The Impact of Plecanatide on Abdominal Pain in Patients With Chronic Idiopathic Constipation and Irritable Bowel Syndrome With Constipation: Analysis From Four Phase 3 Studies

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P1107

Presented at the ACG 2020 Annual Scientific Meeting; October 23-28, 2020; Virtual Meeting

BACKGROUND

- Abdominal pain is a bothersome symptom commonly experienced by patients with chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C).[1-3]
  - The diagnostic criteria for IBS-C includes the presence of abdominal pain, whereas the Rome III criteria for diagnosis of CIC does not include assessment of abdominal pain; however, moderate to severe abdominal pain is reported in ~23% of patients with CIC.[4]
- Plecanatide, a structural analogue of the human intestinal secretion regulator uroguanylin, is a locally-acting, 16-amino-acid peptide. Once daily dosing of plecanatide 3mg is FDA-approved for the treatment of IBS-C and CIC.[5]
- In two pivotal, randomized, double-blind, placebo-controlled, phase 3 studies in CIC (NCT01982240, NCT02122471[6,7]) and two in IBS-C (NCT02387359, NCT02493452[8]), plecanatide has been shown to be safe and efficacious in the treatment of patients with CIC and IBS-C including improvements to their abdominal pain symptoms.[2,3]

OBJECTIVE

- Post hoc analysis of four phase 3 studies of plecanatide was performed to evaluate the impact of plecanatide on abdominal pain in patients with CIC and IBS-C, stratified by baseline abdominal pain severity.

METHODS

- In all four phase 3 trials, patients who met modified Rome III criteria for CIC or IBS-C were randomly assigned (1:1:1) to receive plecanatide 3 mg, plecanatide 6 mg, or placebo for 12 weeks.
- Patients electronically recorded daily abdominal pain symptoms.
  - Patients with CIC utilized a Likert scale (0 = none to 4 = very severe).
  - Patients with IBS-C used a numeric rating scale ("NRS"; 0 = none to 10 = worst possible pain).
- To compare efficacy results in subpopulations with more or less pain at baseline, the intention-to-treat population was stratified by baseline severity. Based on the structures of the individual scales, these categories were defined as:
  - CIC: minimal/mild pain (0–2); moderate/severe pain (3–4)
  - IBS-C: minimal/mild pain (0–5); moderate/severe pain (6–10)
  - Primary efficacy endpoints (i.e. overall durable CSBM responder [CIC] and overall responder [IBS-C]) were consistent with current FDA-recommended guidance standards.

RESULTS

Table 1. Demographics and Clinical Characteristics in CIC and IBS-C Patients With Moderate to Severe Pain at Baseline (ITT)

	CIC (Pain >2)			IBS-C (Pain >5)		
	Placebo (n=328)	Plecanatide 3 mg (n=313)	Plecanatide 6 mg (n=355)	Placebo (n=510)	Plecanatide 3 mg (n=510)	Plecanatide 6 mg (n=502)
Age (years), mean (SD)	44.9 (13.5)	44.9 (14.6)	45.1 (13.8)	43.4 (14.3)	43.5 (13.7)	42.9 (13.5)
Female, n (%)	255 (77.7)	240 (76.7)	286 (80.6)	383 (75.1)	375 (73.5)	377 (75.1)
Race, n (%)						
White/Caucasian	238 (72.6)	224 (71.6)	258 (72.7)	375 (73.5)	382 (74.9)	378 (75.3)
Black or African American	80 (24.4)	81 (25.9)	82 (23.1)	119 (23.3)	110 (21.6)	112 (22.3)
BMI (kg/m^2), mean (SD)	28.7 (5.49)	28.8 (5.05)	28.4 (52.0)	28.1 (4.82)	28.6 (4.71)	28.2 (4.94)

BMI, body mass index; CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; SD, standard deviation.

- Patients who met modified Rome III criteria for CIC (N=2639) and criteria IBS-C (N=2176) were included; 2638 patients with CIC and 2152 patients with IBS-C had pain scores available for analysis.
  - 38% (N=996) of CIC patients and 71% (N=1522) of IBS-C patients had moderate to severe pain at baseline (Table 1).
- Baseline mean abdominal pain scores for CIC were 1.59-1.68 (range) compared to 6.22-6.26 for IBS-C.

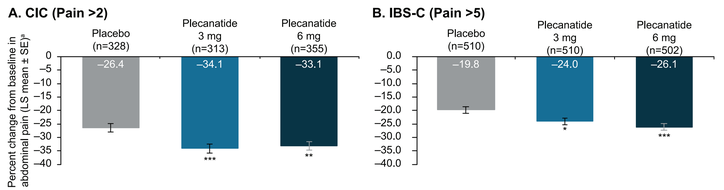
Table 2. Summary of Adverse Events in CIC and IBS-C Patients With Moderate to Severe Pain at Baseline (Safety)

	CIC (Pain >2)			IBS-C (Pain >5)		
n (%)	Placebo (n=327)	Plecanatide 3 mg (n=312)	Plecanatide 6 mg (n=353)	Placebo (n=508)	Plecanatide 3 mg (n=509)	Plecanatide 6 mg (n=501)
Patients with ≥1 TEAE	90 (27.5)	91 (29.2)	100 (28.3)	94 (18.5)	112 (22.0)	89 (17.8)
TEASs experience by ≥2% of patients in any treatment group						
Diarrhea	2 (0.6)	12 (3.8)	15 (4.2)	6 (1.2)	19 (3.7)	21 (4.2)
Urinary tract infection	7 (2.1)	3 (1.0)	8 (2.3)	2 (0.4)	4 (0.8)	4 (0.8)
Headache	9 (2.8)	7 (2.2)	7 (2.0)	12 (2.4)	13 (2.6)	8 (1.6)
Discontinued treatment due to TEAE	10 (3.1)	11 (3.5)	13 (3.7)	2 (0.4)	10 (2.0)	13 (2.6)
Diarrhea	1 (0.3)	3 (1.0)	5 (1.4)	0	2 (0.4)	7 (1.4)
Patients with ≥1 SAE	6 (1.8)	7 (2.2)	4 (1.1)	5 (1.0)	5 (1.0)	5 (1.0)

CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

- Patients with moderate to severe pain in the safety population experienced similar low rates of adverse events across treatment groups; diarrhea was more common in the plecanatide-treated groups.

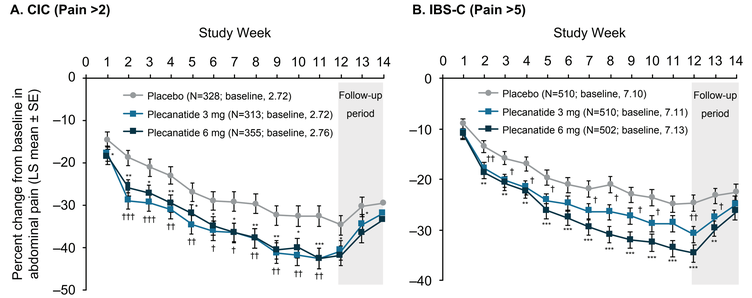
Figure 1. Overall Percent Change From Baseline in Abdominal Pain Severity in Patients With (A) CIC and (B) IBS-C and Moderate to Severe Pain at Baseline (ITT)



*P<0.05, **P<0.01,***P<0.001 vs placebo. CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; LS, least squares; SE, standard error.

- In both patients with CIC and IBS-C with moderate to severe pain at baseline, plecanatide treatment groups experienced a significantly greater percent reduction in abdominal pain scores across 12 weeks compared with the placebo group (Figure 1).

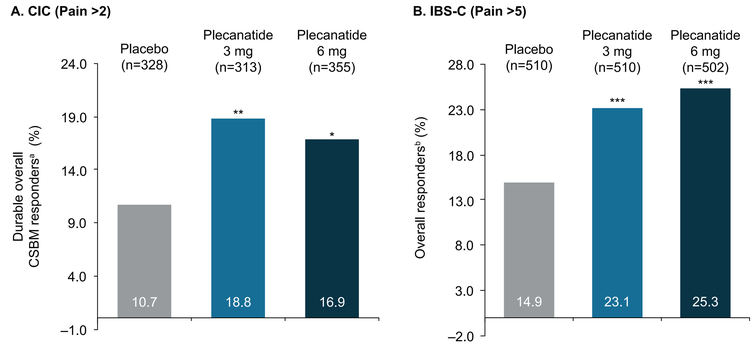
Figure 2. Weekly Percent Change From Baseline in Abdominal Pain Severity Scores in (A) CIC and (B) IBS-C Patients With Moderate to Severe Abdominal Pain at Baseline (ITT)



Plecanatide 3 mg: †P<0.05, ††P≤0.01, †††P≤0.001 vs placebo. Plecanatide 6 mg: *P<0.05, **P≤0.01, ***P≤0.001 vs placebo. LS, least squares; SE, standard error.

- In patients with moderate to severe abdominal pain at baseline, significant percent change in abdominal pain with plecanatide 3 mg was apparent by Week 1 in CIC and by Week 2 in IBS-C (Figure 2) and was significant in both IBS-C and CIC groups at Week 12 (end of treatment).
- During the follow-up period, the severity of pain increased in all groups but remained lower than at baseline.

Figure 3. Impact of Plecanatide on (A) Percentage of Overall Durable CSBM Responders (CIC) and (B) Overall Responder Rate (IBS-C) in Patients With Moderate to Severe Baseline Pain (ITT)



*P<0.05, **P<0.01,***P<0.001 vs placebo. [a]Durable overall CSBM responder was defined as having ≥3 CSBMs/week and ≥1 CSBM increase from baseline for at least 9/12 weeks including 3 of the 4 four weeks. [a]Overall responder was defined as having ≥1 CSBM/week increase from baseline plus ≥30% improvement in abdominal pain for at least 6/12 weeks. CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement; IBS-C, irritable bowel syndrome with constipation.

- Plecanatide-treated patients demonstrated significant improvements in primary efficacy endpoints compared to placebo (i.e., percentage of CSBM responders in CIC and percentage of overall responders In IBS-C; Figure 3).

DISCUSSION

- Among patients with CIC and IBS-C who have moderate to severe pain at baseline, treatment with plecanatide was accompanied by an improvement in abdominal pain, beginning at Week 1 for CIC and Week 2 for IBS-C.
- After plecanatide and placebo were discontinued, treatment-associated differences among groups were lost, which supports the benefits of plecanatide.
- In patients with CIC and IBS-C and moderate to severe pain at baseline, plecanatide treatment yielded significant improvements in overall durable CSBM responder rates (CIC) and overall responder rates (IBS-C).

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Disclosures: A.E. Bharucha has filed for/been awarded patents jointly with Medspira, Medtronic, and Minnesota Medical Technologies. J. Rosenberg participated in speakers bureaus for Allergan, Salix, and Takeda. R. Patel is an employee and stockholder at Bausch Health. S. Lorenzen is an employee at Salix Pharmaceuticals. G.S. Sayuk is a consultant and speaker for Salix Pharmaceuticals, and Allergan/Ironwood Pharmaceuticals, and is a consultant for the GI Health Foundation.

Acknowledgments: Funding for this study and poster support was provided by Salix Pharmaceuticals, Inc. (Bridgewater, NJ, USA). Medical writing and editorial support was provided by The Medicine Group (New Hope, PA, USA), in accordance with Good Publication Practice guidelines.

This poster was funded by Salix Pharmaceuticals.