



## Clinical trial results:

### A Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Safety and Efficacy Study of Linacotide in Pediatric Participants, Ages 6 to 17 Years, With Irritable Bowel Syndrome With Constipation (IBS-C) and of Linacotide Versus Placebo in Pediatric Participants With Functional Constipation (FC)

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2019-001500-38             |
| Trial protocol           | NL BE GB HU EE DE PL BG IT |
| Global end of trial date | 29 May 2024                |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 16 November 2024 |
| First version publication date | 16 November 2024 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | LIN-MD-64 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04026113 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | AbbVie Deutschland GmbH & Co. KG  |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB                                     |
| Public contact               | Global Medical Services, AbbVie, 001 8006339110, <a href="mailto:abbvieclinicaltrials@abbvie.com">abbvieclinicaltrials@abbvie.com</a> |
| Scientific contact           | Global Medical Services, AbbVie, 001 8006339110, <a href="mailto:abbvieclinicaltrials@abbvie.com">abbvieclinicaltrials@abbvie.com</a> |

Notes:

#### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000927-PIP01-10 |
| 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? | Yes                 |

Notes:

## Results analysis stage

|  |             |
|--|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 29 May 2024 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 29 May 2024 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

The objective of LIN-MD-64 is to evaluate the safety and efficacy of 12 weeks of linaclotide therapy (72 µg daily) in comparison with placebo in pediatric participants, 6 to 17 years of age, who fulfill modified Rome III Criteria for Child/Adolescent FC.

The objective of LIN-MD-64 is to evaluate the safety and efficacy of 12 weeks of linaclotide therapy (145 µg or 290 µg daily) in pediatric participants, 7 to 17 years of age, who fulfill the Rome III criteria for child/adolescent IBS and modified Rome III criteria for child/adolescent FC.

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 01 October 2019 |
| 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 | Canada: 5          |
| Country: Number of subjects enrolled | Estonia: 1         |
| Country: Number of subjects enrolled | Israel: 4          |
| Country: Number of subjects enrolled | Italy: 1           |
| Country: Number of subjects enrolled | Netherlands: 6     |
| Country: Number of subjects enrolled | Ukraine: 5         |
| Country: Number of subjects enrolled | United States: 416 |
| Worldwide total number of subjects   | 438                |
| EEA total number of subjects         | 8                  |

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)                    | 226 |
| Adolescents (12-17 years)                | 212 |
| Adults (18-64 years)                     | 0   |
| From 65 to 84 years                      | 0   |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 64 sites, in 7 countries.

Participants were randomized in a 1:1 ratio for 12 weeks during the double-blind (DB) study intervention period:

- FC participants received either linaclotide 72 µg or placebo
- IBS-C participants received either linaclotide 145 µg or 290 µg

### Pre-assignment

Screening details:

Participants were considered to have completed the study after the DB and Post-Intervention periods. However, the Post-Intervention period was not required for those who enrolled into an open-label, long-term safety study after completing the DB period.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Double-Blind Treatment Period (12 Weeks)        |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                         |
| Blinding used                | Double blind                                    |
| Roles blinded                | Subject, Investigator, Monitor, Carer, Assessor |

Blinding implementation details:

A list of participant randomization codes were generated by statistical programming and implemented by the interactive Web response system vendor (an electronic version will be stored on a secure server). This list will identify each participant by randomization number and include the participant's corresponding intervention assignment.

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| <b>Arm title</b>             | FC Participants: Placebo |

Arm description:

Placebo single dose, once daily at approximately the same time each day, 30 minutes before any meal.

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

Dosage and administration details:

Oral capsule (For participants who do not wish to take the dose as a capsule, a sprinkled dose may be prepared)

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | FC Participants: Linaclotide 72 µg |
|------------------|------------------------------------|

Arm description:

Linaclotide 72 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.

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

Dosage and administration details:

Oral capsule (For participants who do not wish to take the dose as a capsule, a sprinkled dose may be

prepared)

|                  |  |
|------------------|--|
| <b>Arm title</b> | IBS-C Participants: Linaclotide 145 µg |
|------------------|--|

Arm description:

Linaclotide 145 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.

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

Dosage and administration details:

Oral capsule (For participants who do not wish to take the dose as a capsule, a sprinkled dose may be prepared)

|                  |  |
|------------------|--|
| <b>Arm title</b> | IBS-C Participants: Linaclotide 290 µg |
|------------------|--|

Arm description:

Linaclotide 290 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.

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

Dosage and administration details:

Oral capsule (For participants who do not wish to take the dose as a capsule, a sprinkled dose may be prepared)

| <b>Number of subjects in period 1</b> | <b>FC Participants:<br/>Placebo</b> | <b>FC Participants:<br/>Linaclotide 72 µg</b> | <b>IBS-C Participants:<br/>Linaclotide 145 µg</b> |
|---------------------------------------|-------------------------------------|---|---|
| Started                               | 164                                 | 166   | 55  |
| Randomized and Treated                | 164                                 | 164   | 55  |
| Completed                             | 145                                 | 148   | 52  |
| Not completed                         | 19                                  | 18  | 3   |
| Consent withdrawn by subject          | 7                                   | 5   | 1   |
| Physician decision                    | 1                                   | 1   | 1   |
| Other, not specified                  | 4                                   | 3   | -   |
| Adverse event                         | 2                                   | 2   | -   |
| Noncompliance with study drug         | -                                   | 4   | -   |
| Lost to follow-up                     | 4                                   | -   | 1   |
| Lack of efficacy                      | 1                                   | 2   | -   |
| Protocol deviation                    | -                                   | 1   | -   |

| Number of subjects in period 1 | IBS-C Participants:<br>Linaclotide 290 µg |
|--------------------------------|---|
| Started                        | 53  |
| Randomized and Treated         | 53  |
| Completed                      | 46  |
| Not completed                  | 7   |
| Consent withdrawn by subject   | 5   |
| Physician decision             | -   |
| Other, not specified           | 1   |
| Adverse event                  | -   |
| Noncompliance with study drug  | -   |
| Lost to follow-up              | -   |
| Lack of efficacy               | 1   |
| Protocol deviation             | -   |

## Period 2

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 2 title               | Post-Intervention Period (1 Week) |
| Is this the baseline period? | No                                |
| Allocation method            | Not applicable                    |
| Blinding used                | Not blinded                       |

## Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| <b>Arm title</b>             | FC Participants: Placebo |

Arm description:

Placebo single dose, once daily at approximately the same time each day, 30 minutes before any meal.

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | FC Participants: Linaclotide 72 µg |
|------------------|------------------------------------|

Arm description:

Linaclotide 72 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |  |
|------------------|--|
| <b>Arm title</b> | IBS-C Participants: Linaclotide 145 µg |
|------------------|--|

Arm description:

Linaclotide 145 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |  |
|------------------|--|
| <b>Arm title</b> | IBS-C Participants: Linaclotide 290 µg |
|------------------|--|

Arm description:

Linaclotide 290 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| <b>Number of subjects in period 2<sup>[1]</sup></b> | FC Participants: Placebo | FC Participants: Linaclotide 72 µg | IBS-C Participants: Linaclotide 145 µg |
|---|--------------------------|------------------------------------|--|
| Started   | 66                       | 75                                 | 20                                     |
| Completed   | 65                       | 75                                 | 19                                     |
| Not completed                                       | 1                        | 0                                  | 1                                      |
| Other, not specified                                | 1                        | -                                  | 1                                      |

| <b>Number of subjects in period 2<sup>[1]</sup></b> | IBS-C Participants: Linaclotide 290 µg |
|---|--|
| Started   | 20                                     |
| Completed   | 20                                     |
| Not completed                                       | 0                                      |
| Other, not specified                                | -                                      |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The Post-Intervention period was not required for those who enrolled into an open-label, long-term safety study after completing the DB period.

## Baseline characteristics

### Reporting groups

|   |  |
|---|--|
| Reporting group title   | FC Participants: Placebo               |
| Reporting group description:<br>Placebo single dose, once daily at approximately the same time each day, 30 minutes before any meal.            |  |
| Reporting group title   | FC Participants: Linaclotide 72 µg     |
| Reporting group description:<br>Linaclotide 72 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.  |  |
| Reporting group title   | IBS-C Participants: Linaclotide 145 µg |
| Reporting group description:<br>Linaclotide 145 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal. |  |
| Reporting group title   | IBS-C Participants: Linaclotide 290 µg |
| Reporting group description:<br>Linaclotide 290 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal. |  |

| Reporting group values                    | FC Participants: Placebo | FC Participants: Linaclotide 72 µg | IBS-C Participants: Linaclotide 145 µg |
|---|--------------------------|------------------------------------|--|
| Number of subjects                        | 164                      | 166                                | 55                                     |
| Age categorical<br>Units: Subjects        |                          |                                    |  |
| 6-11 years                                | 91                       | 92                                 | 22                                     |
| 12-17 years                               | 73                       | 74                                 | 33                                     |
| Gender categorical<br>Units: Subjects     |                          |                                    |  |
| Female                                    | 86                       | 96                                 | 31                                     |
| Male                                      | 78                       | 70                                 | 24                                     |
| Race<br>Units: Subjects                   |                          |                                    |  |
| White                                     | 114                      | 116                                | 40                                     |
| Black or African American                 | 45                       | 42                                 | 13                                     |
| Asian                                     | 2                        | 3                                  | 2                                      |
| American Indian or Alaska Native          | 1                        | 0                                  | 0                                      |
| Native Hawaiian or other Pacific Islander | 1                        | 3                                  | 0                                      |
| Multiple                                  | 1                        | 2                                  | 0                                      |
| Missing                                   | 0                        | 0                                  | 0                                      |
| Ethnicity<br>Units: Subjects              |                          |                                    |  |
| Hispanic or Latino                        | 77                       | 72                                 | 19                                     |
| Not Hispanic or Latino                    | 87                       | 94                                 | 36                                     |

| Reporting group values             | IBS-C Participants: Linaclotide 290 µg | Total |  |
|------------------------------------|--|-------|--|
| Number of subjects                 | 53                                     | 438   |  |
| Age categorical<br>Units: Subjects |  |       |  |
| 6-11 years                         | 21                                     | 226   |  |



|             |    |     |  |
|-------------|----|-----|--|
| 12-17 years | 32 | 212 |  |
|-------------|----|-----|--|

|   |    |     |  |
|---|----|-----|--|
| Gender categorical                        |    |     |  |
| Units: Subjects                           |    |     |  |
| Female                                    | 34 | 247 |  |
| Male                                      | 19 | 191 |  |
| Race                                      |    |     |  |
| Units: Subjects                           |    |     |  |
| White                                     | 35 | 305 |  |
| Black or African American                 | 14 | 114 |  |
| Asian                                     | 1  | 8   |  |
| American Indian or Alaska Native          | 0  | 1   |  |
| Native Hawaiian or other Pacific Islander | 0  | 4   |  |
| Multiple                                  | 1  | 4   |  |
| Missing                                   | 2  | 2   |  |
| Ethnicity                                 |    |     |  |
| Units: Subjects                           |    |     |  |
| Hispanic or Latino                        | 17 | 185 |  |
| Not Hispanic or Latino                    | 36 | 253 |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | FC Participants: Placebo               |
| Reporting group description:<br>Placebo single dose, once daily at approximately the same time each day, 30 minutes before any meal.            |  |
| Reporting group title   | FC Participants: Linaclotide 72 µg     |
| Reporting group description:<br>Linaclotide 72 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.  |  |
| Reporting group title   | IBS-C Participants: Linaclotide 145 µg |
| Reporting group description:<br>Linaclotide 145 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal. |  |
| Reporting group title   | IBS-C Participants: Linaclotide 290 µg |
| Reporting group description:<br>Linaclotide 290 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal. |  |
| Reporting group title   | FC Participants: Placebo               |
| Reporting group description:<br>Placebo single dose, once daily at approximately the same time each day, 30 minutes before any meal.            |  |
| Reporting group title   | FC Participants: Linaclotide 72 µg     |
| Reporting group description:<br>Linaclotide 72 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.  |  |
| Reporting group title   | IBS-C Participants: Linaclotide 145 µg |
| Reporting group description:<br>Linaclotide 145 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal. |  |
| Reporting group title   | IBS-C Participants: Linaclotide 290 µg |
| Reporting group description:<br>Linaclotide 290 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal. |  |

### Primary: Functional Constipation (FC) Participants: Change From Baseline in 12-week SBM (Spontaneous Bowel Movement) Frequency Rate (SBMs/Week) During the Study Intervention Period

|  |  |
|--|--|
| End point title  | Functional Constipation (FC) Participants: Change From Baseline in 12-week SBM (Spontaneous Bowel Movement) Frequency Rate (SBMs/Week) During the Study Intervention Period <sup>[1]</sup> |
| End point description:<br><br>An SBM is defined as a BM that occurs in the absence of laxative, enema, or suppository use on the calendar day of the bowel movement (BM) or the calendar day before the BM. Assessments of BM characteristics that determine occurrences of SBM (ie, BM frequency and rescue medication use) were measured by using the eDiary completed twice daily (morning and evening) on the eDiary (Electronic Diary) device.<br><br>Modified intent to treat (mITT) Population: randomized participants who received ≥1 dose of double-blind (DB) study drug. Participants with analysis values at both baseline and postbaseline during the specified time period. |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline, 12 Weeks   |  |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: IBS-c and FC participant endpoints and analyses are presented separately per protocol.

| End point values                    | FC Participants: Placebo | FC Participants: Linaclotide 72 µg |  |  |
|-------------------------------------|--------------------------|------------------------------------|--|--|
| Subject group type                  | Reporting group          | Reporting group                    |  |  |
| Number of subjects analysed         | 164                      | 164                                |  |  |
| Units: SBMs                         |                          |                                    |  |  |
| least squares mean (standard error) | 1.050 (± 0.187)          | 2.220 (± 0.187)                    |  |  |

## Statistical analyses

| Statistical analysis title              | Statistical Analysis 1  |
|---|---|
| Comparison groups                       | FC Participants: Placebo v FC Participants: Linaclotide 72 µg |
| Number of subjects included in analysis | 328   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001 <sup>[2]</sup>                                       |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Difference  |
| Point estimate                          | 1.17  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.651   |
| upper limit                             | 1.689   |
| Variability estimate                    | Standard error of the mean                                    |
| Dispersion value                        | 0.264   |

Notes:

[2] - ANCOVA model estimates/t-tests comparing specified treatment groups, controlling for age group and baseline value.

| Statistical analysis title              | Statistical Analysis 2  |
|---|---|
| Comparison groups                       | FC Participants: Placebo v FC Participants: Linaclotide 72 µg |
| Number of subjects included in analysis | 328   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.4323 <sup>[3]</sup>                                       |
| Method                                  | ANCOVA  |

Notes:

[3] - Treatment-by-Age Group Interaction P-value: Interaction P-value base on ANCOVA model with treatment, age group, treatment-by-age group interaction as factors and baseline value as a covariate.

## Primary: Irritable Bowel Syndrome With Constipation (IBS-C) Participants: 6/12 Weeks APS (Abdominal Pain and SBM) + 2 Responder Rate

|                 |  |
|-----------------|--|
| End point title | Irritable Bowel Syndrome With Constipation (IBS-C) Participants: 6/12 Weeks APS (Abdominal Pain and SBM) + 2 |
|-----------------|--|

## End point description:

6/12 weeks APS + 2 responder=participant who meets the weekly APS + 2 responder criteria  $\geq 6$  of the 12 weeks of the intervention period. Weekly APS +2 responder=participant who has an increase of  $\geq 2$  in the SBM weekly rate from baseline, AND a decrease of  $\geq 30\%$  in mean abdominal pain score from baseline, during that study intervention week. Assessments of abdominal pain and BM characteristics that determine occurrences of SBMs were measured by using an eDiary completed twice daily (AM and PM). Assessments of abdominal pain were measured using a 5-point scale where 0=none and 4=a lot. A participant's abdominal pain score=mean of the non-missing abdominal pain scores during the specified period. Responder rate=percentage of participants who were 6/12 weeks APS + 2 responders. A participant had to have  $\geq 4$  completed diary days in the analysis week to be considered a responder for that week and was otherwise considered a non-responder for that week.

## mITT Population

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

12 Weeks

## Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned statistical analyses are presented in data table.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: IBS-c and FC participant endpoints and analyses are presented separately per protocol.

| End point values                  | IBS-C<br>Participants:<br>Linaclotide 145<br>µg | IBS-C<br>Participants:<br>Linaclotide 290<br>µg |  |  |
|-----------------------------------|---|---|--|--|
| Subject group type                | Reporting group                                 | Reporting group                                 |  |  |
| Number of subjects analysed       | 53  | 47  |  |  |
| Units: percentage of participants |   |   |  |  |
| number (not applicable)           | 22.6  | 23.4  |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Functional Constipation (FC) Participants: Change From Baseline in 12-week Stool Consistency During the Study Intervention Period**

|                 |  |
|-----------------|--|
| End point title | Functional Constipation (FC) Participants: Change From Baseline in 12-week Stool Consistency During the Study Intervention Period <sup>[6]</sup> |
|-----------------|--|

## End point description:

Stool consistency was measured twice daily, once in the morning and once in the evening eDiary, using the 7-point ordinal pediatric Bristol Stool Form Scale (p-BSFS): Type 1: Looks like small hard lumps or balls, like pebbles; Type 2: Looks like fat sausage shape but lumpy and hard; Type 3: Looks like a sausage but with cracks on it; Type 4: Looks like a sausage or snake, smooth and soft; Type 5: Looks like chicken nuggets, soft smooth blobs; Type 6: Looks like oatmeal, fluffy mushy pieces; Type 7: Looks like a milkshake, watery. A participant's p-BSFS score for the study intervention period was the average of the non-missing p-BSFS scores from the SBMs reported by the participant during the 12-week study intervention period.

Modified Intent-to-Treat (mITT) Population: all randomized participants who received at least 1 dose of double-blind study intervention. Participants with analysis values at both baseline and postbaseline during the specified time period.

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

End point timeframe:

Baseline, up to 12 weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: IBS-c and FC participant endpoints and analyses are presented separately per protocol.

| End point values                    | FC Participants: Placebo | FC Participants: Linaclotide 72 µg |  |  |
|-------------------------------------|--------------------------|------------------------------------|--|--|
| Subject group type                  | Reporting group          | Reporting group                    |  |  |
| Number of subjects analysed         | 132                      | 135                                |  |  |
| Units: units on a scale             |                          |                                    |  |  |
| least squares mean (standard error) | 0.685 (± 0.078)          | 1.108 (± 0.077)                    |  |  |

## Statistical analyses

| Statistical analysis title              | Statistical Analysis 1  |
|---|---|
| Comparison groups                       | FC Participants: Linaclotide 72 µg v FC Participants: Placebo |
| Number of subjects included in analysis | 267   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0001 <sup>[7]</sup>                                       |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Difference  |
| Point estimate                          | 0.423   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.208   |
| upper limit                             | 0.638   |
| Variability estimate                    | Standard error of the mean                                    |
| Dispersion value                        | 0.109   |

Notes:

[7] - ANCOVA model estimates/t-tests comparing specified treatment groups, controlling for age group and baseline value.

| Statistical analysis title              | Statistical Analysis 2  |
|---|---|
| Comparison groups                       | FC Participants: Placebo v FC Participants: Linaclotide 72 µg |
| Number of subjects included in analysis | 267   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.4381 <sup>[8]</sup>                                       |
| Method                                  | ANCOVA  |

Notes:

[8] - Treatment-by-Age Group Interaction P-value: Interaction P-value base on ANCOVA model with treatment, age group, treatment-by-age group interaction as factors and baseline value as a covariate.

## Secondary: Irritable Bowel Syndrome With Constipation (IBS-C) Participants: Change From Baseline in 12-week SBM Frequency Rate (SBMs/Week) During the

## Study Intervention Period

|                 |  |
|-----------------|--|
| End point title | Irritable Bowel Syndrome With Constipation (IBS-C)<br>Participants: Change From Baseline in 12-week SBM Frequency Rate (SBMs/Week) During the Study Intervention Period <sup>[9]</sup> |
|-----------------|--|

### End point description:

An SBM is defined as a BM that occurs in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM. Assessments of BM characteristics that determine occurrences of SBM (ie, BM frequency and rescue medication use) were measured by using the eDiary completed twice daily (morning and evening) on the eDiary (Electronic Diary) device. A participant's SBMs/week for the study intervention period was the average of the non-missing SBMs/week reported by the participant during the 12-week study intervention period.

mITT Population: randomized participants who received  $\geq 1$  dose of DB study drug. Participants with analysis values at both baseline and postbaseline during the specified time period.

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

### End point timeframe:

Baseline, up to 12 Weeks

### Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: IBS-c and FC participant endpoints and analyses are presented separately per protocol.

| End point values                     | IBS-C<br>Participants:<br>Linaclotide 145<br>$\mu\text{g}$ | IBS-C<br>Participants:<br>Linaclotide 290<br>$\mu\text{g}$ |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed          | 53   | 47   |  |  |
| Units: SBMs/week                     |  |  |  |  |
| arithmetic mean (standard deviation) | 2.347 ( $\pm$<br>3.3335)                                   | 2.747 ( $\pm$<br>2.8861)                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Irritable Bowel Syndrome With Constipation (IBS-C) Participants: Change From Baseline in 12-week Abdominal Pain During the Study Intervention Period

|                 |   |
|-----------------|---|
| End point title | Irritable Bowel Syndrome With Constipation (IBS-C)<br>Participants: Change From Baseline in 12-week Abdominal Pain During the Study Intervention Period <sup>[10]</sup> |
|-----------------|---|

### End point description:

Assessments of abdominal pain were measured twice daily, once in the morning and once in the evening eDiary, using a 5-point scale where a score of 0 indicates no abdominal pain scores and a score of 4 indicates a lot of abdominal pain. Assessments of abdominal pain were measured using a 5-point scale where '0' indicates no abdominal pain and '4' indicates a lot of abdominal pain. The participant's abdominal pain score was derived as the mean of the non-missing morning and evening abdominal pain scores during the specified period.

mITT Population: randomized participants who received  $\geq 1$  dose of DB study drug. Participants with analysis values at both baseline and postbaseline during the specified time period.

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

### End point timeframe:

Baseline, up to 12 Weeks

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: IBS-c and FC participant endpoints and analyses are presented separately per protocol.

| End point values                     | IBS-C<br>Participants:<br>Linaclotide 145<br>µg | IBS-C<br>Participants:<br>Linaclotide 290<br>µg |  |  |
|--------------------------------------|---|---|--|--|
| Subject group type                   | Reporting group                                 | Reporting group                                 |  |  |
| Number of subjects analysed          | 53  | 47  |  |  |
| Units: units on a scale              |   |   |  |  |
| arithmetic mean (standard deviation) | -0.837 (±<br>0.9313)                            | -0.837 (±<br>0.8809)                            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Irritable Bowel Syndrome With Constipation (IBS-C) Participants: Change From Baseline in 12-week Stool Consistency During the Study Intervention Period

|                 |   |
|-----------------|---|
| End point title | Irritable Bowel Syndrome With Constipation (IBS-C)<br>Participants: Change From Baseline in 12-week Stool<br>Consistency During the Study Intervention Period <sup>[11]</sup> |
|-----------------|---|

End point description:

Stool consistency was measured twice daily, once in the morning and once in the evening eDiary, using the 7-point ordinal p-BSFS (pediatric Bristol Stool Form Scale: Type 1: Looks like small hard lumps or balls, like pebbles Type 2: Looks like fat sausage shape but lumpy and hard Type 3: Looks like a sausage but with cracks on it Type 4: Looks like a sausage or snake, smooth and soft Type 5: Looks like chicken nuggets, soft smooth blobs Type 6: Looks like oatmeal, fluffy mushy pieces Type 7: Looks like a milkshake, watery. A participant's p-BSFS score for the study intervention period was the average of the non-missing p-BSFS scores from the SBMs reported by the participant during the 12-week study intervention period.

mITT Population: randomized participants who received ≥1 dose of DB study drug. Participants with analysis values at both baseline and postbaseline during the specified time period.

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

End point timeframe:

Baseline, up to 12 weeks

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: IBS-c and FC participant endpoints and analyses are presented separately per protocol.

| End point values                     | IBS-C<br>Participants:<br>Linaclotide 145<br>µg | IBS-C<br>Participants:<br>Linaclotide 290<br>µg |  |  |
|--------------------------------------|---|---|--|--|
| Subject group type                   | Reporting group                                 | Reporting group                                 |  |  |
| Number of subjects analysed          | 47  | 39  |  |  |
| Units: units on a scale              |   |   |  |  |
| arithmetic mean (standard deviation) | 0.979 (±<br>1.2900)                             | 1.358 (±<br>1.1288)                             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Irritable Bowel Syndrome With Constipation (IBS-C) Participants: 6/12 Weeks SBM + 2 Responder Rate

|                 |   |
|-----------------|---|
| End point title | Irritable Bowel Syndrome With Constipation (IBS-C)<br>Participants: 6/12 Weeks SBM + 2 Responder Rate <sup>[12]</sup> |
|-----------------|---|

#### End point description:

A 6/12 weeks SBM + 2 responder is a participant that meets the weekly SBM + 2 responder criteria for at least 6 out of the 12 weeks of the intervention period. A weekly SBM +2 responder is a participant who has an increase of at least 2 in the SBM weekly rate from baseline. Assessments of BM characteristics that determine occurrences of SBMs (ie, BM frequency and rescue medication use) were measured by using an eDiary completed twice daily (morning and evening). Responder rate is presented as the percentage of participants who were 6/12 weeks SBM + 2 responders.

mITT Population: randomized participants who received  $\geq 1$  dose of DB study drug. Participants with analysis values at both baseline and postbaseline during the specified time period.

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

#### End point timeframe:

12 Weeks

#### Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: IBS-c and FC participant endpoints and analyses are presented separately per protocol.

| End point values                  | IBS-C<br>Participants:<br>Linaclotide 145<br>$\mu$ g | IBS-C<br>Participants:<br>Linaclotide 290<br>$\mu$ g |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Reporting group                                      | Reporting group                                      |  |  |
| Number of subjects analysed       | 53   | 47   |  |  |
| Units: percentage of participants |  |  |  |  |
| number (not applicable)           | 30.2   | 29.8   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Irritable Bowel Syndrome With Constipation (IBS-C) Participants: 6/12 Weeks Abdominal Pain Responder

|                 |   |
|-----------------|---|
| End point title | Irritable Bowel Syndrome With Constipation (IBS-C)<br>Participants: 6/12 Weeks Abdominal Pain Responder <sup>[13]</sup> |
|-----------------|---|

#### End point description:

A 6/12 weeks abdominal pain responder is a participant that meets the weekly abdominal pain responder criteria for at least 6 out of the 12 weeks of the intervention period. A weekly abdominal pain responder is a participant who has a decrease of at least 30% in the mean abdominal pain score from



baseline, during that study intervention week. Assessments of abdominal pain were measured by using an eDiary completed twice daily (morning and evening) and were measured using a 5-point scale where '0' indicates no abdominal pain and '4' indicates a lot of abdominal pain. The participant's abdominal pain score was derived as the mean of the non-missing abdominal pain scores during the specified period. Responder rate is presented as the percentage of participants who were 6/12 weeks abdominal pain responders.

mITT Population: randomized participants who received  $\geq 1$  dose of DB study drug. Participants with analysis values at both baseline and postbaseline during the specified time period.

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

End point timeframe:

12 Weeks

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: IBS-c and FC participant endpoints and analyses are presented separately per protocol.

| End point values                  | IBS-C<br>Participants:<br>Linaclotide 145<br>µg | IBS-C<br>Participants:<br>Linaclotide 290<br>µg |  |  |
|-----------------------------------|---|---|--|--|
| Subject group type                | Reporting group                                 | Reporting group                                 |  |  |
| Number of subjects analysed       | 53  | 47  |  |  |
| Units: percentage of participants |   |   |  |  |
| number (not applicable)           | 49.1  | 42.6  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 13 weeks

Adverse event reporting additional description:

All randomized participants

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | IBS-C Participants: Linaclotide 145 µg |
|-----------------------|--|

Reporting group description:

Linaclotide 145 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.

|                       |  |
|-----------------------|--|
| Reporting group title | IBS-C Participants: Linaclotide 290 µg |
|-----------------------|--|

Reporting group description:

Linaclotide 290 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | FC Participants: Placebo |
|-----------------------|--------------------------|

Reporting group description:

Placebo single dose, once daily at approximately the same time each day, 30 minutes before any meal.

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | FC Participants: Linaclotide 72 µg |
|-----------------------|------------------------------------|

Reporting group description:

Linaclotide 72 µg single dose, once daily at approximately the same time each day, 30 minutes before any meal.

| Serious adverse events                            | IBS-C Participants:<br>Linaclotide 145 µg | IBS-C Participants:<br>Linaclotide 290 µg | FC Participants:<br>Placebo |
|---|---|---|-----------------------------|
| Total subjects affected by serious adverse events |   |   |                             |
| subjects affected / exposed                       | 0 / 55 (0.00%)                            | 0 / 53 (0.00%)                            | 2 / 164 (1.22%)             |
| number of deaths (all causes)                     | 0   | 0   | 0                           |
| number of deaths resulting from adverse events    | 0   | 0   | 0                           |
| Gastrointestinal disorders                        |   |   |                             |
| DIARRHOEA   |   |   |                             |
| subjects affected / exposed                       | 0 / 55 (0.00%)                            | 0 / 53 (0.00%)                            | 0 / 164 (0.00%)             |
| occurrences causally related to treatment / all   | 0 / 0                                     | 0 / 0                                     | 0 / 0                       |
| deaths causally related to treatment / all        | 0 / 0                                     | 0 / 0                                     | 0 / 0                       |
| FAECALOMA   |   |   |                             |
| subjects affected / exposed                       | 0 / 55 (0.00%)                            | 0 / 53 (0.00%)                            | 0 / 164 (0.00%)             |
| occurrences causally related to treatment / all   | 0 / 0                                     | 0 / 0                                     | 0 / 0                       |
| deaths causally related to treatment / all        | 0 / 0                                     | 0 / 0                                     | 0 / 0                       |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Psychiatric disorders                           |                |                |                 |
| SUICIDE ATTEMPT                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 2 / 164 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| SUICIDAL IDEATION                               |                |                |                 |
| subjects affected / exposed                     | 0 / 55 (0.00%) | 0 / 53 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

|   |                                       |  |  |
|---|---------------------------------------|--|--|
| <b>Serious adverse events</b>                     | FC Participants:<br>Linaclotide 72 µg |  |  |
| Total subjects affected by serious adverse events |                                       |  |  |
| subjects affected / exposed                       | 2 / 166 (1.20%)                       |  |  |
| number of deaths (all causes)                     | 0                                     |  |  |
| number of deaths resulting from adverse events    | 0                                     |  |  |
| Gastrointestinal disorders                        |                                       |  |  |
| DIARRHOEA   |                                       |  |  |
| subjects affected / exposed                       | 1 / 166 (0.60%)                       |  |  |
| occurrences causally related to treatment / all   | 1 / 1                                 |  |  |
| deaths causally related to treatment / all        | 0 / 0                                 |  |  |
| FAECALOMA   |                                       |  |  |
| subjects affected / exposed                       | 1 / 166 (0.60%)                       |  |  |
| occurrences causally related to treatment / all   | 0 / 1                                 |  |  |
| deaths causally related to treatment / all        | 0 / 0                                 |  |  |
| Psychiatric disorders                             |                                       |  |  |
| SUICIDE ATTEMPT                                   |                                       |  |  |
| subjects affected / exposed                       | 0 / 166 (0.00%)                       |  |  |
| occurrences causally related to treatment / all   | 0 / 0                                 |  |  |
| deaths causally related to treatment / all        | 0 / 0                                 |  |  |
| SUICIDAL IDEATION                                 |                                       |  |  |
| subjects affected / exposed                       | 0 / 166 (0.00%)                       |  |  |
| occurrences causally related to treatment / all   | 0 / 0                                 |  |  |
| deaths causally related to treatment / all        | 0 / 0                                 |  |  |

| <b>Non-serious adverse events</b>  | IBS-C Participants:<br>Linaclotide 145 µg | IBS-C Participants:<br>Linaclotide 290 µg | FC Participants:<br>Placebo |
|--|---|---|-----------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 7 / 55 (12.73%)                           | 4 / 53 (7.55%)                            | 10 / 164 (6.10%)            |
| Gastrointestinal disorders   |   |   |                             |
| ABDOMINAL PAIN   |   |   |                             |
| subjects affected / exposed  | 2 / 55 (3.64%)                            | 0 / 53 (0.00%)                            | 2 / 164 (1.22%)             |
| occurrences (all)  | 2   | 0   | 2                           |
| DIARRHOEA  |   |   |                             |
| subjects affected / exposed  | 4 / 55 (7.27%)                            | 4 / 53 (7.55%)                            | 3 / 164 (1.83%)             |
| occurrences (all)  | 4   | 4   | 3                           |
| CONSTIPATION   |   |   |                             |
| subjects affected / exposed  | 2 / 55 (3.64%)                            | 0 / 53 (0.00%)                            | 0 / 164 (0.00%)             |
| occurrences (all)  | 2   | 0   | 0                           |
| Infections and infestations  |   |   |                             |
| COVID-19   |   |   |                             |
| subjects affected / exposed  | 2 / 55 (3.64%)                            | 1 / 53 (1.89%)                            | 5 / 164 (3.05%)             |
| occurrences (all)  | 2   | 1   | 5                           |

| <b>Non-serious adverse events</b>  | FC Participants:<br>Linaclotide 72 µg |  |  |
|--|---------------------------------------|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 11 / 166 (6.63%)                      |  |  |
| Gastrointestinal disorders   |                                       |  |  |
| ABDOMINAL PAIN   |                                       |  |  |
| subjects affected / exposed  | 1 / 166 (0.60%)                       |  |  |
| occurrences (all)  | 1                                     |  |  |
| DIARRHOEA  |                                       |  |  |
| subjects affected / exposed  | 6 / 166 (3.61%)                       |  |  |
| occurrences (all)  | 6                                     |  |  |
| CONSTIPATION   |                                       |  |  |
| subjects affected / exposed  | 1 / 166 (0.60%)                       |  |  |
| occurrences (all)  | 1                                     |  |  |
| Infections and infestations  |                                       |  |  |
| COVID-19   |                                       |  |  |
| subjects affected / exposed  | 4 / 166 (2.41%)                       |  |  |
| occurrences (all)  | 4                                     |  |  |



**More information**

**Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment  |
|--------------|--|
| 05 June 2020 | The purpose of Global Protocol Amendment 1 was to include enrollment of pediatric participants ages 7 – 17 years with IBS-C, to include a plan for a potential interim analysis to assess futility for FC participants, and to provide additional clarification and updates to the LIN-MD-64 protocol (dated 17 April 2019). |

Notes:

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**Interruptions (globally)**

Were there any global interruptions to the trial? No

**Limitations and caveats**

None reported