Pre-Registered  
N = 46

Registered  
N = 24

Screen failure reasons (N=22)  
- Participant Decision 4  
- Alternates* 5  
- Lost to Follow-up** 4  
- Polyps found at baseline 2  
- Proctitis 2  
- Investigator Decision 1  
- Other reasons 4

Stage I Linaclotide/Placebo 0.87mg Days 1-7  
N = 6

Stage II (Full colonoscopy prep) Linaclotide/Placebo 0.87mg Day 1-7  
N = 6

Stage III (Tap water enema prep) Linaclotide/Placebo 0.87mg Day 1-7  
N = 6

Stage III (Peg enema prep) Linaclotide/Placebo 0.87mg Day 1-7  
N = 6

*Subjects not needed due to full stage accrual by time of eligibility assessment completion.

**Subjects did not show up for sigmoidoscopy.
Figure 2

Cyclic GMP Pharmacodynamic Response

Stage I

- black bars: Linaclotide
- crossed bars: Placebo

Subject: C, TC, R

Cyclic GMP
Pharmacodynamic Response

2 4 5 6 8 9

Subject
Figure 3

Cecum

<table>
<thead>
<tr>
<th>Subject</th>
<th>Relative VASP Phosphorylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td>TC</td>
<td>3</td>
</tr>
<tr>
<td>R</td>
<td>4</td>
</tr>
</tbody>
</table>

D1 D7 D1 D7 D1 D7 D1 D7

2 4 5 6 8 9

Rectum

<table>
<thead>
<tr>
<th>Subject</th>
<th>Relative VASP Phosphorylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>1</td>
</tr>
<tr>
<td>TC</td>
<td>2</td>
</tr>
<tr>
<td>R</td>
<td>3</td>
</tr>
</tbody>
</table>

D1 D7 D1 D7 D1 D7 D1 D7

2 4 5 6 8 9

Graph showing Relative VASP Phosphorylation across different subjects and treatments.

- **Linaclotide**
- **Placebo**

*Significant differences indicated by asterisks.*
Figure 4

Relative Ki67 Cells per Crypt

CPN0002

CPN0004

CPN0005

CPN0006

CPN0008

CPN0009

Subject

Linaclotide
Placebo

Relative Ki67 Cells per Crypt

Subject
Figure 5

A. Cyclic GMP Pharmacodynamic Response

Stage II

- Subject 13: 1.23
- Subject 14: 4.67
- Subject 15: 1.73
- Subject 20: -0.18
- Subject 21: 1.73
- Subject 22: -0.32

Stage III Tap Water

- Subject 47: 0.39
- Subject 53: 5.0
- Subject 54: 47
- Subject 94: -2.06
- Subject 97: -3.42
- Subject 98: 0.32

Stage III PEG

- Subject 157: -3.46
- Subject 158: -0.86
- Subject 159: -0.96
- Subject 182: -2.54
- Subject 195: -0.24
- Subject 198: -0.45

B. Cyclic GMP Pharmacodynamic Response

Stage III Tap Water

- Subject 47: 0.39
- Subject 53: 5.0
- Subject 54: 47
- Subject 94: -2.06
- Subject 97: -3.42
- Subject 98: 0.32

C. Cyclic GMP Pharmacodynamic Response

- Subject 157: -4.45
- Subject 158: -4.46
- Subject 159: -2.54
- Subject 182: -0.36
- Subject 195: -0.86
- Subject 198: -1.19