Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Safety and Efficacy Study of Linaclotide in Pediatric Participants, Ages 6 to 17 Years, With Irritable Bowel Syndrome With Constipation (IBS-C) and of Linaclotide 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, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.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?	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
Arm title	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)

Arm title	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)

Arm title	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)	

Arm title	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)	

Number of subjects in period 1	FC Participants: Placebo	FC Participants: Linaclotide 72 µg	IBS-C Participants: Linaclotide 145 µg
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: 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
Arm title	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

Arm title	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

Arm title	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

Arm title	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	

Number of subjects in period 2[1]	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

Number of subjects in period 2[1]	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:	
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.	
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 values	FC Participants: Placebo	FC Participants: Linaclotide 72 µg	IBS-C Participants: Linaclotide 145 µg
Number of subjects	164	166	55
Age categorical Units: Subjects			
6-11 years	91	92	22
12-17 years	73	74	33
Gender categorical Units: Subjects			
Female	86	96	31
Male	78	70	24
Race 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 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 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:	
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.	
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.	
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.	

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[1]

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 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.

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:

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 [2]
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 [3]
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

	Responder Rate[4][5]

End point description:

6/12 weeks APS + 2 responder=participant who meets the weekly APS + 2 responder criteria ≥6 of the 12 weeks of the intervention period. Weekly APS +2 responder=participant who has an increase of ≥2 in the SBM weekly rate from baseline, AND a decrease of ≥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 ≥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 Participants: Linaclotide 145 µg	IBS-C Participants: Linaclotide 290 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[6]

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 [7]
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 [8]
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) Participants: Change From Baseline in 12-week SBM Frequency Rate (SBMs/Week) During the Study Intervention Period[9]

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 ≥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 Participants: Linaclotide 145 µg	IBS-C Participants: Linaclotide 290 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	47		
Units: SBMs/week				
arithmetic mean (standard deviation)	2.347 (± 3.3335)	2.747 (± 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) Participants: Change From Baseline in 12-week Abdominal Pain During the Study Intervention Period[10]

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 ≥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 Participants: Linaclotide 145 µg	IBS-C Participants: Linaclotide 290 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 (± 0.9313)	-0.837 (± 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) Participants: Change From Baseline in 12-week Stool Consistency During the Study Intervention Period[11]

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 Participants: Linaclotide 145 µg	IBS-C Participants: Linaclotide 290 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 (± 1.2900)	1.358 (± 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) Participants: 6/12 Weeks SBM + 2 Responder Rate[12]

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 ≥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 Participants: Linaclotide 145 µg	IBS-C Participants: Linaclotide 290 µg		
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) Participants: 6/12 Weeks Abdominal Pain Responder[13]

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 ≥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 Participants: Linaclotide 145 µg	IBS-C Participants: Linaclotide 290 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: Linaclotide 145 µg	IBS-C Participants: Linaclotide 290 µg	FC Participants: 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

Serious adverse events	FC Participants: 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		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	IBS-C Participants: Linaclotide 145 µg	IBS-C Participants: Linaclotide 290 µg	FC Participants: Placebo
Total subjects affected by non-serious adverse events			
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

Non-serious adverse events	FC Participants: Linaclotide 72 µg		
Total subjects affected by non-serious adverse events			
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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported