

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

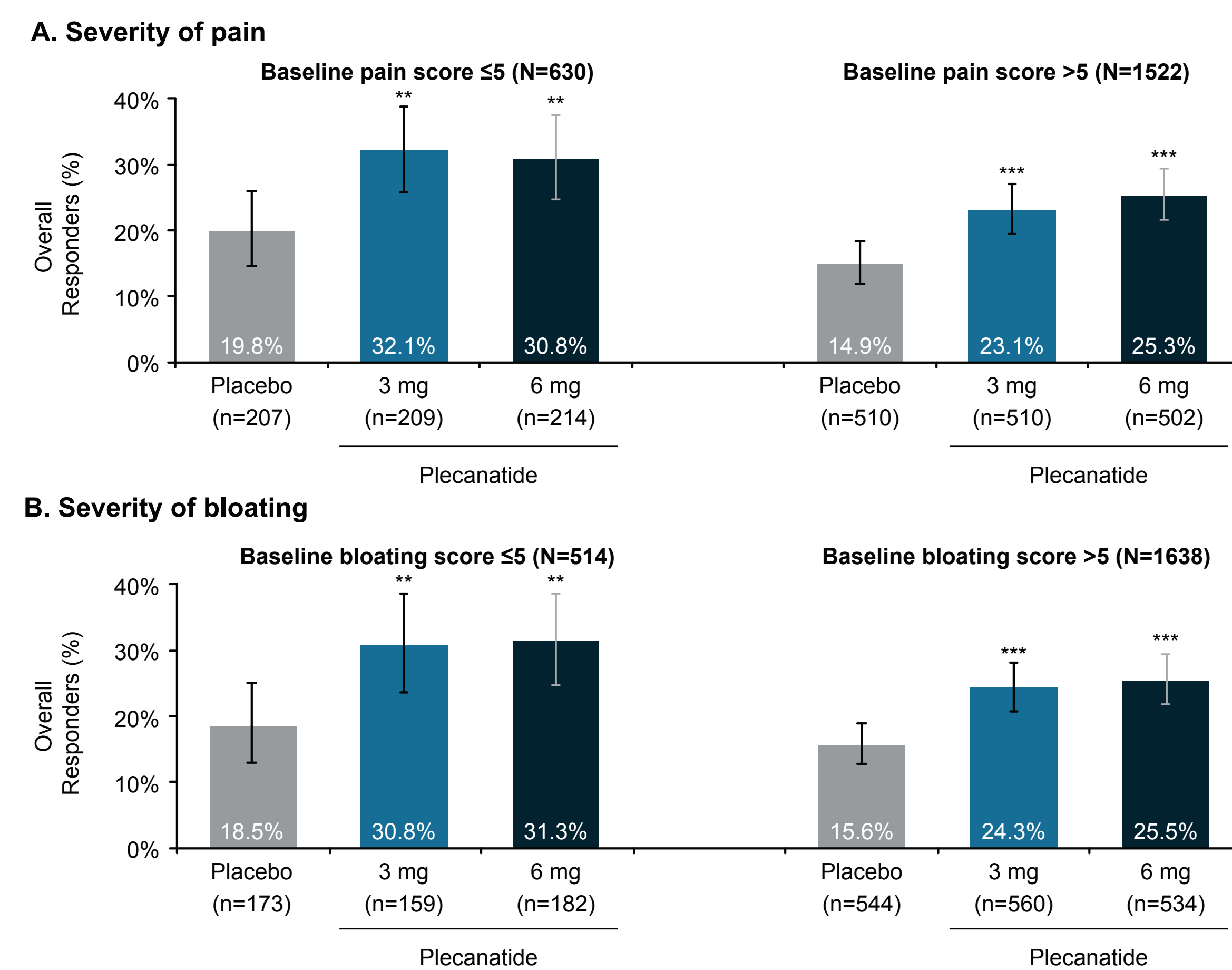
Table 1. Demographics and Baseline Characteristics (ITT)

Patients stratified by pain	Baseline pain score ≤5			Baseline pain score >5		
	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/m ²), 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)
Patients stratified by bloating	Baseline bloating score ≤5			Baseline bloating score >5		
	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/m ²), 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.

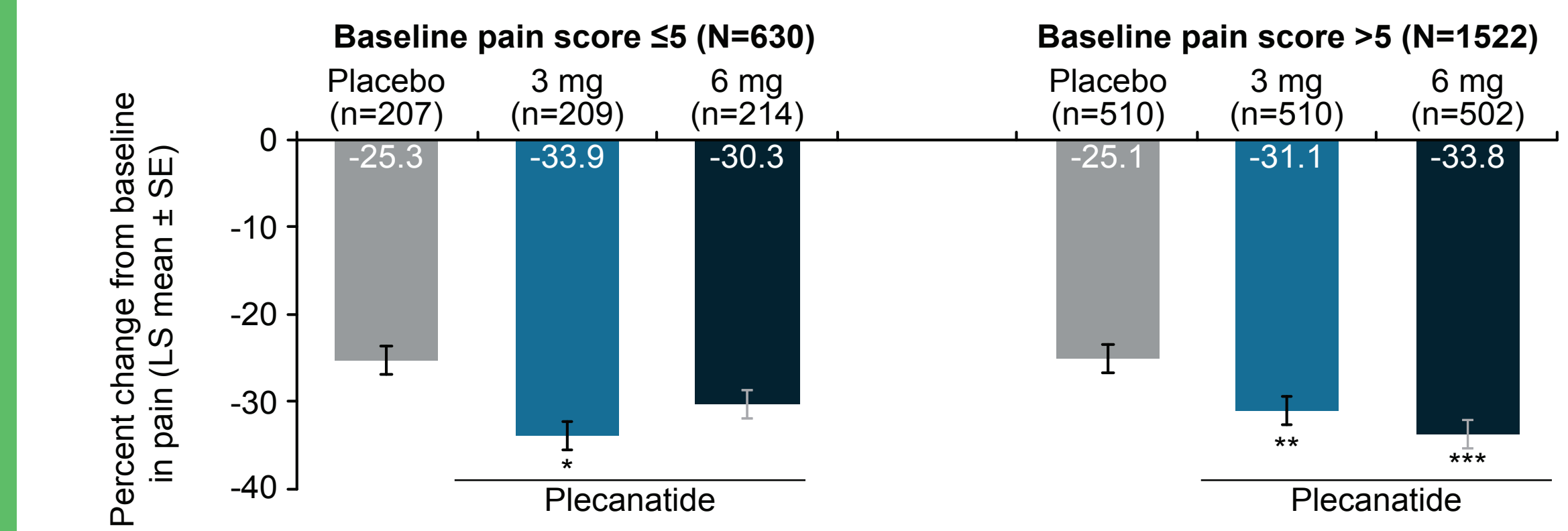
Figure 1. Overall Responder Rates in Patients With IBS-C Stratified by Baseline A) Pain Severity and B) Bloating Severity (ITT)



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).

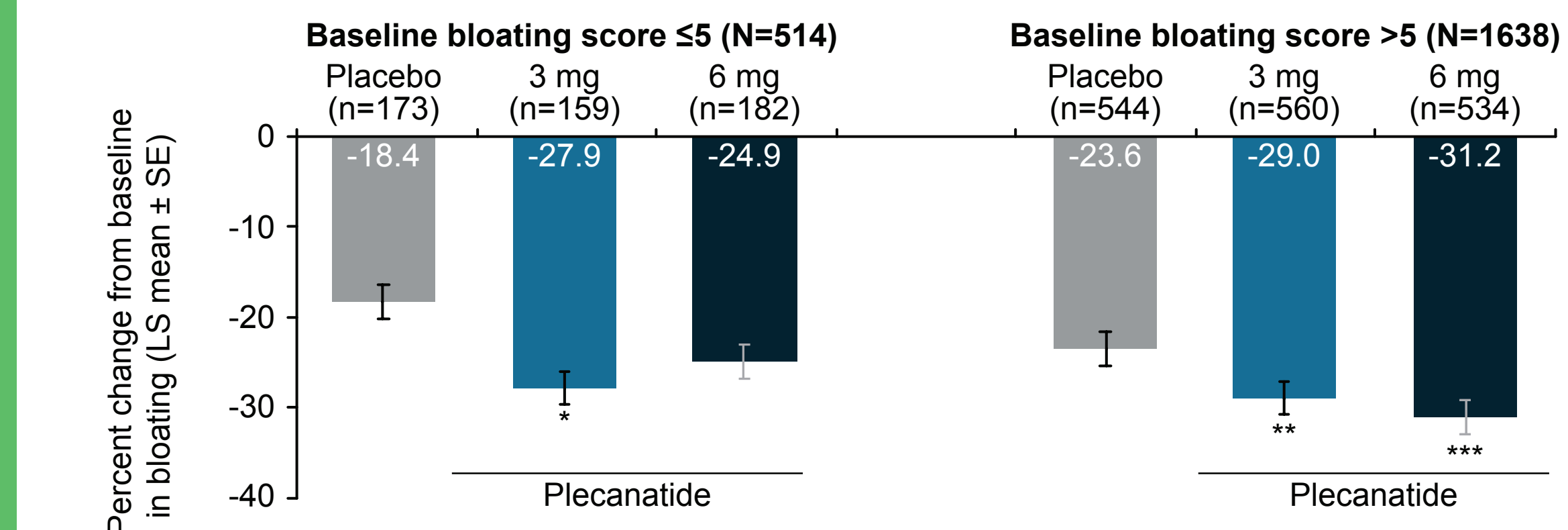
Figure 2. Percent Change From Baseline in Abdominal Pain Score at Week 12 in Patients With IBS-C Stratified by Baseline Pain Severity (ITT)



*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)

Patients stratified by pain	Baseline pain score ≤5			Baseline pain score >5		
	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)
n (%)						
≥1 TEAE	39 (18.9)	59 (28.2)	54 (25.3)	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)
Patients stratified by bloating	Baseline bloating score ≤5			Baseline bloating score >5		
	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)
n (%)						
≥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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Disclosures: A.E. Bharucha has filed/been awarded patents jointly with Medspira, Medtronic, and Minnesota Medical Technologies. G.S. Sayuk is a consultant and speaker for Salix Pharmaceuticals, Alnylam, and Allergan/Ironwood Pharmaceuticals, and is a consultant for the GI Health Foundation. J. Rosenberg participated in speakers bureaus for Allergan, Salix, and Takeda. A. Sharma served on advisory boards for Ironwood Pharmaceuticals and Salix Pharmaceuticals. A. Walker has nothing to disclose. S. Lorenzen is an employee at Salix Pharmaceuticals. D.M. Brenner is a consultant and speaker for Salix Pharmaceuticals, and is supported in research by an unrestricted gift from the IDP Foundation.

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