontinuation due to diarrhea was 1.4% in the acid suppression group and 2.1% in the group without acid suppression therapy.

In addition to diarrhea, other TEAEs experienced by ≥2% of patients in any treatment group were nausea, vomiting, abdominal pain, nasopharyngitis, sinusitis, urinary tract infection, upper respiratory tract infection, headache, and dizziness (Table IV). Among patients using acid suppression medication, rates for nausea and vomiting were lowest in the plecanatide 3 mg group compared with the plecanatide 6 mg and placebo groups (nausea: plecanatide 3 mg, 0.9%; plecanatide 6 mg, 2.7%; placebo, 3.4%; vomiting: plecanatide 3 mg, 1.9%; plecanatide 6 mg, 2.7%; placebo, 2.5%). Serious adverse events were experienced by 3.3% of patients using concomitant acid suppression (plecanatide 3 mg, 3.7%; plecanatide 6 mg, 0.9%; placebo, 5.1%) and 1.0% of those who did not use acid suppression (plecanatide 3 mg, 1.2%; plecanatide 6 mg, 1.0%; placebo, 0.8%).

## DISCUSSION

The result of this *post hoc* analysis of 2 large randomized, placebo-controlled Phase III studies suggests that plecanatide is safe and effective as a treatment for CIC when administered with concomitant acid suppression therapy. Stringent efficacy response rates in the previously published source trials were 20.1% (NCT02122471) and 21.0% (NCT01982240) among patients who received plecanatide 3 mg (the approved dose), 20.0% and 19.5% among patients who received plecanatide 6 mg, vs 12.8% and 10.2% among patients who received placebo; differences between each dose of plecanatide and placebo were statistically significant in both trials.[16,17] In this analysis, efficacy response rates remained significantly greater with plecanatide 3 mg or 6 mg vs placebo, both among patients using acid suppression medication (23.6% and 22.1% vs 7.6%) and among those not using acid suppression medication (20.4% and 19.6% vs 12.1%). Patients using concomitant acid suppression medication also had significant improvements on secondary and other endpoints, including more regular and well-formed bowel movements, improved patient-reported constipation symptoms, and greater satisfaction with treatment relative to placebo. The TEAE profile found no new safety signals among patients using acid suppression medication. Patients using acid suppression were older (mean age, 54.8 years) compared with those not undergoing acid suppression (mean age, 43.9 years); however, despite their age difference (GERD is more common with increasing age), the efficacy of plecanatide was unaffected. Furthermore, recently published evidence in patients ≥65 years of age with CIC and IBS-C supports the efficacy and safety of plecanatide in varied age groups.[21]

Most of the patients in the acid suppressor cohort were receiving PPIs. The potential for these agents to affect the activity of concomitantly administered oral medications by way of altering gastric pH and drug solubility has been established.[22,23] However, previous studies[12,13,24] have found that PPIs do not significantly

Table IV. Summary of TEAEs (safety population).

| TEAE | No. (%) of Patients Receiving Concomitant Acid Suppression Therapy | | | No. (%) of Patients Not Receiving Concomitant Acid Suppression Therapy | | |
|---|---|---|---|---|---|---|
| | Placebo (n = 118) | Plecanatide 3 mg (n = 107) | Plecanatide 6 mg (n = 112) | Placebo (n = 757) | Plecanatide 3 mg (n = 768) | Plecanatide 6 mg (n = 765) |
| ≥1 TEAE | 39 (33.1) | 44 (41.1) | 41 (36.6) | 218 (28.8) | 230 (29.9) | 242 (31.6) |
| ≥1 Severe TEAE | 7 (5.9) | 4 (3.7) | 5 (4.5) | 6 (0.8) | 16 (2.1) | 18 (2.4) |
| ≥1 Serious TEAE | 6 (5.1) | 4 (3.7) | 1 (0.9) | 6 (0.8) | 9 (1.2) | 8 (1.0) |
| TEAE experienced by ≥2.0% of patients in any treatment group | | | | | | |
| Diarrhea | 3 (2.5) | 7 (6.5) | 7 (6.3) | 8 (1.1) | 36 (4.7) | 40 (5.2) |
| Nausea | 4 (3.4) | 1 (0.9) | 3 (2.7) | 9 (1.2) | 7 (0.9) | 7 (0.9) |
| Vomiting | 3 (2.5) | 2 (1.9) | 3 (2.7) | 1 (0.1) | 4 (0.5) | 1 (0.1) |
| Abdominal pain | 2 (1.7) | 0 | 3 (2.7) | 6 (0.8) | 6 (0.8) | 8 (1.0) |
| Nasopharyngitis | 2 (1.7) | 0 | 3 (2.7) | 12 (1.6) | 9 (1.2) | 17 (2.2) |
| Sinusitis | 0 | 3 (2.8) | 0 | 3 (0.4) | 9 (1.2) | 6 (0.8) |
| Urinary tract infection | 1 (0.8) | 5 (4.7) | 1 (0.9) | 15 (2.0) | 9 (1.2) | 12 (1.6) |
| Upper respiratory tract infection | 2 (1.7) | 3 (2.8) | 1 (0.9) | 8 (1.1) | 9 (1.2) | 4 (0.5) |
| Headache | 2 (1.7) | 2 (1.9) | 3 (2.7) | 16 (2.1) | 14 (1.8) | 13 (1.7) |
| Dizziness | 4 (3.4) | 0 | 2 (1.8) | 3 (0.4) | 5 (0.7) | 3 (0.4) |
| Discontinued plecanatide therapy | | | | | | |
| Due to TEAE | 5 (4.2) | 6 (5.6) | 4 (3.6) | 15 (2.0) | 32 (4.2) | 38 (5.0) |
| Due to diarrhea | 1 (0.8) | 0 | 3 (2.7) | 3 (0.4) | 18 (2.3) | 14 (1.8) |

TEAE = treatment-emergent adverse event.

alter the pH of the duodenum. Edsbäcker et al.[24] found that pH-dependent budesonide pharmacodynamic properties are not affected by antacids. The results of this study are congruent with findings that acid suppression therapy does not affect the therapeutic effects of pH-dependent drug activity in the small bowel. In addition, if acid suppression therapy did change the small bowel pH, then native uroguanylin binding to GC-C receptor would have been affected, leading to PPI-related constipation. In fact, PPIs can lead to the development of bowel symptoms, with the most common being diarrhea.[25–28] Therefore, it was not surprising to observe higher rates of diarrhea in patients using acid suppression therapy compared with those not using acid suppression therapy. These results establish the efficacy and safety of the concomitant use of plecanatide and PPI in the treatment of patients diagnosed with CIC.

This study has several limitations. Acid suppression therapy was not homogeneous (i.e., patients used a

variety of drugs with different doses, administration schedules, and durations of therapy) because the use of stable acid suppression therapy was permitted but not standardized in the original trials. In addition, acid suppression use was self-reported, and details regarding the dosing, schedule administration, and duration were not collected. Acid suppression use was defined by PPI and/or $H_2$ blocker use; however, exploratory analysis of the primary and bowel movement endpoints suggests that similar results would be expected in patients who only used PPIs. This analysis was performed *post hoc*. Patients were not randomized based on acid suppression use, and this analysis did not control for demographic and baseline characteristics across the acid suppression cohorts. Thus, comparison between the groups is observational and could be subject to confounding.

Plecanatide has been proven effective compared with placebo for the treatment of CIC. Although few studies have focused on the pH-dependent pharmacodynamic properties of small bowel–targeted therapies,[29] to our knowledge, this is the first study to investigate the efficacy and safety of concomitant acid suppressive therapy and plecanatide in a large population of patients with CIC. Because acid suppression therapy has no significant effect on efficacy or safety when administered concomitantly with plecanatide, plecanatide can be administered with concomitant acid suppression medication without affecting efficacy or safety.

## DISCLOSURE

B. Moshiree has been a consultant for or participated in advisory boards for Allergan/Ironwood Pharmaceuticals, Takeda, Progenity, Medtronic, Alfasigma, Alnylam, Nestle Science Institute, QOL Medical, and Salix Pharmaceuticals, and has received grant support from Medtronic and Prometheus Lab. P. Schoenfeld has been a consultant and advisory board member for Salix Pharmaceuticals, Allergan/Ironwood Pharmaceuticals, Phathom Pharmaceuticals, and Takeda Pharmaceuticals, and has received honoraria from Salix Pharmaceuticals, Allergan/Ironwood Pharmaceuticals, and Alnylam Pharmaceuticals. H. Franklin is an employee of Salix Pharmaceuticals. A. Rezaie reports support for research and consultation from Salix Pharmaceuticals, Bayer, and Synergy Pharmaceuticals. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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## SUPPLEMENTARY MATERIALS

Table S1. Primary and bowel movement frequency endpoints in patients with concomitant proton pump inhibitor use

| | With Concomitant PPI Therapy | | | Without Concomitant PPI Therapy | | |
|---|---|---|---|---|---|---|
| | Placebo (n = 102) | Plecanatide 3 mg (n = 92) | Plecanatide 6 mg (n = 97) | Placebo (n = 783) | Plecanatide 3 mg (n = 785) | Plecanatide 6 mg (n = 780) |
| **Primary Endpoint** | | | | | | |
| Responders, n (%) | 7 (6.9) | 21 (22.8) | 19 (19.6) | 95 (12.1) | 161 (20.5) | 156 (20.0) |
| 95% CI (%) | (2.8, 13.6) | (14.7, 32.8) | (12.2, 28.9) | (9.9, 14.6) | (17.7, 23.5) | (17.2, 23.0) |
| *P* value vs placebo | | 0.001 | 0.008 | | <0.001 | <0.001 |
| **CSBMs/week*** | | | | | | |
| LS mean (SE) | 0.96 (0.293) | 2.37 (0.299) | 2.49 (0.306) | 1.25 (0.121) | 2.30 (0.121) | 2.18 (0.122) |
| Difference from placebo (95% CI) | | 1.41 (0.63, 2.19) | 1.53 (0.75, 2.30) | | 1.05 (0.73, 1.37) | 0.93 (0.61, 1.24) |
| *P* value vs placebo | | < 0.001 | < 0.001 | | < 0.001 | < 0.001 |
| **SBMs/week*** | | | | | | |
| LS mean (SE) | 1.13 (0.399) | 3.32 (0.401) | 3.71 (0.419) | 1.31 (0.159) | 2.71 (0.160) | 2.95 (0.160) |
| Difference from placebo (95% CI) | | 2.19 (1.17, 3.22) | 2.58 (1.56, 3.59) | | 1.40 (0.99, 1.81) | 1.64 (1.23, 2.05) |
| *P* value vs placebo | | < 0.001 | < 0.001 | | < 0.001 | < 0.001 |

CI = confidence interval; CSBM = complete spontaneous bowel movement; LS = least squares; PPI = proton pump inhibitor; SBM = spontaneous bowel movement; SE = standard error. *Represents change from baseline (overall average estimate across the 12-week treatment period).