# A Phase III Study of the Efficacy and Safety of Plecanatide in the Treatment of Chronic Idiopathic Constipation (CIC) (Study -00)

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## Background

- Chronic Idiopathic Constipation (CIC) is a common gastrointestinal disorder affecting approximately 14% of the North American population [1]
- CIC is a symptom-based disorder that is characterized by infrequent stools, difficult stool passage, or both [2]
- Plecanatide is currently under development as an oral, QD treatment of CIC with no detectable systemic absorption in clinically utilized doses [3]
- Plecanatide is the first uroguanylin (UG) analog developed for the treatment of CIC
- Plecanatide replicates the activity of $UG_2$, an endogenous ligand, which binds to the guanylate cyclase C (GC-C) receptor in a pH-dependent manner [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

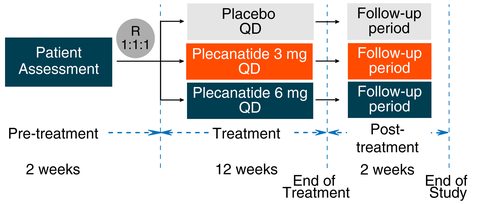
**Eligibility Criteria**

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 abdominal bloating 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=1346)
- Safety analyses were conducted with the safety population which included all patients who had at least one dose of study medication

## Results

This study is one of two pivotal phase III trials in which plecanatide has become the first drug to successfully meet new, more stringent FDA criteria defining primary efficacy endpoints. The new criteria for the primary efficacy endpoint evaluates the durability of the response, requiring patients be CSBM responders in 3 of the last 4 treatment weeks in addition to 9 of 12 weeks.

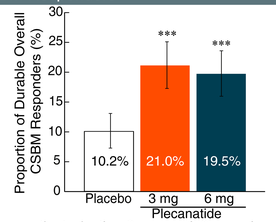
Table 1. Demographic and Baseline Characteristics of ITT Population

| | Placebo N = 452 | Plecanatide 3 mg N = 453 | Plecanatide 6 mg N = 441 |
|---|---|---|---|
| Mean age (range) | 46.4 (18-78) | 45.0 (18-79) | 45.1 (18-79) |
| Female % | 79.0 | 81.2 | 82.1 |
| Male % | 21.0 | 18.8 | 17.9 |
| Race % [a] | | | |
| White | 71.5 | 66.7 | 68.5 |
| Black | 23.9 | 28.5 | 24.5 |
| Other | 4.6 | 4.8 | 7.0 |
| Mean weekly baseline values [b] | | | |
| CSBMs | 0.38 ± 0.57 | 0.32 ± 0.51 | 0.32 ± 0.51 |
| SBMs | 2.17 ± 2.03 | 1.97 ± 1.77 | 1.82 ± 1.82 |
| Abdominal-bloating score [c] | 1.96 ± 0.85 | 1.90 ± 0.83 | 1.96 ± 0.89 |

[a] Race was self-reported
[b] Values are means ± SD unless otherwise noted
[c] Abdominal-bloating was assessed on a 5-point Likert scale where 0 = none, 1= mild, 2 = moderate, 3 = severe, 4 = very severe

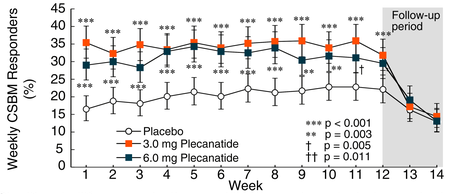
## Results

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



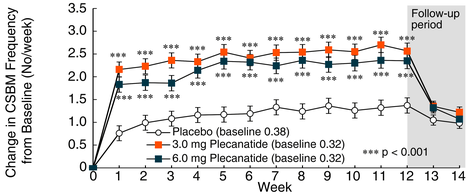

Significantly more patients in the 3 mg and 6 mg plecanatide treatment groups were durable overall CSBM responders compared with placebo. (***p < 0.001)

Figure 2. Proportion of Patients who were Weekly CSBM Responders



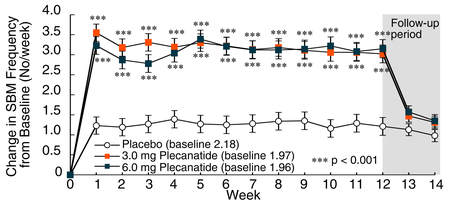

Significant differences in the weekly responder rate between both plecanatide groups and placebo were apparent as early as week 1 of treatment and remained consistent through the 12-week treatment period.

Figure 3. Change in CSBM Frequency from Baseline



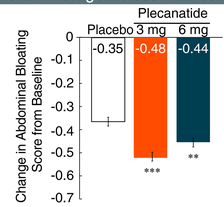

Both doses of plecanatide showed significant increases from baseline in CSBM frequency rates relative to placebo, starting from week 1 through the 12-week treatment period.

Figure 4. Change in SBM Frequency from Baseline



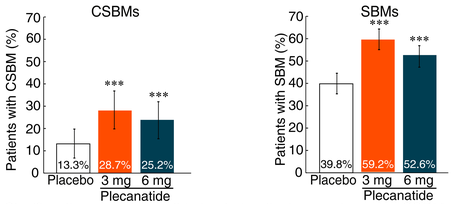

Both doses of plecanatide showed a significant increase from baseline in SBM frequency rate starting from week 1 over the 12-week treatment period relative to placebo.

Figure 5. Change in Bloating from Baseline– Overall Average Across 12-week Treatment Period




Plecanatide at both 3 mg and 6 mg doses displayed statistically significant improvements over 12-weeks relative to placebo in the severity of abdominal bloating. (***p = 0.002, **p < 0.05)

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)

## Safety

- A total of 469 patients (33.8%) experienced at least one TEAE.
- Treatment with plecanatide (3 mg and 6 mg) for 12 weeks was associated with an incidence of TEAEs (35.4% and 33.0%) similar to that in placebo-treated patients (32.8%)
- A total of 13 patients experienced an SAE: 4 (0.9%) in the placebo group, 4 (0.8%) in the 3 mg plecanatide group, and 5 (1.1%) in the 6 mg plecanatide group
- Rates of discontinuation due to TEAEs were 1.3% (placebo), 5.1% (3 mg plecanatide) and 5.3% (6 mg plecanatide)
- Rates of diarrhea were 1.3% (placebo), 5.9% (3 mg) and 5.7% (6 mg plecanatide)
- Rates of discontinuation due to diarrhea were 0.4% (placebo), 2.7% (3 mg plecanatide) and 2.6% (6 mg plecanatide)

**Table 2. Summary of Treatment-Emergent Adverse Events (safety population)**

| Number (%) patients | Placebo N = 458 | Plecanatide 3 mg N = 474 | Plecanatide 6 mg N = 457 |
|---|---|---|---|
| Any TEAE | 150 (32.8) | 168 (35.4) | 151 (33.0) |
| Discontinued study medication due to TEAE | 6 (1.3) | 24 (5.1) | 24 (5.3) |
| All Diarrhea TEAEs | 6 (1.3) | 28 (5.9) | 26 (5.7) |
| Discontinued study medication due to diarrhea | 2 (0.4) | 13 (2.7) | 12 (2.6) |

## 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 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 rated as 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 that plecanatide offers a promising new treatment for patients with CIC**

## References

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## Acknowledgements

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