Intestinal, non-intestinal, and extra-digestive response to linaclotide in patients with IBS-C: results at Week 4 predict sustained response

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Study sponsored by Allergan plc
Disclosures

- Study sponsored by Allergan plc
- Prof Enrique Rey:
  - Attended advisory boards for Allergan plc, Norgine Iberia, Farmasierra SL, and Bayer
  - Received research grants from Allergan plc and Norgine Iberia
Introduction

- Irritable bowel syndrome with constipation (IBS-C) is a functional bowel disorder characterized by recurrent abdominal pain and constipation.\(^1\)

- Linaclotide is an oral guanylate cyclase-C agonist, approved by the FDA and the EMA for the treatment of IBS-C in adults.\(^2\)

- Two Phase 3, randomized, double-blind, parallel-group, placebo-controlled clinical trials demonstrated the efficacy and safety of linaclotide in patients with IBS-C.\(^3,4\)

  - However, the effect of linaclotide on non-intestinal / extra-digestive symptoms frequently associated with IBS-C has not been characterized

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1. Lacy BE et al. Gastroenterology 2016; Epub ahead of print
2. LINZESS® (linaclotide) prescribing information. Allergan plc and Ironwood Pharmaceuticals, Inc. 2017
Objectives

Evaluate possible factors predicting a clinical response to linaclotide

Assess the impact of linaclotide on intestinal, digestive non-intestinal, and extra-digestive symptoms associated with IBS
## Methods: study design

### Design
- Multicenter, open-label, uncontrolled, single-arm Phase IIIb clinical trial

### Treatment
- Linaclotide capsule 290 micrograms once daily for 12 weeks

### Key inclusion criteria
- Age ≥18 years
- Diagnosed with moderate-to-severe IBS-C based on Rome III criteria
- Irritable bowel syndrome symptoms severity score (IBS-SSS) >175

### Study outline

<table>
<thead>
<tr>
<th>Oral linaclotide 290 µg once daily</th>
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<tbody>
<tr>
<td><strong>Week -4</strong></td>
</tr>
<tr>
<td>Visit 0</td>
</tr>
<tr>
<td>Baseline screening visit</td>
</tr>
</tbody>
</table>
Methods: study endpoints

Primary efficacy endpoint
- Decrease in IBS-SSS of >30% after 12 weeks of treatment vs. baseline, or an IBS-SSS <75 at Week 12 AND
- A subjective (self-reported) improvement via the Likert scale of “subjective score response” as better or much better than baseline

Possible predictive factors for clinical response at Week 12 assessed in multivariate logistic regression model
- Age
- Time from IBS diagnosis
- IBS-SSS
- Pain score
- Pain / constipation index
- PHQ12 score
- Fear score
- Non-intestinal digestive symptoms scores
- Medicine confidence score
- Anxiety / depression score
- Clinical response at Week 4

Gastrointestinal symptom assessment
- Individual symptom scores for constipation, pain, and bloating assessed based on IBS-SSS

Digestive non-intestinal symptom assessment
- Digestive non-intestinal symptoms score assessed based on Rome III questionnaire (heartburn / acid regurgitation, postprandial fullness, early satiety, epigastric pain, nausea, and vomiting)

Extra-digestive symptoms
- Extra-digestive symptoms score was assessed based on PHQ-12 (back pain, headaches, chest pain, dizziness, fainting spells, heart pounding / racing, shortness of breath, problem with intercourse, pain in arms / legs or joints, feeling tired, pain or problems during sex, menstrual cramps, and trouble sleeping)
Results: patient disposition

Included in screening phase (N=121) -> Screening phase completed (N=109) -> Included in treatment phase (N=96) -> Treatment phase completed (N=60)

- Protocol deviation or consent withdrawal (n=12)
- Consent withdrawal (n=7)
- Protocol deviation or consent withdrawal (n=12)
- Not meeting criteria to enter treatment phase (n=6)
- Withdrawal due to adverse event\(^a\) (n=12)
- Withdrawal due to lack of efficacy (n=12)

\(^a\)In all 12 patients, the adverse event was diarrhea.

ITT, intent-to-treat; PP, per protocol
### Results: patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Mean (SD) unless otherwise stated</th>
<th>ITT population (n=96)</th>
<th>PP population (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD (min, max)</td>
<td>47.4 ± 14.7 (18, 80)</td>
<td>43.0 ± 14.7 (18, 80)</td>
</tr>
<tr>
<td>Patients age ≥50 years, n (%)</td>
<td>41 (43)</td>
<td>28 (47)</td>
</tr>
<tr>
<td>Years since last colonoscopy for patients age ≥50 years</td>
<td>0.8 (1.2)</td>
<td>0.8 (1.3)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>91 (94.8)</td>
<td>58 (96.7)</td>
</tr>
<tr>
<td>Years from IBS-C diagnosis</td>
<td>7.5 (10.0)</td>
<td>8.0 (9.3)</td>
</tr>
<tr>
<td>IBS-SSS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>371.0 (72.5)</td>
<td>376.7 (68.5)</td>
</tr>
<tr>
<td>Pain score&lt;sup&gt;b&lt;/sup&gt;</td>
<td>68.4 (19.5)</td>
<td>67.4 (18.1)</td>
</tr>
<tr>
<td>Constipation score&lt;sup&gt;b&lt;/sup&gt;</td>
<td>65.9 (21.7)</td>
<td>66.4 (21.3)</td>
</tr>
<tr>
<td>Pain / constipation index</td>
<td>1.2 (0.8)</td>
<td>1.2 (0.7)</td>
</tr>
<tr>
<td>Distention score&lt;sup&gt;b&lt;/sup&gt;</td>
<td>76.3 (20.2)</td>
<td>79.0 (17.8)</td>
</tr>
<tr>
<td>PHQ12 score&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10.7 (4.2)</td>
<td>10.5 (4.5)</td>
</tr>
<tr>
<td>Non-intestinal digestive score&lt;sup&gt;d&lt;/sup&gt;</td>
<td>8.9 (3.9)</td>
<td>9.1 (3.9)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Scale of 0–500 based on scores for abdominal pain, distention, bowel habit, and interference with life; 
<sup>b</sup>Assessed via IBS-SSS on a visual analog scale of 0–100 (0=none, 100=very severe); 
<sup>c</sup>Scored on a scale of 0–24 based on sum of scores for each of the 12 non-intestinal symptoms (0=not bothersome, 2=very bothersome); 
<sup>d</sup>Based on Rome III questionnaire

SD, standard deviation
At Week 12, the proportions of patients with a clinical response\textsuperscript{a} to linaclotide in the ITT and PP populations were:
- 25% and 36.7% based on meeting IBSSS and subjective criteria
- 61.5% and 80% based on meeting either criteria

Clinical response to linaclotide at Week 4 predicted a response at Week 12 (odds ratio = 6.5; 95% CI: 2.1–19.8)
None of the baseline variables investigated were found to be predictive of a response at Week 12

\\textsuperscript{a}Decrease in IBS-SSS of >30% after 12 weeks of treatment vs. baseline, or an IBS-SSS <75 at Week 12 AND a subjective improvement via the Likert scale of “subjective score response” as better or much better than baseline

CI, confidence interval
Results: change in IBS-SSS at Week 12

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<table>
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<tbody>
<tr>
<td></td>
<td>47.0%</td>
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<td></td>
<td>56.7%</td>
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</table>
Results: gastrointestinal symptom response

- Constipation, pain, and bloating scores were all significantly decreased from baseline at Weeks 4, 8, and 12 in the ITT and PP populations (PP data not shown)

Assessed via IBS-SSS using a visual analog scale of 0–100 assessing intensity of each symptom (0=none, 100=very severe)

*p<0.05; **p<0.001; ***p<0.0001 vs. Week 0; error bars indicate standard deviation
During the screening phase, a slight worsening of extra-digestive symptoms\textsuperscript{a} was observed, without any change in non-intestinal symptoms\textsuperscript{b}.

At Week 12, digestive non-intestinal symptoms score showed a 21.2\% improvement and extra-digestive symptoms score showed a 41.5\% improvement compared to the scores at the beginning of linaclotide treatment.

Improvements in non-intestinal and extra-digestive symptoms did not correlate with change in anxiety score in the 12 weeks of treatment:
- Change in non-intestinal symptoms: \( r=0.11 \) (\( p=\text{NS} \))
- Change in extra-digestive symptoms: \( r=-0.06 \) (\( p=\text{NS} \))

\textsuperscript{a}Extra-digestive symptoms score based on PHQ-12 questionnaire assessing: back pain, headaches, chest pain, dizziness, fainting spells, heart pounding / racing, shortness of breath, problem with intercourse, pain in arms / legs or joints, feeling tired, pain or problems during sex, menstrual cramps, and trouble sleeping.

\textsuperscript{b}Digestive non-intestinal symptoms score based on Rome III questionnaire assessing symptoms including: heartburn / acid regurgitation, postprandial fullness, early satiety, epigastric pain, nausea, and vomiting.\*\( p<0.05 \) (paired t-test) compared to Visit -4;

\**p<0.001 \) (paired t-test) compared to Visit 0

NS=not significant

Results: digestive non-intestinal and extra-digestive symptom response
Results: laxative use decreased during linaclotide treatment

- All laxatives / enemas / suppositories were stopped at Week -4 and allowed only as rescue medication
  - A maximum of 12 days of laxative use was allowed by protocol during the treatment phase

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th>PP population (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Laxatives / enemas / suppositories n (%)</td>
<td>Days of laxative use, mean (SD)</td>
<td>Days of enema / suppository use, mean (SD)</td>
</tr>
<tr>
<td>Baseline</td>
<td>41 (42.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Screening period</td>
<td>25 (26.0)</td>
<td>2.8 (3.9)</td>
<td>1.9 (2.4)</td>
</tr>
<tr>
<td>Week 0 to Week 4</td>
<td>12 (12.5)</td>
<td>0.8 (1.4)</td>
<td>1.7 (2.0)</td>
</tr>
<tr>
<td>Week 4 to Week 12</td>
<td>11 (11.5)</td>
<td>0</td>
<td>1.5 (0.5)</td>
</tr>
</tbody>
</table>

*A protocol deviation at the screening visit was allowed for one patient using laxatives due to misinterpretation of instructions

NA, not applicable
Results: safety overview

<table>
<thead>
<tr>
<th>ITT population (n=96)</th>
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<tbody>
<tr>
<td>Treatment-emergent AEs, a n</td>
</tr>
<tr>
<td>Serious AEs, n</td>
</tr>
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</table>

Most common treatment-emergent AEs, n (%)

<table>
<thead>
<tr>
<th>AEs</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>37 (25.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (5.4)</td>
</tr>
<tr>
<td>Nausea / vomiting</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>5 (3.4)</td>
</tr>
</tbody>
</table>

- The most common AEs included diarrhea, headache, and nausea / vomiting
- No serious AEs occurred
- 31% of patients (n=30) had at least one episode of treatment-related diarrhea (total number of episodes = 37)
  - 46% (n=17) = mild
  - 46% (n=17) = moderate
  - 8% (n=3) = severe
- Diarrhea led to treatment discontinuation in 12 patients
- Average duration of diarrhea was 9 days; 40% lasted ≤7 days

a AEs classified according to MedDRA English V 4.0.0.97; an additional 40 AEs occurred during the screening phase (none serious)
Conclusions

- Linaclotide is effective at improving ALL symptoms of IBS-C over 12 weeks
- Linaclotide significantly improved intestinal symptoms, non-intestinal digestive symptoms, and extra-digestive symptoms of IBS-C
- The clinical response to linaclotide at Week 4 predicted the response at Week 12
  - No baseline variables were identified that could predict whether a patient with IBS-C had a higher probability of responding to linaclotide
- AEs reported in this study were consistent with the known safety profile of linaclotide
Thank you

Questions…