Efficacy and Safety of Plecanatide in the Treatment of Chronic Idiopathic Constipation (CIC): Results from a Multicenter Phase III Study (Study -03)

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Background

- Chronic Idiopathic Constipation (CIC) is a common symptom-based gastrointestinal disorder characterized by infrequent stools, difficult stool passage, or both [1]
- Because of the critical role it plays in the maintenance of intestinal fluid and electrolyte homeostasis, the guanylate cyclase-C (GC-C) receptor has recently emerged as a promising target for treating CIC [2]
- Plecanatide is a GC-C receptor agonist and the first uroguanylin (UG) analog designed for the treatment of CIC [3]
- Plecanatide replicates the actions of UG, which binds to the GC-C receptor in a pH-dependent manner in the small intestine, contributing to fluid secretion and normal bowel function [4]
- Plecanatide has been shown to be effective and well-tolerated in previous clinical trials in CIC patients [3,5]

Aim

The objective of this randomized, double-blind, placebo-controlled phase III clinical study was to assess the efficacy and safety of 3 mg and 6 mg doses of plecanatide once-daily compared to placebo for 12 weeks in patients with CIC.

Methods

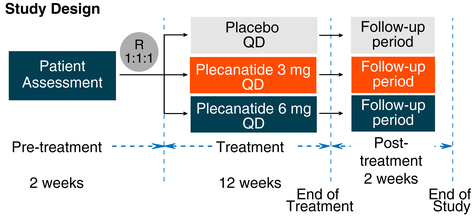
Eligibility Criteria

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)

Study Design



- Patients were instructed to record their daily bowel movements (BMs), stool consistency scores and rate abdominal symptoms on electronic hand-held devices with no ability to report data from the 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
- A post-treatment, end-of-study visit was held two weeks after the end of treatment

Assessments

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of patients who were durable overall complete spontaneous BM (CSBM) responders.

- A patient was considered a durable overall CSBM responder if he or she was a weekly responder for at least 9 of the 12 treatment weeks, including at least 3 of the final 4 weeks of treatment
- A patient was considered a weekly responder if he or she experienced ≥3 CSBMs in a given week and a ≥1 increase in CSBMs from baseline in that same week

Secondary and Additional Efficacy Endpoints

- Change in weekly CSBM frequency from baseline over the 12-week treatment period
- Change in weekly spontaneous BM (SBM) frequency from baseline over the 12-week treatment period
- Change in weekly straining score from baseline over the 12-week treatment period
- Percentage of patients who experienced a CSBM or SBM within 24 hours after the first dose of study medication

Safety Endpoints

Safety outcomes were measured by collecting

- Treatment-Emergent Adverse Events (TEAEs)
- Serious Adverse Events (SAEs)
- Adverse Events (AEs) leading to withdrawal

Statistical Analysis

- Efficacy analyses were conducted with the intention-to-treat (ITT) population (N=1337)
- Safety analyses were conducted with the safety population which included all patients who had at least one dose of study medication

Results

Plecanatide is the first CIC treatment to successfully meet more stringent primary endpoint criteria in which the investigational drug needs to demonstrate durability, with a weekly CSBM response in 9 out of 12 study weeks as well as 3 of the last 4 study weeks.

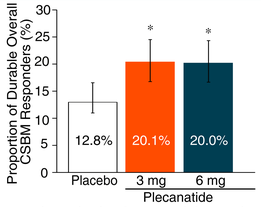
Table 1. Demographic and Baseline Characteristics of ITT Population

	Placebo N = 445	Plecanatide 3 mg N = 443	Plecanatide 6 mg N = 449
Mean age (range)	44.6 (18-80)	45.5 (18-80)	45.3 (18-80)
Female %	78.7	77.9	78.6
Male %	21.3	22.1	21.4
Race % [a]			
White	74.4	77.0	72.2
Black	20.4	19.9	22.7
Other	5.2	3.1	5.1
Mean weekly baseline values [b]			
CSBMs	0.31 ± 0.50	0.28 ± 0.55	0.25 ± 0.44
SBMs	1.55 ± 1.60	1.80 ± 2.05	1.60 ± 1.66
Straining score [c]	2.41 ± 0.85	2.45 ± 0.85	2.47 ± 0.88

[a] Race was self-reported
[b] Values are means ± SD unless otherwise noted
[c] The severity of straining during bowel movements was assessed on a 5-point Likert scale where:
0 = none, 1= mild, 2 = moderate, 3 = severe, 4 = very severe

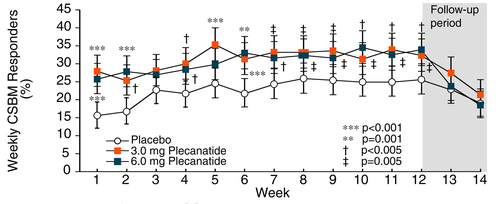
Results

Figure 1. Proportion of Patients who were Durable Overall CSBM Responders



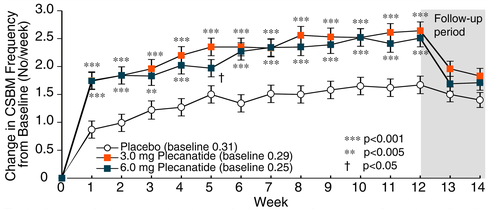
Significantly more patients in the 3 mg and 6 mg plecanatide treatment groups were durable overall CSBM responders compared with the placebo group. (*p = 0.004)

Figure 2. Proportion of Patients who were Weekly CSBM Responders



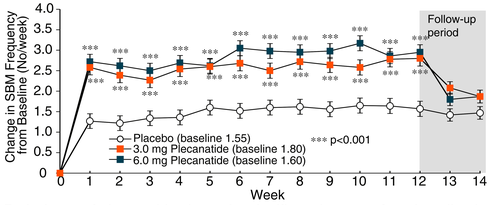
The proportion of weekly CSBM responders in both plecanatide groups compared with placebo increased as early as week 1 and remained consistent through the 12-week treatment period.

Figure 3. Change in CSBM Frequency from Baseline



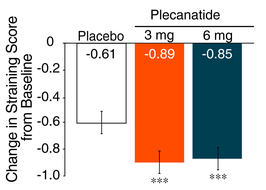
Both doses of plecanatide showed significant increases from baseline in CSBM frequency rates relative to placebo, starting from week 1 through the 12-week treatment period.

Figure 4. Change in SBM Frequency from Baseline



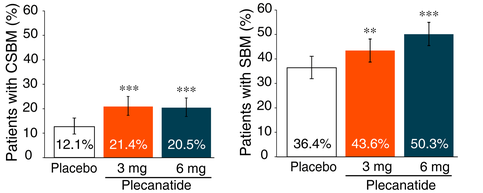
Both doses of plecanatide showed a significant increase from baseline in SBM frequency rates starting from week 1 through the 12-week treatment period relative to placebo.

Figure 5. Change in Straining Score from Baseline– Overall Average Across 12-Week Treatment Period



The straining score improved significantly from baseline over the 12-week treatment period for each dose of plecanatide relative to placebo without worsening over baseline at end of study. (***p<0.001)

Figure 6. Percentage of Patients with CSBM or SBM within 24 Hours after First Dose of Study Medication



Significantly more plecanatide-treated patients experienced a CSBM or an SBM within 24 hours of the first dose of study medication, compared with the placebo group. (***p < 0.001, **p < 0.05)

Safety

- A total of 372 patients (26.5%) experienced at least one TEAE.
- Treatment with plecanatide (3 mg and 6 mg) for 12 weeks was associated with an incidence of TEAEs (25.7% and 29.2%) similar to that in placebo-treated patients (24.7%)
- A total of 17 patients experienced at least one SAE (7 in the placebo group, 7 in the 3 mg plecanatide group, and 3 in the 6 mg plecanatide group)
- Rates of discontinuation due to TEAEs were 3.0% (placebo), 3.2% (3 mg plecanatide) and 3.8% (6 mg plecanatide)
- Rates of diarrhea were 1.3% (placebo), 3.2% (3 mg) and 4.5% (6 mg plecanatide)
- Rates of discontinuation due to diarrhea were 0.4% (placebo), 1.1% (3 mg plecanatide) and 1.1% (6 mg plecanatide)

Table 2. Summary of Adverse Events (Safety Population)

Number (%) patients	Placebo N = 466	Plecanatide 3 mg N = 467	Plecanatide 6 mg N = 469
Any TEAE	115 (24.7)	120 (25.7)	137 (29.2)
Discontinued study medication due to TEAE	14 (3.0)	15 (3.2)	18 (3.8)
Diarrhea TEAEs	6 (1.3)	15 (3.2)	21 (4.5)
Discontinued study medication due to diarrhea	2 (0.4)	5 (1.1)	5 (1.1)

Conclusions

- **Daily treatment with 3 mg or 6 mg of plecanatide significantly improved durable overall CSBM responder rates relative to placebo**
- **Improvements from baseline in CSBM and SBM frequency were noted as early as week 1 and lasted through the end of treatment**
- **Significantly more patients in plecanatide groups had CSBMs and SBMs within 24 hours of the first dose of study medication**
- **Plecanatide was well-tolerated with the majority of all TEAEs mild to moderate in severity**
- **No worsening of bowel symptoms (including CSBM and SBM frequency) and abdominal symptoms relative to baseline was observed following completion of the study drug treatment period**
- **These results suggest plecanatide may be a promising new therapy for CIC patients**

References

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Acknowledgements

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