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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	MCP-103-403

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

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

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Matching Placebo

Arm description:

Placebo once daily for 4 weeks

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

Dosage and administration details:

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

Arm title	290 µg Linaclotide

Arm description:

290 µg linaclotide once daily for 4 weeks

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

Dosage and administration details:

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

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

Baseline characteristics

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

Reporting group values	Matching Placebo	290 µg Linaclotide	Total
Number of subjects	9	11	20
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	35.8	35.2	
standard deviation	± 10.38	± 12.82	-
Gender categorical Units: Subjects			
Female	9	11	20
Male	0	0	0
Race Units: Subjects			
Caucasian	9	11	20
Non-Caucasian	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	9	11	20

End points

End points reporting groups

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

Primary: Change From Baseline in Abdominal Girth at Week 4

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

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

Notes:

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

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

Statistical analyses

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

Secondary: Change From Baseline in Abdominal Girth at Week 2

End point title	Change From Baseline in Abdominal Girth at Week 2

End point description:

Mean change in abdominal girth (physical measure of bloating/distention) as measured by AUC, determined by 24-hour AIP (with hourly averages). The AUC was calculated using the Trapezoidal method from the first reliable hour of measurement to last measurement (bedtime). The AUC for each participant was then individually standardized by dividing the total AUC over the period by that patient's number of hours of measurement included in the AUC.

End point type	Secondary

End point timeframe:

Baseline, Week 2

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Maximal Abdominal Girth at Week 4

End point description:

The maximum change in girth from the first hour, over the period from the 2nd hour to bedtime. The percentage change in maximum distension from baseline to 4 weeks will also be calculated.

End point type	Secondary

End point timeframe:

Baseline, Week 4

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, Week 1

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, Week 2

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, Week 3

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, Week 4

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, Week 2

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, Week 4

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

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of study drug through Day 36 (± 2 days).	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Matching Placebo
Reporting group description: Placebo once daily for 4 weeks	
Reporting group title	290 µg Linaclotide
Reporting group description: 290 µg linaclotide once daily for 4 weeks	

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2016	• Defined the End of Study as the last participant Follow-up Telephone Call (Day 36) • Updated exclusion criteria to exclude participants with known or suspected mechanical gastrointestinal obstruction and participants with hypersensitivity to linaclotide or to any of the excipients • Specified that the United States product insert serves as the Reference Safety Information for the study • Clarified the investigator and sponsor reporting responsibilities for serious adverse events and suspected unexpected serious adverse reactions, consistent with European Directive 2001/20/EC
25 April 2017	• Removed the rectal screening at each physical exam; sigmoidoscopy or colonoscopy will be performed if needed, at the discretion of the investigator • Added window of ±2 days for the Follow-up Period to the Schedule of Evaluations and subsequent sections for consistency with study design figure • Updated inclusion criteria to increase the body mass index (BMI) upper limit to 34.9 kg/m2 • Updated the number of capsules per bottle of study drug from 30 to 35 capsules to reflect how study drug is currently supplied • Removed urinalysis from the screening visit assessments; urine samples still collected for pregnancy testing • Removed the differential white blood cell count from the Clinical Laboratory Determinations • Administrative updates

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: