Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Sequential, Ascending, Multidose Study to Evaluate the Safety and Efficacy of Linaclotide in Pediatric Participants (Age 2 to 5 Years) with Functional Constipation

Summary

EudraCT number	2019-002126-75
Trial protocol	Outside EU/EEA
Global end of trial date	20 April 2021

Results information

Result version number	v1 (current)
This version publication date	04 November 2021
First version publication date	04 November 2021

Trial information

Trial identification

Sponsor protocol code	LIN-MD-67

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04110145
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan
Sponsor organisation address	1st Floor, Marlow International, The Parkway, Marlow Buckinghamshire, United Kingdom, SL7 1YL
Public contact	Therapeutic Area, Head, Allergan, 001 714-246-4500, IR-CTRegistration@Allergan.com
Scientific contact	Therapeutic Area, Head, Allergan, 001 714-246-4500, IR-CTRegistration@Allergan.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the dose response, safety, and efficacy of linaclotide when compared with placebo in pediatric participants, 2 to 5 years of age, with Functional Constipation.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 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	United States: 35
Worldwide total number of subjects	35
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)	35
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized in a 3:1 ratio to receive ascending dose of linaclotide Cohorts 1-3 (18/36/72 µg) to determine the highest dose to be safe or placebo and in a 5:1 ratio for the Final Cohort (72 µg) safe dose or placebo.

Period 1

Period 1 title	Double-Blind Treatment Period (4 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (Linaclotide 18 µg)

Arm description:

Linaclotide 18 microgram (µg), capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

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:

Linaclotide 18 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal).

Arm title	Cohort 2 (Linaclotide 36 µg)

Arm description:

Linaclotide 36 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

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:

Linaclotide 36 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal).

Arm title	Cohort 3 (Linaclotide 72 µg)

Arm description:

Linaclotide 72 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

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:

Linaclotide 72 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal).

Arm title	Final Cohort (Linaclotide 72 µg)

Arm description:

Linaclotide at the highest dose tested/determined to be safe (72 µg), capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

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:

Linaclotide 72 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal).

Arm title	Placebo Pooled

Arm description:

Matching placebo, orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period pooled from Cohorts 1, 2, 3, and Final Cohort.

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

Dosage and administration details:

Matching placebo, orally, once daily in fasted state (30 minutes before any meal).

Number of subjects in period 1	Cohort 1 (Linaclotide 18 µg)	Cohort 2 (Linaclotide 36 µg)	Cohort 3 (Linaclotide 72 µg)
Started	7	7	6
Completed	7	7	6
Not completed	0	0	0
Site Terminated by the Sponsor	-	-	-

Number of subjects in period 1	Final Cohort (Linaclotide 72 µg)	Placebo Pooled
Started	7	8
Completed	6	8
Not completed	1	0
Site Terminated by the Sponsor	1	-

Period 2

Period 2 title	Post-treatment Period (1 week)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (Linaclotide 18 µg)

Arm description:

Linaclotide 18 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

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:

Linaclotide 18 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal).

Arm title	Cohort 2 (Linaclotide 36 µg)

Arm description:

Linaclotide 36 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

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:

Linaclotide 36 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal)

Arm title	Cohort 3 (Linaclotide 72 µg)

Arm description:

Linaclotide 72 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

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:

Linaclotide 72 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal).

Arm title	Final Cohort (Linaclotide 72 µg)

Arm description:

Linaclotide at the highest dose tested/determined to be safe (72 µg), capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

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:

Linaclotide 72 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal).

Arm title	Placebo Pooled

Arm description:

Matching placebo, orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period pooled from Cohorts 1, 2, 3, and Final Cohort.

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

Dosage and administration details:

Matching placebo, orally, once daily in fasted state (30 minutes before any meal).

Number of subjects in period 2[1]	Cohort 1 (Linaclotide 18 µg)	Cohort 2 (Linaclotide 36 µg)	Cohort 3 (Linaclotide 72 µg)
Started	7	7	5
Completed	7	7	5

Number of subjects in period 2[1]	Final Cohort (Linaclotide 72 µg)	Placebo Pooled
Started	6	8
Completed	6	8

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: 1 participant in the Cohort 3 (Linaclotide 72 µg) arm group completed Period 1 but did not participate in Period 2.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 (Linaclotide 18 µg)
Reporting group description:	
Linaclotide 18 microgram (µg), capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Cohort 2 (Linaclotide 36 µg)
Reporting group description:	
Linaclotide 36 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Cohort 3 (Linaclotide 72 µg)
Reporting group description:	
Linaclotide 72 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Final Cohort (Linaclotide 72 µg)
Reporting group description:	
Linaclotide at the highest dose tested/determined to be safe (72 µg), capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Placebo Pooled
Reporting group description:	
Matching placebo, orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period pooled from Cohorts 1, 2, 3, and Final Cohort.	

Reporting group values	Cohort 1 (Linaclotide 18 µg)	Cohort 2 (Linaclotide 36 µg)	Cohort 3 (Linaclotide 72 µg)
Number of subjects	7	7	6
Age categorical Units: Subjects			
Children (2-11 years)	7	7	6
Age Continuous Units: years			
arithmetic mean	3.6	3.3	4.0
full range (min-max)	2 to 5	2 to 5	3 to 5
Sex: Female, Male Units: participants			
Female	4	3	5
Male	3	4	1
Race/Ethnicity, Customized Units: Subjects			
White	2	3	4
Black or African American	5	4	2
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	2	4
Not Hispanic or Latino	6	5	2

Reporting group values	Final Cohort (Linaclotide 72 µg)	Placebo Pooled	Total
Number of subjects	7	8	35

Age categorical Units: Subjects			
Children (2-11 years)	7	8	35
Age Continuous Units: years			
arithmetic mean	3.6	3.5	
full range (min-max)	2 to 5	3 to 4	-
Sex: Female, Male Units: participants			
Female	0	4	16
Male	7	4	19
Race/Ethnicity, Customized Units: Subjects			
White	5	5	19
Black or African American	2	3	16
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	4	3	14
Not Hispanic or Latino	3	5	21

End points

End points reporting groups

Reporting group title	Cohort 1 (Linaclotide 18 µg)
Reporting group description:	
Linaclotide 18 microgram (µg), capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Cohort 2 (Linaclotide 36 µg)
Reporting group description:	
Linaclotide 36 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Cohort 3 (Linaclotide 72 µg)
Reporting group description:	
Linaclotide 72 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Final Cohort (Linaclotide 72 µg)
Reporting group description:	
Linaclotide at the highest dose tested/determined to be safe (72 µg), capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Placebo Pooled
Reporting group description:	
Matching placebo, orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period pooled from Cohorts 1, 2, 3, and Final Cohort.	
Reporting group title	Cohort 1 (Linaclotide 18 µg)
Reporting group description:	
Linaclotide 18 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Cohort 2 (Linaclotide 36 µg)
Reporting group description:	
Linaclotide 36 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Cohort 3 (Linaclotide 72 µg)
Reporting group description:	
Linaclotide 72 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Final Cohort (Linaclotide 72 µg)
Reporting group description:	
Linaclotide at the highest dose tested/determined to be safe (72 µg), capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.	
Reporting group title	Placebo Pooled
Reporting group description:	
Matching placebo, orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period pooled from Cohorts 1, 2, 3, and Final Cohort.	

Primary: Change from Baseline in 4-week Overall Spontaneous Bowel Movement (SBM) Frequency Rate (SBMs/week) During the Study Intervention Period of Each Cohort

End point title	Change from Baseline in 4-week Overall Spontaneous Bowel Movement (SBM) Frequency Rate (SBMs/week) During the Study Intervention Period of Each Cohort[1]

End point description:

A SBM was defined as a bowel movement (BM) that occurred in the absence of laxative, suppository, or enema use on the calendar day of the BM or the calendar day before the BM. Each day caregiver recorded the number of SBMs in the last 24 hours in an electronic diary(eDiary). The SBM frequency rate(SBMs/week) during the analysis period for each participant were calculated as [(total number of SBMs in the analysis period/number of days in the analysis period)*7]. Baseline value was based on values collected 14 days before randomization up to randomization. Change from Baseline was calculated as the SBM frequency rate during the 4-week treatment period - SBM frequency rate at Baseline. A positive change from Baseline indicates improvement. Modified-intent-to-treat (mITT) Population included all Randomized Population who received at least 1 dose of double-blind study intervention and who had at least 1 postbaseline entry on BM characteristic assessments that determine occurrences of SBMs.

End point type	Primary

End point timeframe:

Baseline (14 days prior to randomization) to Day 29

Notes:

[1] - 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: No statistical analyses are reported for this endpoint.

End point values	Cohort 1 (Linaclotide 18 µg)	Cohort 2 (Linaclotide 36 µg)	Cohort 3 (Linaclotide 72 µg)	Final Cohort (Linaclotide 72 µg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	6	7
Units: SBMs per week				
arithmetic mean (standard deviation)				
Baseline	1.379 (± 1.095)	0.621 (± 0.365)	0.724 (± 0.953)	1.034 (± 0.809)
Change from Baseline at Day 29	3.100 (± 5.251)	0.032 (± 0.508)	3.603 (± 2.867)	1.574 (± 1.933)

End point values	Placebo Pooled			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: SBMs per week				
arithmetic mean (standard deviation)				
Baseline	1.267 (± 1.062)			
Change from Baseline at Day 29	0.482 (± 0.773)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in 4-week Stool Consistency Reported by the Caregiver During the Study Intervention Period of Each Cohort

End point title	Change from Baseline in 4-week Stool Consistency Reported by the Caregiver During the Study Intervention Period of Each Cohort[2]

End point description:

The caregiver rated and recorded in an eDiary the consistency of the stool for each bowel movement using the Bristol Stool Form 7-point scale where: 1=Separate hard lumps, like nuts (hard to pass); 2=Sausage-shaped, but lumpy; 3=Like a sausage but with cracks on its surface; 4=Like a sausage or snake, smooth and soft; 5=Soft blobs with clear cut edges (easy to pass); 6=Fluffy pieces with ragged edges, a mushy stool; 7=Watery, no solid pieces. Entirely liquid. Baseline value was based on values collected 14 days before randomization up to randomization. A participant's stool consistency score for the treatment period was the average of the nonmissing consistency scores from the BMs recorded by the caregiver during the 4-week treatment period. mITT Population. Number of subjects analysed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Baseline (14 days prior to randomization) to Day 29

Notes:

[2] - 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: No statistical analyses are reported for this endpoint.

End point values	Cohort 1 (Linaclotide 18 µg)	Cohort 2 (Linaclotide 36 µg)	Cohort 3 (Linaclotide 72 µg)	Final Cohort (Linaclotide 72 µg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	3	7
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	1.633 (± 0.461)	1.700 (± 0.447)	2.733 (± 1.079)	2.021 (± 0.793)
Change From Baseline to Day 29	0.917 (± 1.360)	1.600 (± 1.294)	1.687 (± 2.779)	1.716 (± 1.689)

End point values	Placebo Pooled			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	2.024 (± 0.641)			
Change From Baseline to Day 29	0.596 (± 0.937)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in 4-week Straining Reported by the Caregiver During the Study Intervention Period of Each Cohort

End point title	Change from Baseline in 4-week Straining Reported by the Caregiver During the Study Intervention Period of Each Cohort[3]

End point description:

The caregiver rated and recorded in an eDiary the amount of straining they observed when the child passed the BM (1=Not at all; 2=Yes a little; 3=Yes a lot; 99=I don't know). Baseline value was based

on values collected 14 days before randomization up to randomization. A participant's straining score for the treatment period was the average of the nonmissing straining scores from the BMs recorded by the caregiver during the 4-week treatment period. A negative change from Baseline indicates improvement. mITT Population included all Randomized Population who received at least 1 dose of double-blind study intervention and who had at least 1 postbaseline entry on BM characteristic assessments that determine occurrences of SBMs. Number of subjects analysed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Baseline (14 days prior to randomization) to Day 29

Notes:

[3] - 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: No statistical analyses are reported for this endpoint.

End point values	Cohort 1 (Linaclotide 18 µg)	Cohort 2 (Linaclotide 36 µg)	Cohort 3 (Linaclotide 72 µg)	Final Cohort (Linaclotide 72 µg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	3	7
Units: straining score				
arithmetic mean (standard deviation)				
Baseline	2.310 (± 0.410)	2.600 (± 0.379)	2.600 (± 0.361)	2.571 (± 0.426)
Change From Baseline to Day 29	-0.370 (± 0.631)	-0.320 (± 0.325)	-0.769 (± 0.884)	-0.996 (± 0.759)

End point values	Placebo Pooled			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: straining score				
arithmetic mean (standard deviation)				
Baseline	2.548 (± 0.658)			
Change From Baseline to Day 29	-0.334 (± 0.360)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Days with Fecal Incontinence During the Study Intervention Period (for Participants who have Acquired Toileting Skills During the Daytime and Nighttime or Acquired Toileting Skills During Daytime Only) Within Each Cohort

End point title	Percentage of Days with Fecal Incontinence During the Study Intervention Period (for Participants who have Acquired Toileting Skills During the Daytime and Nighttime or Acquired Toileting Skills During Daytime Only) Within Each Cohort[4]

End point description:

Each day the caregiver recorded in an eDiary if the child had a bowel movement accident (Yes; No; I don't know). The percentage of days with fecal incontinence for the treatment period was the average of the nonmissing incidences of fecal incontinence recorded by the caregiver during the 4-week treatment

period. mITT Population included all Randomized Population who received at least 1 dose of double-blind study intervention and who had at least 1 postbaseline entry on BM characteristic assessments that determine occurrences of SBMs. Number of subjects analysed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

29 days

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: No statistical analyses are reported for this endpoint.

End point values	Cohort 1 (Linaclotide 18 µg)	Cohort 2 (Linaclotide 36 µg)	Cohort 3 (Linaclotide 72 µg)	Final Cohort (Linaclotide 72 µg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	5	5
Units: percentage of days				
arithmetic mean (standard deviation)	0.007 (± 0.016)	0.065 (± 0.107)	0.091 (± 0.063)	0.009 (± 0.019)

End point values	Placebo Pooled			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percentage of days				
arithmetic mean (standard deviation)	0.000 (± 0.000)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Percentage of Participants with Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)[5]

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease. A serious adverse event (SAE) is defined as any untoward medical occurrence that: results in death, is immediately life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, and/or causes a congenital anomaly/birth defect. A TEAE is an AE that begins or worsens after receiving study drug. Safety Population included all participants in the Randomized Population who received at least 1 dose of double-blind study intervention.

End point type	Primary

End point timeframe:

First dose of study drug intervention to within 1 week of last dose (Up to 45 days)

Notes:

[5] - 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: No statistical analyses are reported for this endpoint.

End point values	Cohort 1 (Linaclotide 18 µg)	Cohort 2 (Linaclotide 36 µg)	Cohort 3 (Linaclotide 72 µg)	Final Cohort (Linaclotide 72 µg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	6	7
Units: percentage of participants				
number (not applicable)				
TEAEs	28.6	0.0	0.0	28.6
TESAE	0.0	0.0	0.0	0.0

End point values	Placebo Pooled			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (not applicable)				
TEAEs	12.5			
TESAE	0.0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug intervention to within 1 week of last dose (Up to 45 days)

Adverse event reporting additional description:

All-Cause Mortality: All randomized participants. Serious Adverse Events and Other Adverse Events: Safety Population included all participants in the Randomized Population who received at least 1 dose of double-blind study intervention.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Cohort 2 (Linaclotide 36 µg)

Reporting group description:

Linaclotide 36 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

Reporting group title	Cohort 1 (Linaclotide 18 µg)

Reporting group description:

Linaclotide 18 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

Reporting group title	Final Cohort (Linaclotide 72 µg)

Reporting group description:

Linaclotide at the highest dose tested/determined to be safe (72 µg), capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

Reporting group title	Placebo Pooled

Reporting group description:

Matching placebo once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period pooled from Cohorts 1, 2, 3, and Final Cohort.

Reporting group title	Cohort 3 (Linaclotide 72 µg)

Reporting group description:

Linaclotide 72 µg, capsules, mixed with water and administered orally, once daily in fasted state (30 minutes before any meal) for the 4-week Study Intervention Period.

Serious adverse events	Cohort 2 (Linaclotide 36 µg)	Cohort 1 (Linaclotide 18 µg)	Final Cohort (Linaclotide 72 µg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Placebo Pooled	Cohort 3 (Linaclotide 72 µg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 6 (0.00%)	

number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Cohort 2 (Linaclotide 36 µg)	Cohort 1 (Linaclotide 18 µg)	Final Cohort (Linaclotide 72 µg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	2 / 7 (28.57%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Developmental delay			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

Non-serious adverse events	Placebo Pooled	Cohort 3 (Linaclotide	

		72 µg)	
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
Investigations Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	
General disorders and administration site conditions Developmental delay subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 6 (0.00%) 0	
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 6 (0.00%) 0	
Infections and infestations Otitis media subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2020	The purpose of Global Protocol Amendment 1 was to include an assessment of modified Rome III criteria at the end of treatment as an 'other' efficacy endpoint, to include a fecal impaction assessment prior to randomization and dosing, and to provide additional clarification and updates to the LIN-MD-67 protocol (dated 01 May 2019); European Union (EU) sites would not be included in the study; Information was provided on study conduct during the novel coronavirus pandemic; Appendix: Liver Safety was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported