Safety and Efficacy Evaluation of Plecanatide for the Treatment of Chronic Idiopathic Constipation and Irritable Bowel Syndrome–Constipation in Patients Aged 65 Years or Older

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BACKGROUND

- Chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C) are two chronic gastrointestinal conditions that exist on a continuum of highly prevalent disease states called functional bowel disorders.[1]
- Prevalence estimates for chronic constipation in the United States range from 2% to 27%.[2,3]
- The efficacy of prosecretory agents for short-term treatment of IBS-C and CIC has been demonstrated in phase 3 clinical trials; however, there are limited data on the safety and efficacy of these agents for the treatment of constipation in the elderly population.[4]
- Plecanatide is a guanylate cyclase-C agonist. The 3 mg dose is approved by the FDA for the treatment of adults with CIC and IBS-C.[5]
  - Approval was based on the results of four phase 3 clinical trials: two in CIC (NCT01982240, NCT02122471)[6,7] and two in IBS-C (NCT02387359, NCT02493452).[8]
  - The studies permitted enrollment of patients up to the age of 80 years (for CIC) or 85 years (for IBS-C).

OBJECTIVE

- To evaluate the safety, tolerability, and efficacy of plecanatide in patients aged ≥65 years with CIC or IBS-C from four phase 3 clinical trials.

METHODS

- Patients from two CIC[6,7] and two IBS-C[8] trials who were randomly assigned (1:1:1) to receive plecanatide 3 mg, plecanatide 6 mg, or placebo were included in a post hoc analysis.
  - All studies were 12-week, randomized, double-blind, placebo-controlled. Patients had to meet modified Rome III criteria for CIC or IBS-C.
  - Dose adjustments or treatment interruptions were not permitted during any of the studies.
- The primary efficacy outcome parameters differed for the CIC and IBS-C studies; thus, outcomes for the primary endpoints could not be pooled.
  - All trials shared the following secondary efficacy endpoints to allow the CIC and IBS-C trial populations to be combined:
    - Changes in stool consistency (Bristol Stool Form Scale [BSFS])
    - Changes in weekly frequency of complete spontaneous bowel movements (CSBMs) and spontaneous bowel movements (SBMs)
    - Time from start of therapy to first CSBM and first SBM
- Treatment-emergent adverse events (TEAEs) were reported for patients ≥65 years old and <65 years old in the safety population (ie, patients who took at least one dose), using descriptive statistics.

RESULTS

Table 1. Baseline Demographics and Disease Characteristics (ITT population excluding duplicates)

	Aged <65 Years				Aged ≥65 Years			
		Plecanatide				Plecanatide		
	Placebo (n = 1450)	3 mg (n = 1451)	6 mg (n = 1463)	Pooled (n = 2914)	Placebo (n = 164)	3 mg (n = 150)	6 mg (n = 137)	Pooled (n = 287)
Age (years), mean (SD)	41.9 (12.09)	41.8 (12.35)	41.8 (11.99)	41.8 (12.17)	69.8 (4.14)	70.1 (4.43)	70.1 (4.39)	70.1 (4.40)
Sex, n (%)								
Male	329 (22.7)	320 (22.1)	319 (21.8)	639 (21.9)	48 (29.3)	49 (32.7)	37 (27.0)	86 (30.0)
Female	1121 (77.3)	1131 (77.9)	1144 (78.2)	2275 (78.1)	116 (70.7)	101 (67.3)	100 (73.0)	201 (70.0)
Race, n (%)								
White	1045 (72.1)	1030 (71.0)	1021 (69.8)	2051 (70.4)	138 (84.1)	129 (86.0)	111 (81.0)	240 (83.6)
Non-white	405 (27.9)	421 (29.0)	442 (30.2)	863 (29.6)	26 (15.9)	21 (14.0)	26 (19.0)	47 (16.4)
Baseline disease characteristics, mean (SD)								
Stool consistency (BSFS score)	2.30 (1.108)	2.19 (1.010)	2.25 (1.126)	2.22 (1.069)	2.50 (1.135)	2.41 (1.087)	2.39 (1.041)	2.40 (1.063)
CSBM/wk	0.30 (0.506)	0.28 (0.525)	0.28 (0.510)	0.28 (0.517)	0.35 (0.534)	0.32 (0.541)	0.31 (0.501)	0.31 (0.521)
SBM/wk	1.68 (1.533)	1.73 (1.603)	1.61 (1.417)	1.67 (1.513)	1.93 (1.921)	1.85 (1.833)	2.10 (2.361)	1.97 (2.103)

BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; ITT, intention-to-treat; SBM, spontaneous bowel movement; SD, standard deviation; wk, week; y, year.

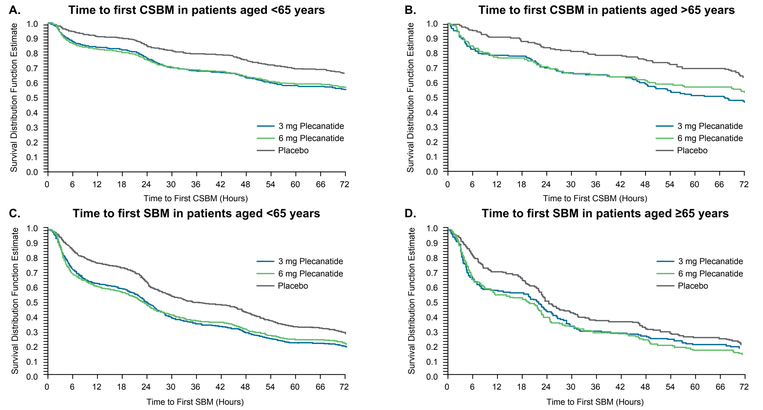
Table 2. Change From Baseline at Week 12 in Stool Consistency and Stool Frequency (ITT population excluding duplicates)

	Aged <65 Years			Aged ≥65 Years		
		Plecanatide			Plecanatide	
	Placebo (n = 1450)	3 mg (n = 1451)	6 mg (n = 1463)	Placebo (n = 164)	3 mg (n = 150)	6 mg (n = 137)
Stool consistency[a]						
ITT, n[b]	1057	1101	1075	119	115	102
LS mean (SE)	0.94 (0.046)	1.48 (0.045)	1.45 (0.046)	0.92 (0.134)	1.49 (0.135)	1.48 (0.147)
P vs placebo		<0.001	<0.001		0.002	0.004
CSBM/week[a]						
ITT, n[b]	1206	1203	1211	141	128	114
LS mean (SE)	1.30 (0.095)	2.22 (0.095)	2.28 (0.095)	1.56 (0.260)	2.63 (0.268)	2.07 (0.289)
P vs placebo		<0.001	<0.001		0.003	0.168
SBM/week[a]						
ITT, n[b]	1206	1203	1211	141	128	114
LS mean (SE)	1.27 (0.114)	2.62 (0.114)	2.69 (0.115)	1.90 (0.321)	3.27 (0.332)	2.61 (0.357)
P vs placebo		<0.001	<0.001		0.003	0.129

[a]Assessed in the ITT population (ie, all unique randomized patients, excluding duplicates) by pairwise comparisons of LS means in the placebo group and in each plecanatide treatment group using an analysis of covariance model with fixed effect for treatment and covariates of gender and baseline BSFS.
[b]Values are ITT patients with data at week 12.
CSBM, complete spontaneous bowel movement; ITT, intention-to-treat; LS, least squares; SBM, spontaneous bowel movement; SE, standard error.

- The mean age of patients aged ≥65 years was 70.0 years; for patients aged <65 years, the mean age was 41.9 years.
- Efficacy data for patients aged ≥65 years appeared consistent with those in the full study populations and in patients aged <65 years (Table 2).
- There were statistically significant improvements in stool consistency from baseline with plecanatide 3 mg and 6 mg versus placebo at week 12, both in patients aged ≥65 years and in those aged <65 years (Table 2).
- Changes from baseline in mean weekly CSBM frequency and in mean weekly SBM frequency at week 12 were statistically significant versus placebo in the plecanatide 3-mg group in patients aged ≥65 years and in both plecanatide groups in patients aged <65 years (Table 2).
  - The differences were numerically greater in the plecanatide 6-mg group of patients aged ≥65 years.

Figure 1. Time to First A) CSBM in Patients Aged <65 Years and B) Patients Aged ≥65 Years, and Time to First C) SBM in Patients <65 Years and D) Patients Aged <65 Years



- Time from start of therapy to first CSBM and first SBM were significantly shorter in the plecanatide groups than in the placebo group in patients aged <65 years ($P < 0.001$ for all; Figure 1).
- In patients aged ≥65 years, the time from start of therapy to first CSBM was significantly shorter in both plecanatide groups ($P < 0.05$ vs placebo for both). The time to first SBM was significantly shorter in the 6-mg group ($P < 0.05$ vs placebo) and nearly significant in the 3-mg group ($P = 0.054$).

Table 3. Summary of Adverse Events (Safety Population Excluding Duplicates)

	Aged <65 Years				Aged ≥65 Years			
		Plecanatide				Plecanatide		
	Placebo (n = 1439)	3 mg (n = 1448)	6 mg (n = 1460)	Pooled (n = 2908)	Placebo (n = 162)	3 mg (n = 150)	6 mg (n = 138)	Pooled (n = 288)
≥1 TEAE	353 (24.5)	393 (27.1)	382 (26.2)	775 (26.7)	40 (24.7)	53 (35.3)	44 (31.9)	97 (33.7)
≥1 severe* TEAE	15 (1.0)	30 (2.1)	32 (2.2)	62 (2.1)	5 (3.1)	7 (4.7)	2 (1.4)	9 (3.1)
≥1 serious† TEAE‡	15 (1.0)	16 (1.1)	12 (0.8)	28 (1.0)	3 (1.9)	3 (2.0)	2 (1.4)	5 (1.7)
TEAE experienced by ≥2.0% of patients in any treatment group								
Diarrhea	15 (1.0)	67 (4.6)	67 (4.6)	134 (4.6)	3 (1.9)	7 (4.7)	9 (6.5)	16 (5.6)
Flatulence	9 (0.6)	8 (0.6)	8 (0.5)	16 (0.6)	0 (0)	3 (2.0)	2 (1.4)	5 (1.7)
Nasopharyngitis	20 (1.4)	19 (1.3)	23 (1.6)	42 (1.4)	3 (1.9)	1 (0.7)	3 (2.2)	4 (1.4)
Headache	32 (2.2)	28 (1.9)	27 (1.8)	55 (1.9)	2 (1.2)	4 (2.7)	3 (2.2)	7 (2.4)
Arthralgia	6 (0.4)	8 (0.6)	6 (0.4)	14 (0.5)	2 (1.2)	4 (2.7)	1 (0.7)	5 (1.7)
Upper respiratory tract infection	16 (1.1)	18 (1.2)	6 (0.4)	24 (0.8)	0 (0)	3 (2.0)	2 (1.4)	5 (1.7)
Discontinued plecanatide	18 (1.3)	49 (3.4)	51 (3.5)	100 (3.4)	5 (3.1)	7 (4.7)	7 (5.1)	14 (4.9)
Due to TEAE								
Diarrhea	2 (0.1)	25 (1.7)	24 (1.6)	49 (1.7)	2 (1.2)	3 (2.0)	3 (2.2)	6 (2.1)

Values are numbers of patients (%). *Severity is a measure of intensity (mild, moderate, or severe) whereas seriousness is a regulatory definition (any untoward medical occurrence at any dose that results in death, is life-threatening, requires hospitalization, or is a congenital anomaly or birth defect). †5 of the 43 serious adverse events reported in patients aged <65 years were non-serious pregnancies (2 in the placebo group and 3 in the plecanatide groups) TEAE, treatment-emergent adverse event.

- The pooled safety population comprised 451 patients aged ≥65 years and 4347 patients aged <65 years, of whom 287 and 2908, respectively, were randomized to plecanatide (Table 3).
- The most common TEAE was diarrhea (Table 3), with rates in the pooled plecanatide dose groups similar in the older and younger cohorts. No cases of serious diarrhea were reported.
- Rates of discontinuation and diarrhea-related discontinuation in the plecanatide groups were low in both the older and younger cohorts. No new safety signals were observed.
- In both placebo and plecanatide groups there were slightly higher rates of TEAE-related treatment discontinuation, including rates of discontinuation due to diarrhea, in patients aged ≥65 years compared with those aged <65 years.

DISCUSSION

- This is the largest pooled analysis of patients with CIC and IBS-C within the elderly population to date (n = 468 patients aged ≥65 years).
- Results indicate that plecanatide is well tolerated and an effective treatment in younger and older adult patients with CIC or IBS-C.
- The pooled data identified no new safety signals with plecanatide treatment among patients aged ≥65 years or <65 years, compared with the full study populations.[6-8]
- No dose-related trend with plecanatide 3 mg or 6 mg was observed in any safety examined. There were no cases of serious diarrhea.
- The pooled findings indicate that efficacy was similar for those aged ≥65 years and those <65 years with respect to stool consistency, CSBM endpoints, and SBM endpoints.

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