Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients With Diarrhea-Predominant Irritable Bowel Syndrome

Summary

EudraCT number	2012-001601-24
Trial protocol	GB
Global end of trial date	09 January 2014

Results information

Result version number	v1 (current)
This version publication date	19 October 2018
First version publication date	19 October 2018

Trial information

Trial identification

Sponsor protocol code	27018966IBS3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01553747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Pharmaceutical International Ltd
Sponsor organisation address	Clonshaugh Business & Technology Park, Coolock, Dublin,, Ireland, D17 E400
Public contact	Clinical Trials Registry Team, Allergan plc, 001 8772778566, IR-CTRegistration@Allergan.com
Scientific contact	Therapeutic Area Head, Allergan plc, 001 862-261-7000, IR-CTRegistration@Allergan.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	09 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this study was to evaluate the clinical response of participants with irritable bowel syndrome, diarrhea predominant (IBS-d) to eluxadoline, relative to placebo and evaluation of the overall safety and tolerability of eluxadoline in the treatment of IBS-d for up to 26 weeks.

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	29 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Puerto Rico: 32
Country: Number of subjects enrolled	United Kingdom: 1097
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	1146
EEA total number of subjects	1097

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)	1020
From 65 to 84 years	126

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

3356 participants were prescreened and entered into interactive voice response system for participation in the study. 1146 participants were randomised. One participant was unintentionally randomised twice and was assigned 2 different participant identification numbers due to participant trying to participate at more than 1 study center at once.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Eluxadoline 75 mg

Arm description:

Eluxadoline 75 mg tablets, orally, twice daily for up to 26 weeks treatment period followed by placebo orally, twice daily for next 4 weeks of blinded-placebo period.

Arm type	Experimental
Investigational medicinal product name	Eluxadoline
Investigational medicinal product code	
Other name	JNJ-27018966
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Eluxadoline tablets, orally, twice daily for up to 26 weeks period.

Arm title	Eluxadoline 100 mg

Arm description:

Eluxadoline 100 mg tablets, orally, twice daily for up to 26 weeks treatment period followed by placebo orally, twice daily for next 4 weeks of blinded-placebo period.

Arm type	Experimental
Investigational medicinal product name	Eluxadoline
Investigational medicinal product code	
Other name	JNJ-27018966
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Eluxadoline tablets, orally, twice daily for up to 26 weeks period.

Arm title	Placebo

Arm description:

Eluxadoline placebo matching tablets, orally, twice daily for up to 26 weeks treatment period followed by placebo orally, twice daily for next 4 weeks of blinded-placebo period.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Eluxadoline placebo matching tablets, orally, twice daily for up to 26 weeks period.

Number of subjects in period 1	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo
Started	381	383	382
Attended Week 12 visit	296	301	312
Attended Week 26 visit	259	271	278
Participated in Blinded-Placebo Period	246 [1]	253 [2]	272 [3]
Completed	250	264	273
Not completed	131	119	109
Voluntarily withdrew	70	66	74
Physician decision: other	10	8	7
Physician decision: lack of efficacy	1	5	3
Sponsor decision, specify	7	5	-
Lost to follow-up	11	5	6
Adverse event or SAE	32	28	19
Protocol deviation	-	2	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects to complete the study is based on the 26-week randomized treatment period. The 4-week blinded placebo period occurs only after the completion of the 26-week randomized treatment period.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects to complete the study is based on the 26-week randomized treatment period. The 4-week blinded placebo period occurs only after the completion of the 26-week randomized treatment period.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects to complete the study is based on the 26-week randomized treatment period. The 4-week blinded placebo period occurs only after the completion of the 26-week randomized treatment period.

Baseline characteristics

Reporting groups	
Reporting group title	Eluxadoline 75 mg
Reporting group description:	
Eluxadoline 75 mg tablets, orally, twice daily for up to 26 weeks treatment period followed by placebo orally, twice daily for next 4 weeks of blinded-placebo period.	
Reporting group title	Eluxadoline 100 mg
Reporting group description:	
Eluxadoline 100 mg tablets, orally, twice daily for up to 26 weeks treatment period followed by placebo orally, twice daily for next 4 weeks of blinded-placebo period.	
Reporting group title	Placebo
Reporting group description:	
Eluxadoline placebo matching tablets, orally, twice daily for up to 26 weeks treatment period followed by placebo orally, twice daily for next 4 weeks of blinded-placebo period.	

Reporting group values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo
Number of subjects	381	383	382
Age, Customized Units: Subjects			
18-40 years	139	146	133
41-64 years	206	198	198
≥65 years	36	39	51
Age Continuous Units: years			
arithmetic mean	45.0	45.7	47.1
standard deviation	± 13.17	± 13.31	± 13.82
Sex: Female, Male Units: Subjects			
Female	261	257	250
Male	120	126	132

Reporting group values	Total		
Number of subjects	1146		
Age, Customized Units: Subjects			
18-40 years	418		
41-64 years	602		
≥65 years	126		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	768		
Male	378		

End points

End points reporting groups

Reporting group title	Eluxadoline 75 mg
Reporting group description:	
Eluxadoline 75 mg tablets, orally, twice daily for up to 26 weeks treatment period followed by placebo orally, twice daily for next 4 weeks of blinded-placebo period.	
Reporting group title	Eluxadoline 100 mg
Reporting group description:	
Eluxadoline 100 mg tablets, orally, twice daily for up to 26 weeks treatment period followed by placebo orally, twice daily for next 4 weeks of blinded-placebo period.	
Reporting group title	Placebo
Reporting group description:	
Eluxadoline placebo matching tablets, orally, twice daily for up to 26 weeks treatment period followed by placebo orally, twice daily for next 4 weeks of blinded-placebo period.	

Primary: Percentage of Participants who Were Composite Responders Based on Improvements From Baseline in Daily Worst Abdominal Pain and Daily Stool Consistency Scores

End point title	Percentage of Participants who Were Composite Responders Based on Improvements From Baseline in Daily Worst Abdominal Pain and Daily Stool Consistency Scores
End point description:	
Composite responders: Participants who met daily response criteria for at least 50% of the days with diary entries during the interval of interest. A participant must have met following criteria on given day to be daily responder:1) Daily pain response: worst abdominal pain scores in past 24 hours improved by ≥30% compared to baseline. 2) Daily stool consistency response: Bristol Stool Scale (BSS) score <5 or the absence of a bowel movement if accompanied by ≥30% improvement in worst abdominal pain compared to baseline pain. BSS is defined as 7-point Scale in which score of 1 = separate hard lumps, 2 = sausage shaped but lumpy, 3 = sausage-like with cracks on the surface, 4 = sausage-like but smooth and soft, 5 = soft blobs with clear cut edges, 6 = fluffy pieces with ragged edges, 7 = watery with no solid pieces. Intent to Treat (ITT) analysis set: All participants who were randomised and presents data for participants according to their randomisation assignment.	
End point type	Primary
End point timeframe:	
Up to 26 weeks	

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: percentage of participants				
number (not applicable)	30.4	32.7	20.2	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The composite responder was analyzed using the CMH (Chi-square) test. The family-wise error rate was controlled by Bonferroni adjustment for each active dose versus placebo.

Comparison groups	Eluxadoline 75 mg v Placebo
Number of subjects included in analysis	763
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001 [1]
Method	Chi-square test statistic

Notes:

[1] - Chi-square test at 0.025 significance level

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The composite responder was analyzed using the CMH (Chi-square) test. The family-wise error rate was controlled by Bonferroni adjustment for each active dose versus placebo.

Comparison groups	Eluxadoline 100 mg v Placebo
Number of subjects included in analysis	764
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [2]
Method	Chi-square test statistic

Notes:

[2] - Chi-square test at 0.025 significance level

Secondary: Percentage of Participants who Were Composite Responders Based on Improvements From Baseline in Daily Worst Abdominal Pain and Daily Stool Consistency Scores

End point title	Percentage of Participants who Were Composite Responders Based on Improvements From Baseline in Daily Worst Abdominal Pain and Daily Stool Consistency Scores

End point description:

Composite responders: Participants who met daily response criteria for at least 50% of the days with diary entries during the interval of interest. A participant must have met following criteria on given day to be daily responder:1) Daily pain response: worst abdominal pain scores in past 24 hours improved by ≥30% compared to baseline. 2) Daily stool consistency response: Bristol Stool Scale (BSS) score <5 or the absence of a bowel movement if accompanied by ≥30% improvement in worst abdominal pain compared to baseline pain. BSS is defined as 7-point Scale in which a score of 1 = separate hard lumps, 2 = sausage shaped but lumpy, 3 = sausage-like with cracks on the surface, 4 = sausage-like but smooth and soft, 5 = soft blobs with clear cut edges, 6 = fluffy pieces with ragged edges, 7 = watery with no solid pieces. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment.

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: percentage of participants				
number (not applicable)	28.9	29.6	16.2	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The composite responder was analyzed using the CMH (Chi-square) test. The family-wise error rate was controlled by Bonferroni adjustment for each active dose versus placebo.

Comparison groups	Placebo v Eluxadoline 75 mg
Number of subjects included in analysis	763
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [3]
Method	Chi-square test statistic

Notes:

[3] - Chi-square test at 0.025 significance level

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The composite responder was analyzed using the CMH (Chi-square) test. The family-wise error rate was controlled by Bonferroni adjustment for each active dose versus placebo.

Comparison groups	Eluxadoline 100 mg v Placebo
Number of subjects included in analysis	764
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [4]
Method	Chi-square test statistic

Notes:

[4] - Chi-square test at 0.025 significance level

Secondary: Percentage of Participants who Were Pain Responders In Daily Worst Abdominal Pain Scores by Intervals

End point title	Percentage of Participants who Were Pain Responders In Daily Worst Abdominal Pain Scores by Intervals

End point description:

Pain responders were defined as participants who met the daily pain response criteria (ie, the worst abdominal pain score in the past 24 hours improved by ≥30% compared to baseline) for at least 50% of days with diary entries during each interval. A participant must have had a minimum of 20 days of diary entries over any 4-week interval, a minimum of 60 days of diary entries over the 12-week interval, and a minimum of 110 days of diary entries over the 26-week interval to be a responder. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment.

End point type	Secondary

End point timeframe:

12-week interval (Weeks 1-12), 26-week interval (Weeks 1-26), and 4-week interval (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24)

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: percentage of participants				
number (not applicable)				
Responders during Weeks 1-12	48.0	51.0	45.3	
Responders during Weeks 1-26	47.5	50.0	44.8	
Responders during Weeks 1-4	46.7	46.6	41.9	
Responders during Weeks 5-8	53.0	52.9	49.2	
Responders during Weeks 9-12	48.0	50.3	46.9	
Responders during Weeks 13-16	47.2	49.0	43.5	
Responders during Weeks 17-20	45.1	47.4	42.7	
Responders during Weeks 21-24	41.7	46.9	40.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Were Responders In Daily Stool Consistency Scores by Intervals

End point title	Percentage of Participants who Were Responders In Daily Stool Consistency Scores by Intervals

End point description:

Stool consistency responders: Participants who met daily stool consistency response criterion (ie,score of 1, 2, 3, or 4 or absence of bowel movement if accompanied by ≥30% improvement in worst abdominal pain compared to baseline pain) for at least 50% of days with diary entries during each interval. BSS was defined as 7-point Scale in which score of 1= separate hard lumps, 2= sausage shaped but lumpy, 3= sausage-like with cracks on the surface, 4= sausage-like but smooth and soft, 5= soft blobs with clear cut edges, 6= fluffy pieces with ragged edges, and 7= watery with no solid pieces. A participant must have had a minimum of 20 days of diary entries over any 4-week interval, a minimum of 60 days of diary entries over 12-week interval, and a minimum of 110 days of diary entries over 26-week interval to be a responder. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment.

End point type	Secondary

End point timeframe:

12-week interval (Weeks 1-12), 26-week interval (Weeks 1-26), and 4-week interval (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24)

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: percentage of participants				
number (not applicable)				
Responders during Weeks 1-12	37.0	35.6	20.9	

Responders during Weeks 1-26	34.4	39.8	23.6	
Responders during Weeks 1-4	34.6	37.2	18.1	
Responders during Weeks 5-8	37.5	38.2	23.3	
Responders during Weeks 9-12	37.5	39.3	26.4	
Responders during Weeks 13-16	36.2	41.4	24.9	
Responders during Weeks 17-20	33.9	36.1	24.9	
Responders during Weeks 21-24	32.5	38.2	22.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Were Responders In Irritable Bowel Syndrome, Diarrhea Predominant (IBS-d) Global Symptom Scale by Intervals

End point title	Percentage of Participants who Were Responders In Irritable Bowel Syndrome, Diarrhea Predominant (IBS-d) Global Symptom Scale by Intervals

End point description:

IBS-d global symptom responders were defined as those participants who met the daily IBS-d global symptom response criteria (ie, IBS-d global symptom score of 0 [none] or 1 [mild]; or a daily IBS-d global symptom score improved by ≥2.0 compared to the baseline average) for at least 50% of days with diary entries during each interval. IBS-d Global Symptom Scale was a 5-point scale, score ranging from 0 to 4. 0= no symptoms, 1= mild symptoms, 2= moderate symptoms, 3= severe symptoms and 4 = very severe symptoms. A participant must have had a minimum of 20 days of diary entries over any 4-week interval, a minimum of 60 days of diary entries over the 12-week interval, and a minimum of 110 days of diary entries over the 26-week interval to be a responder. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment.

End point type	Secondary

End point timeframe:

12-week interval (Weeks 1-12), 26-week interval (Weeks 1-26), and 4-week interval (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24)

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: percentage of participants				
number (not applicable)				
Responders during Weeks 1-12	43.6	42.4	29.6	
Responders during Weeks 1-26	45.1	43.2	34.3	
Responders during Weeks 1-4	40.2	36.9	25.7	
Responders during Weeks 5-8	45.1	45.0	35.1	
Responders during Weeks 9-12	44.9	43.5	34.0	
Responders during Weeks 13-16	43.8	42.9	33.0	
Responders during Weeks 17-20	42.5	40.8	33.2	
Responders during Weeks 21-24	41.7	41.6	33.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Were Responders to the Irritable Bowel Syndrome Quality of Life Measure (IBS-QoL) Scale

End point title	Percentage of Participants who Were Responders to the Irritable Bowel Syndrome Quality of Life Measure (IBS-QoL) Scale

End point description:

IBS-QoL responders were defined as participants who achieved at least a 14-point improvement in IBS-QoL total score from baseline to the applicable visit. The IBS-QoL consists of 34 items each with a 5-point response scale, where 1 generally represents better responses on items and 5 represents worse responses. The individual responses to the answered items were summed and standardized for a total score and then transformed to a 0- to 100-point (0= worst; 100=better) scale for ease of interpretation. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 18, 26 and 30 (End of Treatment [EOT])

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: percentage of participants				
number (not applicable)				
Responders at Week 4	45.1	45.5	40.1	
Responders at Week 8	48.8	50.0	43.7	
Responders at Week 12	48.3	49.5	45.0	
Responders at Week 18	45.1	45.0	41.9	
Responders at Week 26	45.4	44.8	41.4	
Responders at Week 30 /EOT	54.3	53.9	52.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Irritable Bowel Syndrome – Adequate Relief (IBS-AR) Scale

End point title	Percentage of Participants With Irritable Bowel Syndrome – Adequate Relief (IBS-AR) Scale

End point description:

Adequate relief of IBS symptoms was assessed once weekly by participants answering the IBS-AR item in the electronic diary. IBS-AR responders were defined as participants with a weekly response of "Yes" to adequate relief of their IBS symptoms for at least 50% of the total weeks during the interval. A participant must have had a positive response on ≥6 weeks for the 12-week interval and ≥13 weeks for the 26-week interval, regardless of diary compliance, to be a responder. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment.

End point type	Secondary

End point timeframe:

12-week interval (Weeks 1-12) and 26-week interval (Weeks 1-26)

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: percentage of participants				
number (not applicable)				
Responders during Weeks 1-12	60.1	58.4	49.2	
Responders during Weeks 1-26	52.8	53.7	43.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Daily Abdominal Discomfort Scores

End point title	Change From Baseline in Daily Abdominal Discomfort Scores

End point description:

Symptoms of abdominal discomfort were recorded on a 0 to 10 scale, where 0 corresponded to no discomfort and 10 corresponded to worst imaginable discomfort. A negative change from Baseline indicates the discomfort decreased. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment. Here, "n" indicates the number of participants who were evaluable at specific time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 12 and 26

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 4 (n= 348, 351, 364)	-2.44 (± 2.219)	-2.19 (± 2.120)	-2.06 (± 2.063)	
Change at Week 12 (n= 298, 303, 316)	-2.88 (± 2.417)	-2.90 (± 2.175)	-2.56 (± 2.461)	
Change at Week 26 (n= 255, 267, 267)	-3.19 (± 2.454)	-3.16 (± 2.362)	-2.76 (± 2.582)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Daily Abdominal Bloating Scores

End point title	Change From Baseline in Daily Abdominal Bloating Scores

End point description:

Symptoms of abdominal bloating were recorded on a 0 to 10 scale, where 0 corresponded to no bloating and 10 corresponded to worst imaginable bloating. A negative change from Baseline indicates the bloating decreased. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment. Here, "n" indicates the number of participants who were evaluable at specific time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 12 and 26

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 4 (n= 292, 305, 302)	-1.89 (± 2.170)	-1.80 (± 2.204)	-1.73 (± 2.081)	
Change at Week 12 (n= 247, 262, 259)	-2.24 (± 2.445)	-2.41 (± 2.396)	-2.08 (± 2.492)	
Change at Week 26 (n= 210, 229, 214)	-2.38 (± 2.619)	-2.68 (± 2.673)	-2.17 (± 2.682)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bowel Movements per Day

End point title	Number of Bowel Movements per Day

End point description:

Participants recorded the number of bowel movements over 24 hours daily throughout the treatment. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment. Here, "n" indicates the number of participants who were evaluable at specific time point.

End point type	Secondary

End point timeframe:

Weeks 4, 12 and 26

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: number of bowel movements				
arithmetic mean (standard deviation)				
Week 4 (n= 348, 351, 364)	3.03 (± 2.021)	3.05 (± 1.962)	3.38 (± 1.856)	
Week 12 (n= 298, 303, 316)	2.89 (± 2.057)	2.80 (± 1.685)	3.15 (± 1.991)	
Week 26 (n= 255, 267, 267)	2.57 (± 1.637)	2.66 (± 1.625)	2.96 (± 1.931)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bowel Incontinence Episodes

End point title	Number of Bowel Incontinence Episodes

End point description:

Participants recorded the number of incontinence episodes over 24 hours daily throughout the treatment. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment. Here, "n" indicates the number of participants who were evaluable at specific time point.

End point type	Secondary

End point timeframe:

Weeks 4, 12 and 26

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: incontinence episodes				
arithmetic mean (standard deviation)				
Week 4 (n= 348, 351, 364)	0.47 (± 1.304)	0.41 (± 1.230)	0.50 (± 1.195)	
Week 12 (n= 298, 303, 316)	0.40 (± 1.083)	0.28 (± 0.875)	0.46 (± 1.269)	
Week 26 (n= 255, 267, 267)	0.30 (± 0.982)	0.27 (± 0.844)	0.50 (± 1.503)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bowel Incontinence Free Days

End point title	Number of Bowel Incontinence Free Days

End point description:

An incontinence free day was one where the participant reports zero incontinence episodes. The number of incontinence free days for a participant was assessed each week based on the number of reported days. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment. Here, "n" indicates the

number of participants who were evaluable at specific time point.

End point type	Secondary

End point timeframe:

Weeks 4, 12 and 26

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: days				
arithmetic mean (standard deviation)				
Week 4 (n= 348, 351, 364)	5.53 (± 2.282)	5.46 (± 2.264)	5.31 (± 2.444)	
Week 12 (n= 298, 303, 316)	5.38 (± 2.320)	5.56 (± 2.164)	5.28 (± 2.364)	
Week 26 (n= 255, 267, 267)	5.53 (± 2.129)	5.59 (± 2.216)	5.29 (± 2.322)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Urgency Episodes per Day

End point title	Number of Urgency Episodes per Day

End point description:

Participants recorded the number of urgency episodes over 24 hours daily throughout the treatment. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment. Here, "n" indicates the number of participants who were evaluable at specific time point.

End point type	Secondary

End point timeframe:

Weeks 4, 12 and 26

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: episode				
arithmetic mean (standard deviation)				
Week 4 (n= 348, 351, 364)	1.62 (± 1.948)	1.58 (± 1.732)	2.00 (± 1.779)	
Week 12 (n= 298, 303, 316)	1.37 (± 1.884)	1.32 (± 1.675)	1.73 (± 1.785)	
Week 26 (n= 255, 267, 267)	1.13 (± 1.580)	1.12 (± 1.576)	1.54 (± 1.826)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in IBS-QoL Total Scores

End point title	Change From Baseline in IBS-QoL Total Scores

End point description:

The IBS-QoL consists of 34 items each with a 5-point response scale, where 1 generally represents better responses on items and 5 represents worse responses. The individual responses to the answered items were summed and standardized for a total score and then transformed to a 0- to 100- point scale (0=worst; 100=better) for ease of interpretation. A positive change from Baseline indicates that quality of life improved. ITT analysis set included all participants who were randomised into a treatment group and presents data for participants according to their randomisation assignment. Here, "n" indicates the number of participants who were evaluable at specific time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 18, 26 and 30/EOT

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	382	
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 4 (n= 335, 342, 357)	17.51 (± 19.755)	17.26 (± 18.980)	14.07 (± 18.787)	
Change at Week 8 (n= 318, 319, 333)	21.60 (± 20.762)	21.10 (± 21.925)	16.62 (± 20.856)	
Change at Week 12 (n= 293, 300, 311)	22.69 (± 21.723)	22.62 (± 24.017)	19.50 (± 21.636)	
Change at Week 18 (n= 275, 281, 293)	24.17 (± 22.761)	23.52 (± 24.029)	20.64 (± 23.268)	
Change at Week 26 (n= 258, 271, 277)	24.91 (± 22.638)	24.19 (± 24.599)	21.50 (± 23.709)	
Change at Week 30/EOT (n= 335, 344, 342)	22.79 (± 22.329)	20.92 (± 23.724)	21.63 (± 23.376)	

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 up to 30 weeks

Adverse event reporting additional description:

Safety Set: all participants who received at least 1 dose of drug per actual treatment received. 1 participant in 100 mg arm received 75 mg, 2 participants in Placebo arm received eluxadoline 75 mg and 100 mg. AEs for each period were analyzed separately. In the Non Serious AE section, a result of 0 in an arm means the ≥5% threshold was not met.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Eluxadoline 75 mg (Treatment Period)

Reporting group description:

Eluxadoline 75 mg tablets, orally, twice daily for up to 26 weeks period.

Reporting group title	Eluxadoline 100 mg (Treatment Period)

Reporting group description:

Eluxadoline 100 mg tablets, orally, twice daily for up to 26 weeks period.

Reporting group title	Placebo (Treatment Period)

Reporting group description:

Eluxadoline placebo matching tablets, orally, twice daily for up to 26 weeks period.

Reporting group title	Eluxadoline 75 mg (Blinded-Placebo Period)

Reporting group description:

Participants who received eluxadoline 75 mg in treatment period were administered with placebo orally, twice daily for next 4 weeks.

Reporting group title	Eluxadoline 100 mg (Blinded-Placebo Period)

Reporting group description:

Participants who received eluxadoline 100 mg in treatment period were administered with placebo orally, twice daily for next 4 weeks.

Reporting group title	Placebo (Blinded-Placebo Period)

Reporting group description:

Participants who received placebo matching tablets in treatment period were administered with placebo orally, twice daily for next 4 weeks.

Serious adverse events	Eluxadoline 75 mg (Treatment Period)	Eluxadoline 100 mg (Treatment Period)	Placebo (Treatment Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 379 (2.37%)	14 / 380 (3.68%)	8 / 381 (2.10%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 379 (0.26%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac pain			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst ruptured			
subjects affected / exposed	1 / 379 (0.26%)	0 / 380 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	0 / 379 (0.00%)	0 / 380 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
ECG T wave abnormal			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 379 (0.26%)	0 / 380 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomeningocele			
subjects affected / exposed	1 / 379 (0.26%)	0 / 380 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 379 (0.00%)	0 / 380 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 379 (0.26%)	0 / 380 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 379 (0.00%)	0 / 380 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenia gravis			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal discomfort			

subjects affected / exposed	1 / 379 (0.26%)	0 / 380 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischemic			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 379 (0.26%)	0 / 380 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 379 (0.26%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 379 (0.00%)	0 / 380 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			

subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 379 (0.00%)	0 / 380 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 379 (0.00%)	0 / 380 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 379 (0.26%)	0 / 380 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial pyelonephritis			
subjects affected / exposed	1 / 379 (0.26%)	0 / 380 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infections			
subjects affected / exposed	0 / 379 (0.00%)	0 / 380 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			

subjects affected / exposed	0 / 379 (0.00%)	0 / 380 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 379 (0.26%)	0 / 380 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 379 (0.00%)	1 / 380 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Eluxadoline 75 mg (Blinded-Placebo Period)	Eluxadoline 100 mg (Blinded-Placebo Period)	Placebo (Blinded-Placebo Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Non-cardiac pain			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Ovarian cyst ruptured			

subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Uterine prolapse			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Investigations			
ECG T wave abnormal			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Hepatic enzyme increased			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Pseudomeningocele			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Angina pectoris			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Coronary artery disease			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Myasthenia gravis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Colitis ischemic			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Dyspepsia			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Gastric ulcer			

subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Hiatus hernia			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Pancreatitis acute			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Umbilical hernia			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Bacterial pyelonephritis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Enterocolitis infections			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Liver abscess			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Pyelonephritis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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
Urinary tract infection			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (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

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Eluxadoline 75 mg (Treatment Period)	Eluxadoline 100 mg (Treatment Period)	Placebo (Treatment Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 379 (25.59%)	97 / 380 (25.53%)	69 / 381 (18.11%)
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 379 (3.69%)	23 / 380 (6.05%)	22 / 381 (5.77%)
occurrences (all)	15	26	23
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	33 / 379 (8.71%)	30 / 380 (7.89%)	8 / 381 (2.10%)
occurrences (all)	35	32	12
Nausea			
subjects affected / exposed	31 / 379 (8.18%)	33 / 380 (8.68%)	22 / 381 (5.77%)
occurrences (all)	36	34	24
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	19 / 379 (5.01%)	13 / 380 (3.42%)	15 / 381 (3.94%)
occurrences (all)	20	15	17
Upper respiratory tract infection			
subjects affected / exposed	13 / 379 (3.43%)	22 / 380 (5.79%)	17 / 381 (4.46%)
occurrences (all)	13	22	19

Non-serious adverse events	Eluxadoline 75 mg (Blinded-Placebo Period)	Eluxadoline 100 mg (Blinded-Placebo Period)	Placebo (Blinded-Placebo Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (0.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 246 (0.00%)	0 / 253 (0.00%)	0 / 272 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2012	Included feedback from regulatory agencies (US FDA and EMA) regarding the efficacy endpoints, clarified eligibility criteria, and clarified the timing of assessments. The following changes affecting study conduct were specified: • added daily assessment of abdominal discomfort to electronic diary collection • clarified eligibility criteria and added exclusion criteria for lactose intolerance and gastrointestinal infection • added triglycerides evaluation at Baseline and clarified lipase and triglyceride evaluations should be completed for any participant with confirmed or suspected pancreatitis • added tramadol to the list of prohibited medications
24 August 2012	Clarified eligibility criteria and the reporting period for pregnancies, and modified administrative language related to Investigator obligations. The following changes affecting study conduct were specified: • Clarified eligibility criteria and added microscopic colitis as an example of an excluded inflammatory bowel disease • Changed the pregnancy reporting requirement from the start of the study to the time of the first dose of study drug to be consistent with the inclusion criteria
30 October 2012	Clarified eligibility criteria, clarified electronic diary notifications, added guidance in the event of elevated liver enzymes, and noted the procedures that should be performed prior to randomization. The following changes affecting study conduct were specified: • clarified eligibility criteriaparticipant • clarified that the electronic diary determines whether a participant met the study entry criteria for diary compliance, loperamide rescue medication use, and averages of worst abdominal pain, BSS, and IBS-d global symptoms, but does not send a notification of eligibility to the sites • clarified that Investigators must re-verify the participant meets all inclusion/exclusion criteria at the time of randomization • added guidance in the event of elevation in liver enzymes, including the timing of repeat labs and the criteria for withdrawal from the study
04 December 2013	Incorporated recent scientific advice from the EMA and clarified a change in the Medical Monitor for the study. This amendment clarified that to support a potential Marketing Authorisation Application (MAA) to the EMA, composite responder status over 26 weeks should be considered the primary efficacy endpoint rather than the previously designated co-primary endpoints of pain responder status and global symptom responder status

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported