Plecanatide Provides Meaningful Improvements in Patients With Chronic Idiopathic Constipation and Irritable Bowel Syndrome With Constipation Reporting Reduced Quality of Life: Analyses From Four Randomized Phase 3 Trials

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INTRODUCTION

- Chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C) are common disorders affecting 6.9% and 1.4% of the US population, respectively, and significantly impact quality of life (QOL).[1]
  - In 60% of CIC and about 50% of IBS-C patients, symptoms interfered with personal activities approximately 4 days/month (CIC) or 1 day/month (IBS-C).[2,3]
  - CIC and IBS-C also frequently impact work and/or school attendance.[2,3]
- 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.[4,5]
- Plecanatide has demonstrated clinical efficacy with a benign safety and tolerability profile in four large double-blind, placebo-controlled, phase 3 clinical trials (2 in patients with CIC [NCT02122471 and NCT01982240], two in IBS-C [NCT02387359 and NCT02493452]) and is approved for the treatment of adults with CIC and IBS-C in the United States.[6-8]
  - Plecanatide treatment resulted in significant improvements from baseline in Patient Assessment of Constipation (PAC)-QOL total score at each assessment (Weeks 4, 8, and 12).[6,7]
  - In the pivotal IBS-C trials, significantly more plecanatide-treated patients indicated being satisfied with treatment compared with placebo-treated patients at Week 12.[8]
- The objective of this post hoc analysis is to evaluate the impact of plecanatide on QOL among the subgroup of patients with the lowest CIC/IBS-C-targeted QOL at baseline (i.e., patients experiencing the greatest impact of CIC/IBS-C on their QOL and therefore may have the most to gain from effective treatment) from four phase 3 trials (2 in CIC, 2 in IBS-C).

METHODS

- Patients who met Rome III criteria for CIC or IBS-C were randomized to receive plecanatide 3 mg or placebo. Data were pooled separately for the two CIC and two IBS-C studies.
- PAC-QOL, a validated 28-item questionnaire measuring worries/concerns, physical discomfort, psychosocial discomfort, satisfaction, and overall effects, was administered to CIC patients.
  - Patients rated their responses using a scale of 0 (not at all) to 4 (extremely/all the time).
  - ≥1-point reduction in PAC-QOL total score is a validated threshold for clinically meaningful response.
- IBS-QOL, a validated 34-item questionnaire measuring dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual items, relationship, and overall effects, was administered to IBS-C patients.
  - Patients rated their responses using a scale of 1 (not at all) to 5 (extremely/a great deal).
  - ≥14-point reduction in IBS-QOL total score is a validated indicator for clinically meaningful response.
- PAC-QOL and IBS-QOL were administered on Day 1 and Weeks 4, 8, and 12.
  - Higher scores indicate lower QOL.
- Subgroup analysis focused on the quintile (20%) of patients with the lowest QOL at baseline.

RESULTS

Table 1. Quintile Distribution of Baseline QOL Scores

Quintile	CIC Studies		IBS-C Studies	
	PAC-QOL Total Score, range	Patients, n (%)	IBS-QOL Total Score, range	Patients, n (%)
1st	0–1.46	416 (20.6%)	0–21.32	417 (20.2%)
2nd	1.47–1.96	410 (20.3%)	21.33–37.50	424 (20.5%)
3rd	1.97–2.39	414 (20.5%)	37.51–51.47	401 (19.4%)
4th	2.40–2.86	383 (19%)	51.48–69.12	423 (20.4%)
5th	2.87–4.00	396 (19.6%)	69.13–100	404 (19.5%)

CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; IBS-QOL, Irritable Bowel Syndrome Quality of Life; PAC-QOL, Patient Assessment of Constipation Quality of Life; QOL, quality of life.

- Subgroup analysis included patients with the poorest QOL, defined as the quintile of patients with the highest PAC-QOL or IBS-QOL total scores at baseline.
  - Variations in the percentage of the actual subgroup population were present due to multiple occasions of the same score (Table 1).

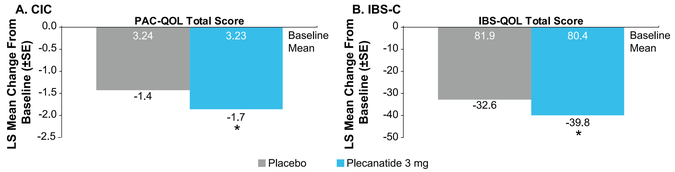
Table 2. Demographics and Clinical Characteristics of CIC and IBS-C Patients in the Lowest QOL Quintile at Baseline

	CIC		IBS-C	
	Placebo n=123	Plecanatide 3 mg n=146	Placebo n=127	Plecanatide 3 mg n=144
Age, yrs, mean (SD)	45.0 (13.1)	43.8 (11.7)	43.1 (12.9)	44.0 (12.5)
Sex, n (%)				
Male	32 (26.0)	23 (15.8)	24 (18.9)	35 (24.3)
Female	91 (74.0)	123 (84.2)	103 (81.1)	109 (75.7)
Race, n (%)				
White	86 (69.9)	106 (72.6)	88 (69.3)	100 (69.4)
Black/African American	32 (26.0)	36 (24.7)	36 (28.3)	37 (25.7)
Asian	3 (2.4)	2 (1.4)	3 (2.4)	5 (3.5)
Other	2 (1.6)	2 (1.4)	0	2 (1.4)
Ethnicity, n (%)				
Hispanic/Latino	61 (49.6)	71 (48.6)	66 (52.0)	79 (54.9)
Non-Hispanic/Latino	62 (50.4)	75 (51.4)	61 (48.0)	65 (45.1)
BMI (kg/m^2), mean (SD)	29.0 (5.8)	28.9 (5.2)	29.2 (5.1)	28.8 (4.6)

CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; QOL, quality of life; SD, standard deviation.

- Of 1762 (CIC) and 1453 (IBS-C) patients treated with placebo or plecanatide 3 mg in the intention-to-treat populations, 269 patients with CIC (PBO, n=123; plecanatide, n=146) and 271 patients with IBS-C (PBO n=127; plecanatide n=144) were included in the lowest QOL subgroup (Table 2).
- Demographics in the lowest QOL subgroup were similar to those in the total pooled populations.[5-7]

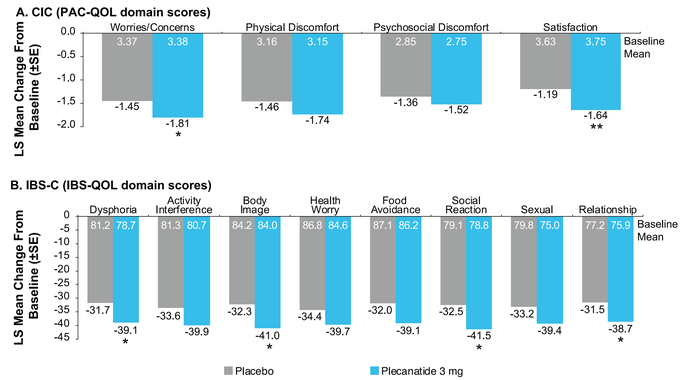
Figure 1. QOL Total Scores: Change From Baseline to Week 12 for (A) CIC and (B) IBS-C Patients in the Poorest QOL Quintile



**P<0.05 vs placebo. CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; IBS-QOL, Irritable Bowel Syndrome Quality of Life; PAC-QOL, Patient Assessment of Constipation Quality of Life; QOL, quality of life.*

- At Week 12, plecanatide-treated patients reported total score improvements from baseline in PAC-QOL (Figure 1A) and IBS-QOL (Figure 1B); both were significant compared to placebo ($P<0.05$).
- A greater percentage of plecanatide-treated patients reported a ≥1-point reduction in PAC-QOL (3 mg, 58.2%; placebo, 52.0%; $P=0.0674$) and ≥14-point reduction in IBS-QOL (3 mg, 70.8%; placebo, 55.9%; $P<0.01$).

Figure 2. QOL Domain Scores: Change From Baseline to Week 12 for (A) CIC and (B) IBS-C Patients in the Poorest QOL Quintile



**P<0.05, **P<0.01 vs placebo. CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; IBS-QOL, Irritable Bowel Syndrome Quality of Life; LS, least squares; PAC-QOL, Patient Assessment of Constipation Quality of Life; QOL, quality of life; SE, standard error.*

- At Week 12, PAC-QOL domain scores showed significant improvements in satisfaction and worries/concerns (Figure 2A).
- IBS-QOL domain scores showed significant improvements in dysphoria, body image, social reaction, and relationship items (Figure 2B).

KEY FINDINGS

- Plecanatide appears effective in improving CIC/IBS-C-targeted QOL factors in a population of individuals most severely impacted by their CIC and IBS-C symptom profiles.
- Across two CIC and two IBS-C phase 3 trials, plecanatide 3 mg led to clinically meaningful improvements in QOL compared to placebo in patients with the poorest QOL at baseline (last quintile).
- Plecanatide was associated with significant improvements in satisfaction and worries/concerns (CIC), and dysphoria, body image, social reaction, and relationship improvements (IBS-C).

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