Effect of Plecanatide on Stool Consistency in the Treatment of Chronic Idiopathic Constipation: Results from Two Phase III Studies

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Background

- Chronic Idiopathic Constipation (CIC) is one of the most common gastrointestinal functional disorders characterized by symptoms that include infrequent stools, incomplete bowel movements (BMs), straining, bloating, and hard/lumpy stool [1]
- Treatment of CIC is usually based on increased dietary fiber and supplementation with bulking agents, exercise, and bowel habit training; however, often only partial relief is obtained[2]
- Stool consistency, as measured by the Bristol Stool Form Scale (BSFS), is readily defined and has emerged as a key component in measuring clinically meaningful CIC treatment responses [3]
- Plecanatide, the first uroguanylin analog, is currently being developed as an oral, QD CIC treatment with no detectable systemic absorption in clinically utilized doses[4]
- Plecanatide binds to the guanylate cyclase (GC-C) receptor expressed on epithelial cells that line the intestinal lumen in a pH-dependent manner similar to uroguanylin, stimulating fluid secretion and promoting bowel movements with low rates of diarrhea[5]
- Clinical trials with plecanatide have shown it to be effective and safe in relieving CIC symptoms including improvements in stool consistency [6]

Aim

Two randomized, double-blind, placebo-controlled phase III clinical studies assessed the efficacy and safety of 3 mg and 6 mg plecanatide QD compared with placebo for 12 weeks in patients with CIC. The change from baseline in stool consistency based upon the mean weekly Bristol Stool Form Scale (BSFS) scores was evaluated in both studies and results are presented here.

Eligibility Criteria

Male and female patients who met modified Rome III functional constipation criteria for 3 months before the screening visit with symptom onset for at least 6 months before the diagnosis were eligible for participation.

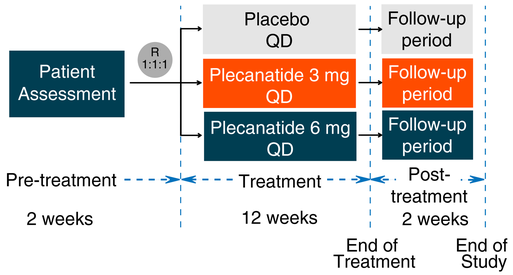
The Rome III criteria as modified for this study required the following:

- Patient reported that loose stools were rarely present without the use of laxatives
- Patient did not meet the Rome III criteria for IBS-C
- Patient did not use manual maneuvers (e.g., digital evacuation, support of the pelvic floor) to facilitate defecations
- Patient reported a history of less than three defecations per week
- Patient reported at least two of the following:
  - Straining during at least 25% of defecations
  - Lumpy or hard stool in at least 25% of defecations
  - Sensation of incomplete evacuation for at least 25% of defecations
  - Sensation of anorectal obstruction/blockage for at least 25% of defecations (no anatomic obstruction found)

Table 1. Intention-to-Treat Population

	Total	Placebo	Plecanatide 3 mg	Plecanatide 6 mg
	n	n	n	n
Study -00	1346	452	453	441
Study -03	1337	445	443	449

Study Design



- Patients were instructed to record their BMs, stool consistency and abdominal symptoms on electronic diaries on a daily basis with no ability to enter data from a previous day
- During screening a pre-treatment diary assessment was completed to ensure diary eligibility and establish baseline values
- Patients were seen at the clinical sites for randomization at the beginning of treatment. On Weeks 4, 8, and 12, patients returned to the clinic to undergo efficacy and safety assessments
- Patients returned to the clinic two weeks after the end of treatment for an end-of-study visit

Assessment of Stool Consistency

Bristol Stool Form Scale

Patients rated stool consistency using the BSFS, with scores ranging from Type 1 (hard and difficult to pass) to Type 7 (watery stools). Results were recorded by patients using an electronic diary. As with other electronic diary inputs, patients were not allowed to enter data from a previous day.

Type 1 Separate hard lumps, like nuts (hard to pass)

Type 2 Sausage-shaped, but lumpy

Type 3 Like a sausage but with cracks on its surface

Type 4 Like a sausage, smooth and soft. ***Considered to be normal stool form***

Type 5 Soft blobs with clear-cut edges (passed easily)

Type 6 Fluffy pieces with ragged edges, a mushy stool

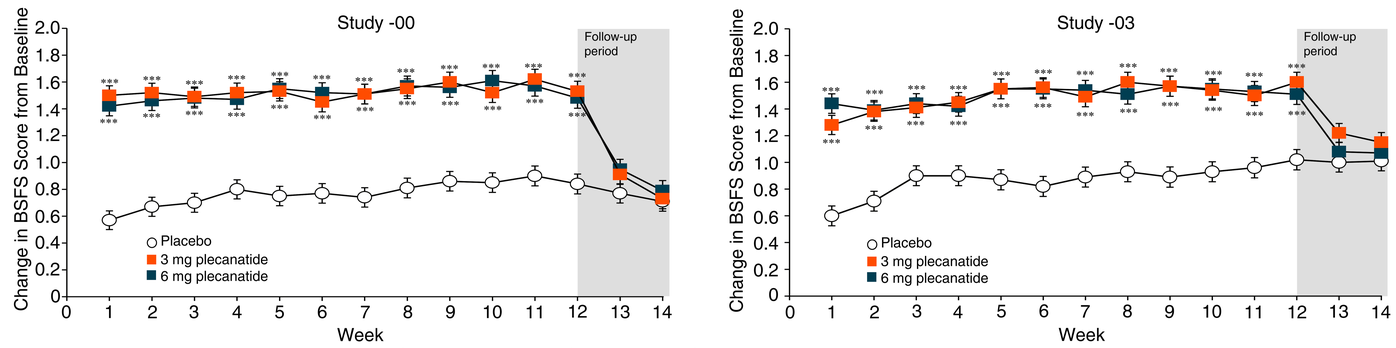
Type 7 Watery, no solid pieces. Entirely liquid

Statistical Analysis

Changes from baseline in BSFS scores over the treatment period were measured as average weekly scores (calculated from BSFS daily entries during that treatment week)and compared to placebo in the ITT population

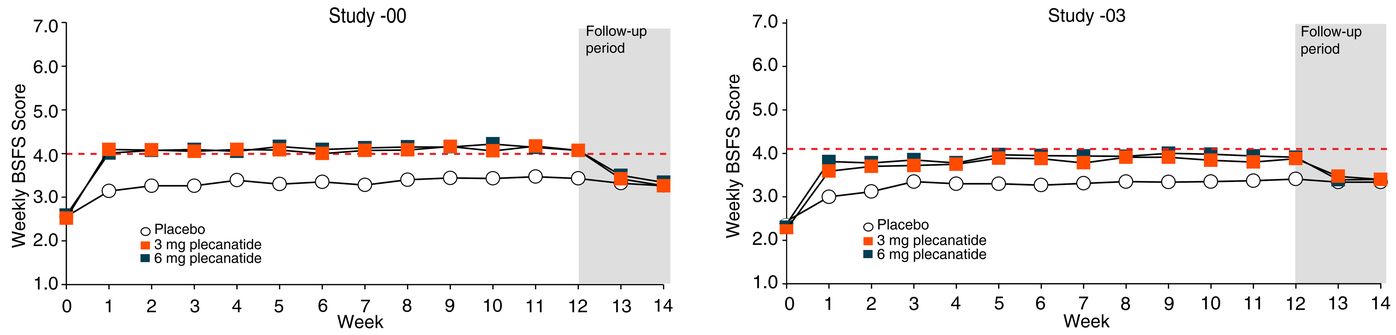
Results

Figure 1. Change from Baseline in Mean Weekly BSFS Score



In both studies, plecanatide showed a significant improvement from baseline (over the 12-week treatment period and at each treatment week) in BSFS scores compared with placebo. These improvements in BSFS scores compared to placebo were seen as early as week 1 and were maintained through the end of treament (***p<0.001).

Figure 2. Weekly BSFS Scores



At all treatment weeks, there was an improvement in stool consistency with bother pleacantide dose groups. BSFS scores for patients taking 3mg or 6 mg plecantide reached values consistent with normal stool form (BSFS score=4) within the first treatment week.

Conclusions

- **Plecanatide at 3 mg and 6 mg significantly improved stool consistency compared with placebo over the 12-week treatment period**
- **Stool consistency was restored to what is widely considered to be the normal physiological BSFS value (“4”) in the first treatment week and was maintained throughout the 12-week treatment period**
- **The findings from these studies indicate that plecanatide is effective in providing patients with a rapid improvement in stool consistency scores as well as sustained efficacy with continued treatment**

References

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