Plecanatide Significantly Reduces Global Symptoms, Abdominal Pain, and Bloating in Individuals With Irritable Bowel Syndrome With Constipation Experiencing Varying Levels of Abdominal Pain and Bloating at Baseline

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BACKGROUND

- Abdominal pain and bloating are bothersome symptoms in patients with irritable bowel syndrome with constipation (IBS-C).[1]
  - The diagnostic criteria for IBS-C includes the presence of abdominal pain.[2]
  - Next to pain, bloating is the most frequently reported abdominal symptom in patients with IBS-C.[1]
- Plecanatide is an analogue of human uroguanylin that acts as a pH-dependent guanylate cyclase-C (GC-C) agonist.
  - Activation of GC-C receptors increases intestinal fluid secretion and may also modulate pain and decrease visceral hypersensitivity.[3]
  - Plecanatide (3 mg once daily) is FDA-approved for the treatment of IBS-C and chronic idiopathic constipation in adults.[4]
- In two randomized, double-blind, placebo-controlled phase 3 studies in IBS-C (NCT02387359, NCT02493452), plecanatide significantly improved abdominal pain and bloating symptoms compared to placebo.[5]

OBJECTIVE

- Pooled data from two randomized, phase 3 clinical trials were analyzed post hoc to determine the impact of plecanatide on overall responder rate, abdominal pain, and bloating stratified by pain and bloating severity at baseline.

METHODS

- In two phase 3 studies, patients meeting Rome III criteria for IBS-C were randomized (1:1:1) to receive plecanatide 3 mg, plecanatide 6 mg, or placebo once daily for 12 weeks.[5]
- The primary endpoint was an **overall responder rate**, defined as a patient who was a weekly responder (≥1 complete spontaneous bowel movement [CSBM]/ week increase from baseline plus ≥30% improvement in abdominal pain) for ≥6 of 12 treatment weeks.
- Daily abdominal pain and bloating symptoms were electronically recorded using a numeric rating scale (0=none to 10=worst possible).
- Baseline severity was defined as none to mild (≤5) or moderate to severe (>5).
- Percent change from baseline at Week 12 in abdominal pain and bloating severity was calculated.

RESULTS

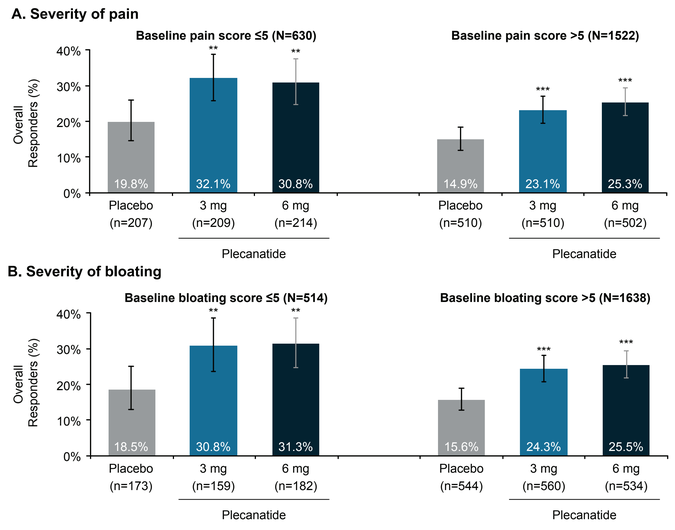
Table 1. Demographics and Baseline Characteristics (ITT)

	Baseline pain score ≤5			Baseline pain score >5		
Patients stratified by pain	**Placebo (n=207)**	**Plecanatide 3 mg (n=209)**	**Plecanatide 6 mg (n=214)**	**Placebo (n=510)**	**Plecanatide 3 mg (n=510)**	**Plecanatide 6 mg (n=502)**
Age (yrs), M (SD)	45.7 (13.9)	43.5 (15.4)	44.0 (14.3)	43.4 (14.3)	43.5 (13.7)	42.9 (13.5)
Sex: Female, n (%)	151 (72.9)	155 (74.2)	154 (72.0)	383 (75.1)	375 (73.5)	377 (75.1)
Race, n (%)						
White/Caucasian	156 (75.4)	142 (67.9)	136 (63.6)	375 (73.5)	382 (74.9)	378 (75.3)
Black/AA	35 (16.9)	43 (20.6)	60 (28.0)	119 (23.3)	110 (21.6)	112 (22.3)
BMI (kg/m²), M (SD)	27.9 (4.7)	27.6 (4.9)	27.9 (4.9)	28.1 (4.8)	28.6 (4.7)	28.2 (4.9)
Baseline pain, M (SD)	4.2 (0.5)	4.2 (0.5)	4.1 (0.5)	7.1 (1.2)	7.1 (1.2)	7.1 (1.2)
	Baseline bloating score ≤5			**Baseline bloating score >5**		
Patients stratified by bloating	**Placebo (n=173)**	**Plecanatide 3 mg (n=159)**	**Plecanatide 6 mg (n=182)**	**Placebo (n=544)**	**Plecanatide 3 mg (n=560)**	**Plecanatide 6 mg (n=534)**
Age (yrs), M (SD)	46.7 (14.0)	43.0 (15.7)	44.3 (14.5)	43.2 (14.2)	43.7 (13.7)	42.9 (13.5)
Sex: Female, n (%)	121 (69.9)	112 (70.4)	125 (68.7)	413 (75.9)	418 (74.6)	406 (76.0)
Race, n (%)						
White/Caucasian	124 (71.7)	103 (64.8)	121 (66.5)	407 (74.8)	421 (75.2)	393 (73.6)
Black/AA	32 (18.5)	35 (22.0)	46 (25.3)	122 (22.4)	118 (21.1)	126 (23.6)
BMI (kg/m²), M (SD)	27.7 (4.7)	27.5 (5.0)	27.5 (4.6)	28.1 (4.8)	28.5 (4.7)	28.3 (5.0)
Baseline bloating, M (SD)	4.1 (0.9)	4.1 (0.8)	4.1 (0.9)	7.2 (1.2)	7.2 (1.2)	7.2 (1.2)

AA, African American; BMI, body mass index; IBS-C, irritable bowel syndrome with constipation; ITT, intention to treat; M, mean; SD, standard deviation.

- Average age was 43.3-44.7 years; most patients were female (69.6–75.5%) and white (67.7–74.6%).
- Data for pain and bloating were available in 2152 of 2176 patients who participated in these trials.
  - Of those, 71% (n=1522) and 76% (n=1638) had moderate to severe pain and bloating, respectively, at baseline.

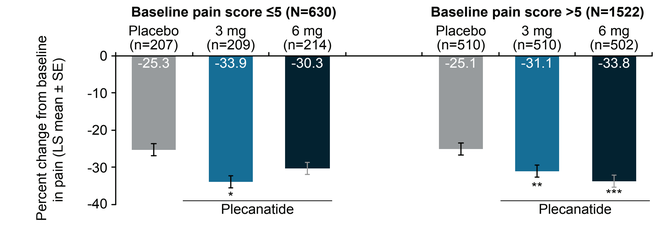
Figure 1. Overall Responder Rates in Patients With IBS-C Stratified by Baseline A) Pain Severity and B) Bloating Severity (ITT)



**P<0.01, ***P≤0.001 vs placebo. IBS-C, irritable bowel syndrome with constipation; ITT, intention to treat.

- Significant improvements in overall response favored plecanatide over placebo regardless of baseline severity of pain or bloating (**Figure 1**).

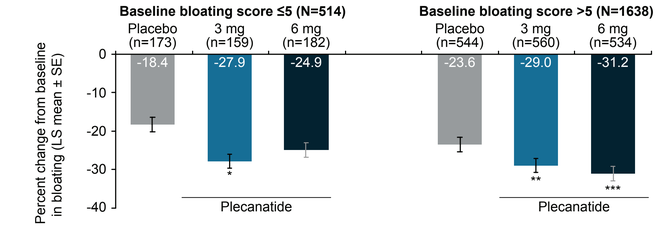
Figure 2. Percent Change From Baseline in Abdominal Pain Score at Week 12 in Patients With IBS-C Stratified by Baseline Pain Severity (ITT)



*P<0.05, **P<0.01, ***P<0.001 vs placebo. IBS-C, irritable bowel syndrome with constipation; ITT, intention to treat; LS, least squares; SE, standard error.

- At Week 12, the pain response for plecanatide versus placebo was as follows:
  - 3 mg was associated with significant improvements in pain regardless of baseline pain severity; 6 mg was associated with significant pain improvements in patients with moderate to severe pain at baseline (**Figure 2**).

Figure 3. Percent Change From Baseline in Abdominal Bloating Score at Week 12 in Patients With IBS-C Stratified by Baseline Bloating Severity (ITT)



*P<0.05, **P<0.01, ***P<0.001 vs placebo. IBS-C, irritable bowel syndrome with constipation; ITT, intention to treat; LS, least squares; SE, standard error.

- At Week 12, the bloating response for plecanatide versus placebo was as follows:
  - 3 mg was associated with significant improvements in bloating regardless of baseline bloating severity; 6 mg was associated with significant bloating improvements in patients with moderate to severe bloating at baseline (**Figure 3**).

Table 2. Summary of Treatment-Emergent Adverse Events (Safety)

	Baseline pain score ≤5			Baseline pain score >5		
Patients stratified by pain						
n (%)	**Placebo (n=206)**	**Plecanatide 3 mg (n=209)**	**Plecanatide 6 mg (n=213)**	**Placebo (n=508)**	**Plecanatide 3 mg (n=509)**	**Plecanatide 6 mg (n=501)**
≥1 TEAE	39 (18.9)	59 (28.2)	54 (28.2)	94 (18.5)	112 (22.0)	89 (17.8)
Diarrhea	0	12 (5.7)	8 (3.8)	6 (1.2)	19 (3.7)	21 (4.2)
≥1 TEAE discontin.	0	8 (3.8)	3 (1.4)	2 (0.4)	10 (2.0)	13 (2.6)
Diarrhea	0	7 (3.3)	3 (1.4)	0	2 (0.4)	7 (1.4)
≥1 TE SAE	0	1 (0.5)	0	5 (1.0)	5 (1.0)	5 (1.0)
	Baseline bloating score ≤5			**Baseline bloating score >5**		
Patients stratified by bloating						
n (%)	**Placebo (n=173)**	**Plecanatide 3 mg (n=159)**	**Plecanatide 6 mg (n=181)**	**Placebo (n=541)**	**Plecanatide 3 mg (n=559)**	**Plecanatide 6 mg (n=533)**
≥1 TEAE	37 (21.4)	39 (24.5)	43 (23.8)	96 (7.7)	132 (23.6)	100 (18.8)
Diarrhea	1 (0.6)	3 (1.9)	9 (5.0)	5 (0.9)	28 (5.0)	20 (3.8)
≥1 TEAE discontin.	1 (0.6)	3 (1.9)	5 (2.8)	1 (0.2)	15 (2.7)	11 (2.1)
Diarrhea	0	2 (1.3)	4 (2.2)	0	7 (1.3)	6 (1.1)
≥1 TE SAE	2 (1.2)	1 (0.6)	0	3 (0.6)	5 (0.9)	5 (0.9)

Discontin, leading to discontinuation; IBS-C, irritable bowel syndrome with constipation; SAE, serious adverse event; TE, treatment emergent; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.

- In the safety population, patients with varying levels of abdominal pain and bloating at baseline experienced similarly low rates of adverse events among treatment groups; diarrhea was more common in the plecanatide-treated groups (**Table 2**).

DISCUSSION

Among IBS-C patients:

- In this analysis, ≥2/3 of individuals reported moderate to severe abdominal pain and bloating.
- The overall responder rate was greater for plecanatide (3 mg and 6 mg) than placebo regardless of the severity of abdominal pain and bloating at baseline.
- Compared to placebo, plecanatide 3 mg significantly improved abdominal pain and bloating in patients with both mild and moderate to severe baseline pain.
- Compared to placebo, plecanatide 6 mg significantly improved abdominal pain and bloating in patients with moderate to severe but not in patients with mild pain.
- Low rates of adverse events were experienced regardless of abdominal pain and bloating at baseline.
- Overall, plecanatide–at the FDA-approved, commercially-available dose of 3 mg–significantly improved global and abdominal IBS symptoms regardless of baseline pain and bloating severity.

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