Early Response to Plecanatide Predicts Overall Treatment Response in Patients With Chronic Idiopathic Constipation

Nicole Martinez de Andino, APRN[1]; Sarah Lorenzen, PhD[2]; Eamonn M. M. Quigley, MD[3]

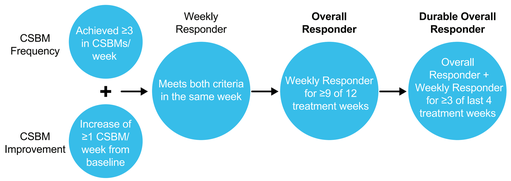
[1]Digestive Health Center, Augusta University, Augusta, GA, USA; [2]Salix Pharmaceuticals, Inc., Bridgewater, NJ, USA; [3]Houston Methodist Hospital, Houston, TX, USA

INTRODUCTION

- Chronic idiopathic constipation (CIC) is a common and bothersome gastrointestinal disorder.[1]
- 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.[2,3]
- Plecanatide has demonstrated clinical efficacy with a benign safety and tolerability profile in two large double-blind, placebo-controlled, phase 3 clinical trials (2 in patients with CIC [NCT02122471 and NCT01982240] and is approved for the treatment of adults with CIC and irritable bowel syndrome with constipation (IBS-C) in the United States.[4,5]
- This pooled analysis evaluated the predictiveness of various demographics, baseline symptom severity, and treatment response during Week 2 or Week 4 on overall treatment response after 12 weeks in patients with CIC.

METHODS

Figure 1. Definitions of Responder Endpoints



CSBM, complete spontaneous bowel movement; BM, bowel movement.

- Data were pooled from two double-blind, placebo-controlled, 12-week studies of patients with CIC.[4,5]
- Patients were randomized to placebo, plecanatide 3 mg, or plecanatide 6 mg for 12 weeks.
- Post hoc analyses of Week 2 and 4 responses were evaluated as predictors of overall and durable overall CSBM response (Figure 1).
  - Other explanatory variables included: weekly response during Weeks 2 or 4, age, sex, baseline assessments of bloating, constipation severity, quality of life, constipation symptoms, stool consistency, and straining.
  - Odds Ratios and 95% Confidence Intervals relate early response to non-response.

RESULTS

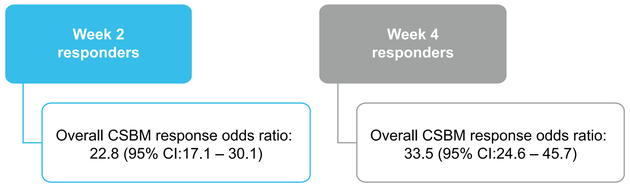
Table 1. Baseline Characteristics

	Placebo N=885	Plecanatide 3 mg N=877	Plecanatide 6 mg N=877
Baseline			
CSBMs/week, mean (SD)	0.35 (0.53)	0.31 (0.55)	0.28 (0.47)
SBMs/week, mean (SD)	1.87 (1.85)	1.89 (1.93)	1.72 (1.75)
Responder rates			
Week 2 responder, n (%)	157 (17.7)	254 (29.0)*	253 (28.8)*
Week 4 responder, n (%)	185 (20.9)	278 (31.7)*	270 (30.8)*
Durable overall CSBM responder, n (%)	102 (11.5)	182 (20.8)*	175 (20.0)*

*In the full ITT-E population excluding duplicates. *P<0.001 vs placebo.*
CSBM, complete spontaneous bowel movement; SBM, spontaneous bowel movement.

- A total of 2639 patients with CIC (placebo, N=885; 3 mg, N=877; 6 mg, N=877) were included.
- Baseline characteristics were similar across arms, and response was greater with plecanatide.
- Baseline mean CSBMs/week and SBMs/week ranged from 0.28-0.35 and 1.72-1.89, respectively, across groups (Table 1).
- During Week 2, 17.7% (placebo), 29.0% (3 mg), and 28.8% (6 mg) of patients were WRs, increasing to 20.9%, 31.7%, and 30.8%, respectively, during Week 4.
- Significantly more plecanatide-treated patients were durable overall CSBM responders than placebo patients (placebo, 11.5%; 3 mg, 20.8%; 6 mg, 20.0%; *P*<0.001 both doses).

Figure 2. Odds of Durable Response With Early Response



Combines all treatment arms. CSBM, complete spontaneous bowel movement; CI, confidence interval.

- Week 2 responders were 22.8 times more likely to be durable overall responders than Week 2 non-responders, while Week 4 responders being 33.5 times more likely to be durable overall responders than Week 4 non-responders (Figure 2).

Table 2. Odds of Durable Overall Response

Variable	Subgroup	OR (95% CI) of Overall Response: Plecanatide 3 mg vs Placebo	OR (95% CI) of Overall Response: Plecanatide 6 mg vs Placebo
Bloating Severity	Score ≥2	2.28 (1.55, 3.34)	2.42 (1.64, 3.57)
	Score >2	2.23 (1.44, 3.45)	1.91 (1.23, 2.96)
Stool Consistency	Score ≤2	2.13 (1.38, 3.30)	2.35 (1.51, 3.67)
	Score >2	2.31 (1.57, 3.39)	2.05 (1.39, 3.01)
PAC-QOL	Score ≤2	2.01 (1.33, 3.05)	2.23 (1.48, 3.36)
	Score >2	2.42 (1.62, 3.62)	2.13 (1.41, 3.22)
PAC-SYM	Score ≤2	1.96 (1.32, 2.92)	2.01 (1.34, 2.99)
	Score >2	2.60 (1.71, 3.96)	2.43 (1.59, 3.72)
PGA Const. Severity	Score ≤3	2.45 (1.57, 3.81)	2.69 (1.73, 4.18)
	Score >3	2.09 (1.43, 3.06)	1.82 (1.23, 2.69)
Straining	Score ≤2	1.83 (1.18, 2.84)	1.92 (1.23, 2.99)
	Score >2	2.59 (1.76, 3.81)	2.40 (1.63, 3.54)
Age	≤65 years	2.23 (1.65, 3.02)	2.25 (1.66, 3.06)
	>65 years	2.36 (0.91, 6.11)	1.36 (0.48, 3.83)
Sex	Female	2.18 (1.58, 3.01)	2.14 (1.54, 2.96)
	Male	2.49 (1.31, 4.73)	2.32 (1.19, 4.52)

CI, confidence interval; PAC-QOL, patient assessment of constipation quality of life; PAC-SYM, patient assessment of constipation-symptoms; PGA, patient global assessment; OR, odds ratio.

- Odds of durable overall CSBM response were greater with plecanatide than placebo across most subgroups (Table 2).
- Within each baseline variable, no statistically significant results were seen between groups.
  - Response to plecanatide was more likely than placebo regardless of baseline bloating, stool consistency, constipation severity, quality of life, constipation symptoms, straining, and sex.

KEY FINDINGS

- Plecanatide is an effective treatment for patients with CIC.
- Significantly more plecanatide-treated patients were treatment responders than placebo over Weeks 2, 4, and 12.
- In patients with CIC, early clinical response—as early as Week 2 or 4—appears to be predictive of durable overall CSBM response after 12 weeks of treatment.
- Patients responded to plecanatide at similar rates regardless of baseline symptom severity.

References

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Disclosures

N. Martinez de Andino is an advisor for Salix Pharmaceuticals.
S. Lorenzen is an employee at Salix Pharmaceuticals. **E.M.M. Quigley** is an advisor for Salix Pharmaceuticals.

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