Plecanatide, A Novel Guanylate Cyclase-C Receptor Agonist, is Efficacious and Safe in Patients with Chronic Idiopathic Constipation: Results from a 951 Patient, 12 Week, Multi-Center Trial

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Plecanatide: Novel Approach to the Treatment of GI Disorders

- Analogue of uroguanylin - natural agonist of guanylate-cyclase C (GC-C) receptor
- Oral once-daily dosing
- Targets GC-C receptor in GI tract
- Essentially non-systemic
- Models normal physiology
Guanylate Cyclase C Receptor Agonists
Physiological mechanism

Cross section of the GI tract

1. Uroguanylin (UroG) activates guanylate cyclase-C (GC-C) receptors on the lumenal side of the gut

2. Activation of GC-C receptors stimulates synthesis of cyclic GMP, activating cystic fibrosis transmembrane conductance regulator (CFTR)

3. Activated CFTR secretes Cl−, HCO3− and fluid into the intestinal lumen. Secretion of fluid into intestine is critical for normal digestion

4. Plecanatide binds to GC-C receptors, promoting spontaneous bowel movement (SBM)

Plecanatide CIC Study
Plecanatide: A Novel Mechanism of Action to Treat Chronic Constipation and IBS-C

- 16 mer peptide with 2 disulfide bonds
- Structurally similar to uroguanylin

Plecanatide binding constant to human GC-C receptors is 8-fold higher than uroguanylin
- No systemic absorption up to single oral doses of 48.6 mg

Phase I and IIA Clinical Summary:
  - Results suggest Plecanatide will be useful in treating CIC and IBS-C
Protocol Design

- **Aim:** Determine safety, effectiveness and dose-response of Plecanatide in CIC patients
- Randomized, double-blind, placebo controlled, parallel group, stratified by gender, multicenter study
- Population: modified Rome III CIC criteria, including < 3 CSBMs/week
- Evaluation of Plecanatide doses: 0.3, 1.0 & 3.0 mg given QD for 12 weeks
Key Protocol Inclusion/Exclusion

- **Inclusion**
  - Modified Rome III for CIC including < 3 CSBM during each week of 2 week pre-treatment

- **Exclusion**
  - Rome III IBS-C diagnosis
  - Previous major GI surgical history
  - Recognized causes of constipation (opioids, iron supplements, hypothyroidism, etc.)
### Patient Populations

<table>
<thead>
<tr>
<th>Disposition</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>1722 at 113 sites in U.S.</td>
</tr>
<tr>
<td>Enrolled</td>
<td>951</td>
</tr>
<tr>
<td>Screen Failures:</td>
<td>771 (44.8)</td>
</tr>
<tr>
<td>Not willing to participate</td>
<td>179 (23)</td>
</tr>
<tr>
<td>IVRS noncompliance</td>
<td>104 (14)</td>
</tr>
<tr>
<td>≥3 CSBM's</td>
<td>91 (12)</td>
</tr>
<tr>
<td>Safety Population</td>
<td>948</td>
</tr>
<tr>
<td>mITT population</td>
<td>946*</td>
</tr>
<tr>
<td>Completed Treatment</td>
<td>738 (77.3)</td>
</tr>
</tbody>
</table>

**Withdrawal Reason:**

<table>
<thead>
<tr>
<th>Reason</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>46 (4.9)</td>
</tr>
<tr>
<td>Administrative</td>
<td>95 (10)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>51 (5.4)</td>
</tr>
</tbody>
</table>

* mITT population for all efficacy analyses
### Patient Demographics By Treatment Group

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo N =234</th>
<th>0.3 mg N =237</th>
<th>1.0 mg N =238</th>
<th>3.0 mg N =237</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Gender</td>
<td>209 (88.6)</td>
<td>203 (85.7)</td>
<td>202 (84.9)</td>
<td>205 (86.5)</td>
</tr>
<tr>
<td>Mean Age (yr) (Min, Max)</td>
<td>46.2 (19, 75)</td>
<td>47.8 (20, 75)</td>
<td>47.1 (18, 75)</td>
<td>47.1 (18, 75)</td>
</tr>
<tr>
<td>Race- White</td>
<td>171 (72.5)</td>
<td>171 (72.2)</td>
<td>170 (71.4)</td>
<td>175 (73.8)</td>
</tr>
<tr>
<td>Race- Other</td>
<td>65 (27.6)</td>
<td>66 (27.8)</td>
<td>68 (28.6)</td>
<td>62 (26.2)</td>
</tr>
<tr>
<td>Mean BMI (SD) (kg/m²)</td>
<td>26.9 (4.5)</td>
<td>27.6 (4.3)</td>
<td>27.2 (4.0)</td>
<td>27.3 (4.1)</td>
</tr>
</tbody>
</table>

Plecanatide CIC Study
Primary Endpoint
Percent CSBM Responders

9 of 12 weeks

![Chart showing percent CSBM responders for Placebo, 0.3, 1.0, and 3.0 with bars for each dose level.]

9 of 12 weeks including 3 of last 4

![Chart showing percent CSBM responders for Placebo, 0.3, 1.0, and 3.0 with bars for each dose level.]

* = p<0.05
** = p<0.01

Plecanatide CIC Study
Weekly Responder Rates
≥3 CSBMs/wk with an increase of ≥ 1 CSBM/wk

Placebo
0.3 mg
1.0 mg
3.0 mg

* = p<0.05;  ** = p < 0.01;  *** = p < 0.001

Plecanatide CIC Study
Patients Reporting an Increase of ≥ 1 CSBM/week

** = p < 0.01; *** = p < 0.001

Plecanatide CIC Study
Time to First SBM & CSBM

**Time to First CSBM**

- Placebo: 124.5 hours
- 0.3: 96.9 hours
- 1.0: 82 hours
- 3.0: 54.7 hours

**Time to First SBM**

- Placebo: 27.3 hours
- 0.3: 21 hours
- 1.0: 21.3 hours
- 3.0: 12.5 hours

**Pts with CSBM w/in 24 hrs**

- Placebo: 11.5%
- 0.3: 20.7%
- 1.0: 23.1%
- 3.0: 31.2%

**Pts with SBMs w/in 24 hrs**

- Placebo: 41.5%
- 0.3: 55.7%
- 1.0: 53.8%
- 3.0: 67.5%

* = p<0.05; ** = p < 0.01; *** = p < 0.001

Plecanatide CIC Study
**Stool Consistency**

Bristol Stool Form Scale Score

- * = p<0.05;
- ** = p < 0.01;
- *** = p < 0.001

**Treatment week**

- Placebo
- 0.3 mg
- 1.0 mg
- 3.0 mg

Plecanatide CIC Study
Weekly Straining Scores

Straining score based on 11-point score (0-10 rating)

* = p<0.05;   ** = p < 0.01;   *** = p < 0.001

Plecanatide CIC Study
Cumulative Days of Rescue Medication Use Per Month

* = p<0.05; ** = p < 0.01; *** = p < 0.001

Plecanatide CIC Study
Global Assessments, Symptoms and QOL

**Constipation Severity**
- Baseline vs. 12 weeks for Placebo and Plecanatide doses 0.3, 1.0, 3.0.
- Severity levels: Severe, Moderate, Mild, None.
- Significant differences indicated by asterisks: * = p<0.05; ** = p<0.01; *** = p<0.001.

**PAC-Symptoms**
- Baseline vs. 12 weeks for Placebo and Plecanatide doses 0.3, 1.0, 3.0.
- Severity levels: Severe, Moderate, Mild.
- Significant differences indicated by asterisks.

**PAC-Quality of Life**
- Baseline vs. 12 weeks for Placebo and Plecanatide doses 0.3, 1.0, 3.0.
- Severity levels: Severe, Moderate, Little bit.
- Significant differences indicated by asterisks.

**Treatment Satisfaction**
- 4 Weeks, 8 Weeks, 12 weeks for Placebo and Plecanatide doses 0.3, 1.0, 3.0.
- Severity levels: Quite, Moderate, Little, Not.
- Significant differences indicated by asterisks.

All Plecanatide doses p<0.001 at all time points.

Plecanatide CIC Study
## Treatment Emergent Adverse Events >2%

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo N=236</th>
<th>0.3 mg N=327</th>
<th>1.0 mg N=238</th>
<th>3.0 mg N=237</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>96 (40.7)</td>
<td>99 (41.8)</td>
<td>103 (43.3)</td>
<td>106 (44.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (1.3)</td>
<td>13 (5.5)</td>
<td>20 (8.4)</td>
<td>23 (9.7)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5 (2.1)</td>
<td>5 (2.1)</td>
<td>3 (1.3)</td>
<td>14 (5.9)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>11 (4.7)</td>
<td>6 (2.5)</td>
<td>9 (3.8)</td>
<td>12 (5.1)</td>
</tr>
<tr>
<td>Abdominal Distension</td>
<td>5 (2.1)</td>
<td>5 (2.1)</td>
<td>10 (4.2)</td>
<td>9 (3.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (2.1)</td>
<td>5 (2.1)</td>
<td>12 (5.0)</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>URI</td>
<td>5 (2.1)</td>
<td>6 (2.5)</td>
<td>5 (2.1)</td>
<td>9 (3.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 (2.1)</td>
<td>5 (2.1)</td>
<td>3 (1.3)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>UTI</td>
<td>6 (2.5)</td>
<td>5 (2.1)</td>
<td>9 (3.8)</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (2.1)</td>
<td>10 (4.2)</td>
<td>11 (4.6)</td>
<td>9 (3.8)</td>
</tr>
</tbody>
</table>
## Summary of AEs and Diarrhea AEs

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>0.3 mg</th>
<th>1.0 mg</th>
<th>3.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>Placebo N=236</td>
<td>0.3 mg N=237</td>
<td>1.0 mg N=238</td>
<td>3.0 mg N=237</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>5 (2.1)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Treatment-emergent (TE) AEs</td>
<td>96 (40.7)</td>
<td>99 (41.8)</td>
<td>103 (43.3)</td>
<td>106 (44.7)</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>8 (3.4)</td>
<td>9 (3.8)</td>
<td>16 (6.7)</td>
<td>13 (5.5)</td>
</tr>
<tr>
<td>All Diarrhea TEAEs</td>
<td>3 (1.3)</td>
<td>13 (5.5)</td>
<td>20 (8.4)</td>
<td>23 (9.7)</td>
</tr>
<tr>
<td>Severe Diarrhea TEAEs</td>
<td>0</td>
<td>0</td>
<td>4 (1.7)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>WD due to Diarrhea</td>
<td>1 (0.4)</td>
<td>2 (0.8)</td>
<td>8 (3.4)</td>
<td>7 (3.0)</td>
</tr>
</tbody>
</table>

Plecanatide CIC Study
## Serious Adverse Events (SAEs)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Placebo 0.3 mg n=1</th>
<th>Plecanatide 1.0 mg n=1</th>
<th>Plecanatide 3.0 mg n=2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension exacerbation</td>
<td>Non-cardiac chest pain</td>
<td>Endometriosis</td>
<td>Acute cholecystitis</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td></td>
<td></td>
<td>Hypoaesthesia with weakness</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma exacerbation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No signals in serum chemistries, hematology, urinalysis, ECG or vital signs

Plecanatide CIC Study
Summary

• Plecanatide 3.0 mg produced a statistically significant improvement in all primary and key secondary endpoints
• Clear dose-response with doses below 3 mg achieving statistical significance in some primary and key secondary endpoints
• Safe and well tolerated with a diarrhea rate at the highest dose below 10%

Conclusion

• This study demonstrates Plecanatide 3.0 mg dose appears to be safe and effective at this phase in development.