



## Clinical trial results:

### A Phase 4, Single-centre, Randomised, Double-blind, Placebo-controlled, Parallel-group, Fixed-dose Study of the Effect of Linacotide on Abdominal Girth in Participants with Irritable Bowel Syndrome with Constipation

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2016-000818-29  |
| Trial protocol           | GB              |
| Global end of trial date | 31 October 2018 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 16 October 2021 |
| First version publication date | 16 October 2021 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | MCP-103-403 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02837783 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Ironwood Pharmaceuticals Inc.  |
| Sponsor organisation address | 100 Summer Street Suite 2300, Boston, MA, United States, 02110                                   |
| Public contact               | Corporate Communications, Ironwood Pharmaceuticals Inc., +1 617621 7722, Info@ironwoodpharma.com |
| Scientific contact           | Corporate Communications, Ironwood Pharmaceuticals Inc., +1 617621 7722, Info@ironwoodpharma.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 31 October 2018 |
| Is this the analysis of the primary completion data? | No              |

|                                  |                 |
|----------------------------------|-----------------|
| Global end of trial reached?     | Yes             |
| Global end of trial date         | 31 October 2018 |
| Was the trial ended prematurely? | Yes             |

Notes:

## General information about the trial

Main objective of the trial:

The objective of this trial is to determine the effect of linaclotide on abdominal girth in IBS-C participants with the baseline symptoms of abdominal bloating and an increased abdominal girth.

Protection of trial subjects:

It is the responsibility of the Investigator (or qualified designee) to give each participant full and adequate information regarding the objectives and procedures of the study and the possible risks involved. The participants must be informed about their right to withdraw from the study at any time. Furthermore, it is the responsibility of the Investigator to obtain signed and dated written informed consent from all participants, and a dated signature from the persons conducting the informed consent discussion, before undertaking any study-related procedure. The written informed consent form must be approved by the Research Ethics Committee (REC) for the purposes of obtaining and documenting consent. The Investigator must be available to answer all participants' questions regarding the study.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 21 December 2016 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Worldwide total number of subjects   | 20                 |
| EEA total number of subjects         | 0                  |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 20 |

|                     |   |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over   | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study included a 14-day screening period and a 7 day pretreatment period. The treatment period began with randomisation and lasted for 4 weeks. Participants who met entry criteria were randomised (1:1) to once daily oral capsules containing 290 µg linaclotide or placebo.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Overall Study (overall period)         |
| Is this the baseline period? | Yes                                    |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Carer, Assessor |

Blinding implementation details:

Both the participants and the research team were blinded to randomisation and allocation of study drug/placebo.

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Matching Placebo |

Arm description:

Placebo once daily for 4 weeks

|  |               |
|--|---------------|
| Arm type                               | Placebo       |
| Investigational medicinal product name | placebo       |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Participants were instructed to take one capsule in the morning at least 30 minutes before breakfast.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | 290 µg Linaclotide |
|------------------|--------------------|

Arm description:

290 µg linaclotide once daily for 4 weeks

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Linaclotide   |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Participants were instructed to take one capsule in the morning at least 30 minutes before breakfast.

| <b>Number of subjects in period 1</b> | Matching Placebo | 290 µg Linaclotide |
|---------------------------------------|------------------|--------------------|
| Started                               | 9                | 11                 |
| Received >= 1 Dose of Study Drug      | 9                | 10                 |
| Completed                             | 7                | 9                  |
| Not completed                         | 2                | 2                  |
| Adverse Event                         | 1                | -                  |
| Other, Not Specified                  | 1                | 2                  |

## Baseline characteristics

### Reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Matching Placebo   |
| Reporting group description:<br>Placebo once daily for 4 weeks            |                    |
| Reporting group title   | 290 µg Linaclotide |
| Reporting group description:<br>290 µg linaclotide once daily for 4 weeks |                    |

| Reporting group values             | Matching Placebo | 290 µg Linaclotide | Total |
|------------------------------------|------------------|--------------------|-------|
| Number of subjects                 | 9                | 11                 | 20    |
| Age categorical<br>Units: Subjects |                  |                    |       |

|   |                 |                 |    |
|---|-----------------|-----------------|----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 35.8<br>± 10.38 | 35.2<br>± 12.82 | -  |
| Gender categorical<br>Units: Subjects                                   |                 |                 |    |
| Female  | 9               | 11              | 20 |
| Male  | 0               | 0               | 0  |
| Race<br>Units: Subjects   |                 |                 |    |
| Caucasian   | 9               | 11              | 20 |
| Non-Caucasian   | 0               | 0               | 0  |
| Ethnicity<br>Units: Subjects  |                 |                 |    |
| Hispanic or Latino  | 0               | 0               | 0  |
| Not Hispanic or Latino  | 9               | 11              | 20 |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title                     | Matching Placebo   |
| Reporting group description:              |                    |
| Placebo once daily for 4 weeks            |                    |
| Reporting group title                     | 290 µg Linaclotide |
| Reporting group description:              |                    |
| 290 µg linaclotide once daily for 4 weeks |                    |

### Primary: Change From Baseline in Abdominal Girth at Week 4

|  |   |
|--|---|
| End point title  | Change From Baseline in Abdominal Girth at Week 4 |
| End point description:   |   |
| Mean change in abdominal girth (physical measure of bloating/distension) as measured by area under the curve (AUC), determined by 24-hour abdominal inductance plethysmography (AIP; with hourly averages). The AUC was calculated using the Trapezoidal method from the first reliable hour of measurement to last measurement (bedtime). The AUC for each participant was then individually standardized by dividing the total AUC over the period by that patient's number of hours of measurement included in the AUC. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Baseline, Week 4   |   |

| End point values                     | Matching Placebo | 290 µg Linaclotide |  |  |
|--------------------------------------|------------------|--------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group    |  |  |
| Number of subjects analysed          | 7 <sup>[1]</sup> | 10 <sup>[2]</sup>  |  |  |
| Units: AUC                           |                  |                    |  |  |
| arithmetic mean (standard deviation) | -3.36 (± 4.04)   | -0.632 (± 11.6)    |  |  |

Notes:

[1] - Participants with an assessment at given time point.

[2] - Participants with an assessment at given time point.

### Statistical analyses

|   |                                       |
|---|---------------------------------------|
| Statistical analysis title              | Statistical Analysis 1                |
| Comparison groups                       | Matching Placebo v 290 µg Linaclotide |
| Number of subjects included in analysis | 17                                    |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.283                               |
| Method                                  | Wilcoxon rank sum test                |

### Secondary: Change From Baseline in Abdominal Girth at Week 2

|   |   |
|---|---|
| End point title   | Change From Baseline in Abdominal Girth at Week 2 |
| End point description:  |   |
| Mean change in abdominal girth (physical measure of bloating/distention) as measured by AUC, determined by 24-hour AIP (with hourly averages). The AUC was calculated using the Trapezoidal method from the first reliable hour of measurement to last measurement (bedtime). The AUC for each participant was then individually standardized by dividing the total AUC over the period by that patient's number of hours of measurement included in the AUC. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Baseline, Week 2  |   |

| End point values                     | Matching Placebo | 290 µg Linaclotide |  |  |
|--------------------------------------|------------------|--------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group    |  |  |
| Number of subjects analysed          | 8 <sup>[3]</sup> | 10 <sup>[4]</sup>  |  |  |
| Units: AUC                           |                  |                    |  |  |
| arithmetic mean (standard deviation) | 0.535 (± 9.15)   | -2.3 (± 13.7)      |  |  |

Notes:

[3] - Participants with an assessment at given time point.

[4] - Participants with an assessment at given time point.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Maximal Abdominal Girth at Week 4

|  |   |
|--|---|
| End point title  | Percent Change From Baseline in Maximal Abdominal Girth at Week 4 |
| End point description:   |   |
| The maximum change in girth from the first hour, over the period from the 2nd hour to bedtime. The percentage change in maximum distension from baseline to 4 weeks will also be calculated. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline, Week 4   |   |

| End point values                     | Matching Placebo | 290 µg Linaclotide |  |  |
|--------------------------------------|------------------|--------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group    |  |  |
| Number of subjects analysed          | 7 <sup>[5]</sup> | 9 <sup>[6]</sup>   |  |  |
| Units: percent change                |                  |                    |  |  |
| arithmetic mean (standard deviation) | -7.13 (± 33.4)   | 15.4 (± 80.3)      |  |  |

Notes:

[5] - Participants with an assessment at given time point.

[6] - Participants with an assessment at given time point.

### Statistical analyses

No statistical analyses for this end point

**Secondary: Change From Baseline of Symptom Severity (Abdominal Pain, Discomfort, Bloating, and Distension) at Week 1**

|                 |   |
|-----------------|---|
| End point title | Change From Baseline of Symptom Severity (Abdominal Pain, Discomfort, Bloating, and Distension) at Week 1 |
|-----------------|---|

End point description:

Symptom severity was assessed daily on an 11-point numerical rating scale (NRS) from 0 to 10, where 0 represents no symptoms and 10 represents very severe symptoms. Participants rated their abdominal pain, discomfort, bloating, and distension at its worst over the last 24 hours. Weekly average scores were calculated individually for abdominal pain, discomfort, bloating, distension. The abdominal score was calculated as the weekly average from the daily scores of the individual items of pain, discomfort, bloating combined. The abdominal score plus distension was calculated as the weekly average from the daily scores of the individual items of pain, discomfort, bloating and distension combined.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 1

| End point values                     | Matching Placebo | 290 µg Linaclotide |  |  |
|--------------------------------------|------------------|--------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group    |  |  |
| Number of subjects analysed          | 8 <sup>[7]</sup> | 11 <sup>[8]</sup>  |  |  |
| Units: units on a scale              |                  |                    |  |  |
| arithmetic mean (standard deviation) |                  |                    |  |  |
| Pain                                 | -1.25 (± 1.76)   | -0.75 (± 1.88)     |  |  |
| Discomfort                           | -1.93 (± 1.54)   | -0.97 (± 2.05)     |  |  |
| Bloating                             | -2.00 (± 1.48)   | -0.40 (± 1.23)     |  |  |
| Distension                           | -1.91 (± 1.41)   | -0.15 (± 1.02)     |  |  |
| Abdominal Score                      | -1.73 (± 1.50)   | -0.71 (± 1.58)     |  |  |
| Abdominal Score + Distension         | -1.77 (± 1.43)   | -0.57 (± 1.36)     |  |  |

Notes:

[7] - Participants with an assessment at given time point.

[8] - Participants with an assessment at given time point.

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change From Baseline of Symptom Severity (Abdominal Pain, Discomfort, Bloating, and Distension) at Week 2**

|                 |   |
|-----------------|---|
| End point title | Change From Baseline of Symptom Severity (Abdominal Pain, Discomfort, Bloating, and Distension) at Week 2 |
|-----------------|---|

End point description:

Symptom severity was assessed daily on an 11-point NRS from 0 to 10, where 0 represents no symptoms and 10 represents very severe symptoms. Participants rated their abdominal pain, discomfort, bloating, and distension at its worst over the last 24 hours. Weekly average scores were calculated individually for abdominal pain, discomfort, bloating, distension. The abdominal score was calculated as the weekly average from the daily scores of the individual items of pain, discomfort, bloating combined. The abdominal score plus distension was calculated as the weekly average from the daily scores of the individual items of pain, discomfort, bloating and distension combined.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 2

| End point values                     | Matching Placebo | 290 µg Linaclotide |  |  |
|--------------------------------------|------------------|--------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group    |  |  |
| Number of subjects analysed          | 8 <sup>[9]</sup> | 10 <sup>[10]</sup> |  |  |
| Units: units on a scale              |                  |                    |  |  |
| arithmetic mean (standard deviation) |                  |                    |  |  |
| Pain                                 | -1.97 (± 1.60)   | -1.42 (± 1.88)     |  |  |
| Discomfort                           | -2.51 (± 1.15)   | -1.73 (± 2.27)     |  |  |
| Bloating                             | -2.65 (± 1.30)   | -1.04 (± 1.54)     |  |  |
| Distension                           | -2.51 (± 1.37)   | -0.78 (± 1.33)     |  |  |
| Abdominal Score                      | -2.38 (± 1.19)   | -1.40 (± 1.69)     |  |  |
| Abdominal Score + Distension         | -2.41 (± 1.18)   | -1.25 (± 1.52)     |  |  |

Notes:

[9] - Participants with an assessment at given time point.

[10] - Participants with an assessment at given time point.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline of Symptom Severity (Abdominal Pain, Discomfort, Bloating, and Distension) at Week 3

|                 |   |
|-----------------|---|
| End point title | Change From Baseline of Symptom Severity (Abdominal Pain, Discomfort, Bloating, and Distension) at Week 3 |
|-----------------|---|

End point description:

Symptom severity was assessed daily on an 11-point NRS from 0 to 10, where 0 represents no symptoms and 10 represents very severe symptoms. Participants rated their abdominal pain, discomfort, bloating, and distension at its worst over the last 24 hours. Weekly average scores were calculated individually for abdominal pain, discomfort, bloating, distension. The abdominal score was calculated as the weekly average from the daily scores of the individual items of pain, discomfort, bloating combined. The abdominal score plus distension was calculated as the weekly average from the daily scores of the individual items of pain, discomfort, bloating and distension combined.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 3

| End point values                     | Matching Placebo  | 290 µg Linaclotide |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 8 <sup>[11]</sup> | 10 <sup>[12]</sup> |  |  |
| Units: units on a scale              |                   |                    |  |  |
| arithmetic mean (standard deviation) |                   |                    |  |  |
| Pain                                 | -1.60 (± 2.66)    | -2.07 (± 1.88)     |  |  |
| Discomfort                           | -2.01 (± 1.86)    | -2.25 (± 2.26)     |  |  |
| Bloating                             | -2.02 (± 1.67)    | -1.16 (± 1.51)     |  |  |
| Distension                           | -1.79 (± 1.80)    | -1.05 (± 1.37)     |  |  |
| Abdominal Score                      | -1.88 (± 1.95)    | -1.82 (± 1.64)     |  |  |
| Abdominal Score + Distension         | -1.86 (± 1.87)    | -1.64 (± 1.46)     |  |  |

Notes:

[11] - Participants with an assessment at given time point.

[12] - Participants with an assessment at given time point.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline of Symptom Severity (Abdominal Pain, Discomfort, Bloating, and Distension) at Week 4

|                 |   |
|-----------------|---|
| End point title | Change From Baseline of Symptom Severity (Abdominal Pain, Discomfort, Bloating, and Distension) at Week 4 |
|-----------------|---|

End point description:

Symptom severity was assessed daily on an 11-point NRS from 0 to 10, where 0 represents no symptoms and 10 represents very severe symptoms. Participants rated their abdominal pain, discomfort, bloating, and distension at its worst over the last 24 hours. Weekly average scores were calculated individually for abdominal pain, discomfort, bloating, distension. The abdominal score was calculated as the weekly average from the daily scores of the individual items of pain, discomfort, bloating combined. The abdominal score plus distension was calculated as the weekly average from the daily scores of the individual items of pain, discomfort, bloating and distension combined.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 4

| End point values                     | Matching Placebo  | 290 µg Linacotide  |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 8 <sup>[13]</sup> | 10 <sup>[14]</sup> |  |  |
| Units: units on a scale              |                   |                    |  |  |
| arithmetic mean (standard deviation) |                   |                    |  |  |
| Pain                                 | -1.71 (± 2.44)    | -1.90 (± 1.50)     |  |  |
| Discomfort                           | -1.94 (± 1.63)    | -2.24 (± 1.92)     |  |  |
| Bloating                             | -1.84 (± 1.64)    | -1.64 (± 1.74)     |  |  |
| Distension                           | -1.70 (± 1.60)    | -1.22 (± 1.69)     |  |  |
| Abdominal Score                      | -1.83 (± 1.84)    | -1.91 (± 1.39)     |  |  |
| Abdominal Score + Distension         | -1.80 (± 1.75)    | -1.74 (± 1.37)     |  |  |

Notes:

[13] - Participants with an assessment at given time point.

[14] - Participants with an assessment at given time point.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Digestive Sensations (Subjective Bloating, Abdominal Discomfort, Abdominal Distension and Abdominal Pain) at Week 2

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Digestive Sensations (Subjective Bloating, Abdominal Discomfort, Abdominal Distension and Abdominal Pain) at Week 2 |
|-----------------|---|

End point description:

A digestive sensations questionnaire was used to record abdominal pain, discomfort, bloating, and distension symptoms on an hourly basis (waking hours only) during the 24 hours the participants are fitted with the AIP belt, using an 11-point NRS, with 0=no symptomatic sensations and 10=most severe symptomatic sensations. Daily diary scores for each of the digestive symptoms was averaged to obtain 'weekly' scores.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 2

| End point values                     | Matching Placebo  | 290 µg Linaclotide |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 8 <sup>[15]</sup> | 10 <sup>[16]</sup> |  |  |
| Units: units on a scale              |                   |                    |  |  |
| arithmetic mean (standard deviation) |                   |                    |  |  |
| Pain                                 | -1.13 (± 1.38)    | -0.61 (± 1.10)     |  |  |
| Discomfort                           | -1.01 (± 1.53)    | -1.00 (± 1.34)     |  |  |
| Bloating                             | -1.03 (± 1.54)    | -0.58 (± 1.33)     |  |  |
| Distension                           | -0.97 (± 1.50)    | -0.36 (± 1.14)     |  |  |

Notes:

[15] - Participants with an assessment at given time point.

[16] - Participants with an assessment at given time point.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Digestive Sensations (Subjective Bloating, Abdominal Discomfort, Abdominal Distension and Abdominal Pain) at Week 4

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Digestive Sensations (Subjective Bloating, Abdominal Discomfort, Abdominal Distension and Abdominal Pain) at Week 4 |
|-----------------|---|

End point description:

A digestive sensations questionnaire was used to record abdominal pain, discomfort, bloating, and distension symptoms on an hourly basis (waking hours only) during the 24 hours the participants are fitted with the AIP belt, using an 11-point NRS, with 0=no symptomatic sensations and 10=most severe symptomatic sensations. Daily diary scores for each of the digestive symptoms was averaged to obtain 'weekly' scores.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 4

| End point values                     | Matching Placebo  | 290 µg Linaclotide |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 7 <sup>[17]</sup> | 9 <sup>[18]</sup>  |  |  |
| Units: units on a scale              |                   |                    |  |  |
| arithmetic mean (standard deviation) |                   |                    |  |  |
| Pain                                 | -0.97 (± 1.55)    | -0.87 (± 1.33)     |  |  |

|            |                |                |  |  |
|------------|----------------|----------------|--|--|
| Discomfort | -0.89 (± 1.51) | -1.81 (± 1.11) |  |  |
| Bloating   | -1.01 (± 1.57) | -1.66 (± 1.03) |  |  |
| Distension | -1.03 (± 1.49) | -1.42 (± 0.64) |  |  |

Notes:

[17] - Participants with an assessment at given time point.

[18] - Participants with an assessment at given time point.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Bristol Stool Form Scale (BSFS) Over Time

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Bristol Stool Form Scale (BSFS) Over Time |
|-----------------|---|

End point description:

Daily stool consistency analyses were performed using the 7-point Bristol Stool Form Scale (BSFS), whereby a score of 1 = separate hard lumps like nuts (difficult to pass); 2 = sausage shaped but lumpy; 3 = like a sausage but with cracks on surface; 4 = like a sausage or snake, smooth and soft; 5 = soft blobs with clear-cut edges (passed easily); 6 = fluffy pieces with ragged edges, a mushy stool; and 7 = watery, no solid pieces (entirely liquid). Daily average recorded BSFS scores for each participant were computed for each week.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4

| End point values                     | Matching Placebo  | 290 µg Linaclotide |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 8 <sup>[19]</sup> | 11 <sup>[20]</sup> |  |  |
| Units: score on a scale              |                   |                    |  |  |
| arithmetic mean (standard deviation) |                   |                    |  |  |
| Week 1; n=8, 11                      | 0.33 (± 0.88)     | 1.53 (± 1.57)      |  |  |
| Week 2; n=8, 10                      | 0.57 (± 0.86)     | 1.51 (± 1.27)      |  |  |
| Week 3; n=8, 10                      | 0.39 (± 1.15)     | 2.11 (± 1.43)      |  |  |
| Week 4; n=8, 10                      | 0.35 (± 1.11)     | 1.56 (± 1.13)      |  |  |

Notes:

[19] - n=participants with an assessment at given time point.

[20] - n=participants with an assessment at given time point.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through Day 36 ( $\pm$  2 days).

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Matching Placebo |
|-----------------------|------------------|

Reporting group description:

Placebo once daily for 4 weeks

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | 290 µg Linaclotide |
|-----------------------|--------------------|

Reporting group description:

290 µg linaclotide once daily for 4 weeks

| Serious adverse events                            | Matching Placebo | 290 µg Linaclotide |  |
|---|------------------|--------------------|--|
| Total subjects affected by serious adverse events |                  |                    |  |
| subjects affected / exposed                       | 1 / 9 (11.11%)   | 0 / 10 (0.00%)     |  |
| number of deaths (all causes)                     | 0                | 0                  |  |
| number of deaths resulting from adverse events    |                  |                    |  |
| Nervous system disorders                          |                  |                    |  |
| Loss of consciousness                             |                  |                    |  |
| subjects affected / exposed                       | 1 / 9 (11.11%)   | 0 / 10 (0.00%)     |  |
| occurrences causally related to treatment / all   | 0 / 1            | 0 / 0              |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0              |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | Matching Placebo | 290 µg Linaclotide |  |
|---|------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                  |                    |  |
| subjects affected / exposed                           | 1 / 9 (11.11%)   | 7 / 10 (70.00%)    |  |
| Injury, poisoning and procedural complications        |                  |                    |  |
| Back injury   |                  |                    |  |
| subjects affected / exposed                           | 1 / 9 (11.11%)   | 0 / 10 (0.00%)     |  |
| occurrences (all)                                     | 1                | 0                  |  |
| Gastrointestinal disorders                            |                  |                    |  |

|  |                    |                      |  |
|--|--------------------|----------------------|--|
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 9 (0.00%)<br>0 | 1 / 10 (10.00%)<br>1 |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)   | 0 / 9 (0.00%)<br>0 | 1 / 10 (10.00%)<br>1 |  |
| Anal haemorrhage<br>subjects affected / exposed<br>occurrences (all)   | 0 / 9 (0.00%)<br>0 | 1 / 10 (10.00%)<br>1 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 0 / 9 (0.00%)<br>0 | 5 / 10 (50.00%)<br>7 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 9 (0.00%)<br>0 | 1 / 10 (10.00%)<br>1 |  |
| Respiratory, thoracic and mediastinal disorders<br>Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0 | 1 / 10 (10.00%)<br>1 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 26 July 2016  | <ul style="list-style-type: none"><li>Defined the End of Study as the last participant Follow-up Telephone Call (Day 36)</li><li>Updated exclusion criteria to exclude participants with known or suspected mechanical gastrointestinal obstruction and participants with hypersensitivity to linaclotide or to any of the excipients</li><li>Specified that the United States product insert serves as the Reference Safety Information for the study</li><li>Clarified the investigator and sponsor reporting responsibilities for serious adverse events and suspected unexpected serious adverse reactions, consistent with European Directive 2001/20/EC</li></ul>   |
| 25 April 2017 | <ul style="list-style-type: none"><li>Removed the rectal screening at each physical exam; sigmoidoscopy or colonoscopy will be performed if needed, at the discretion of the investigator</li><li>Added window of <math>\pm 2</math> days for the Follow-up Period to the Schedule of Evaluations and subsequent sections for consistency with study design figure</li><li>Updated inclusion criteria to increase the body mass index (BMI) upper limit to 34.9 kg/m<sup>2</sup></li><li>Updated the number of capsules per bottle of study drug from 30 to 35 capsules to reflect how study drug is currently supplied</li><li>Removed urinalysis from the screening visit assessments; urine samples still collected for pregnancy testing</li><li>Removed the differential white blood cell count from the Clinical Laboratory Determinations</li><li>Administrative updates</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early due to insufficient enrollment. Due to an insufficient sample size, no conclusions could be drawn regarding efficacy.

Notes: