



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	2012-001600-38
Trial protocol	GB
Global end of trial date	29 July 2014

Results information

Result version number	v1 (current)
This version publication date	30 June 2018
First version publication date	30 June 2018

Trial information

Trial identification

Sponsor protocol code	27018966IBS3001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01553591
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Pharmaceutical International Ltd
Sponsor organisation address	Clonsaugh 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	29 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 July 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 52 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	United Kingdom: 43
Country: Number of subjects enrolled	United States: 1214
Country: Number of subjects enrolled	Canada: 25
Worldwide total number of subjects	1282
EEA total number of subjects	43

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)	1167
From 65 to 84 years	115
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 2832 participants were entered into the screening phase of the study. Out of these, 158 participants were never screened at sites that never randomised a patient; 2674 participants were screened at sites that randomised at least one participant. A total 1282 participants were enrolled into the study.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Eluxadoline 75 mg

Arm description:

Eluxadoline 75 mg tablets, orally, twice daily for up to 52 weeks 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 52 weeks period.

Arm title	Eluxadoline 100 mg
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Arm description:

Eluxadoline 100 mg tablets, orally, twice daily for up to 52 weeks 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 52 weeks period.

Arm title	Placebo
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Arm description:

Eluxadoline placebo matching tablets, orally, twice daily for up to 52 weeks period.

Arm type	Placebo
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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 52 weeks period.

Number of subjects in period 1	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo
Started	429	426	427
Randomized	428	426	427
Attended Week 12 visit	341	330	342
Attended Week 26 visit	289	291	290
Completed	257	257	269
Not completed	172	169	158
Voluntarily withdrew	94	79	96
Physician decision: other	11	14	16
Physician decision: lack of efficacy	2	3	7
Lost to follow-up	25	23	16
Sponsor decision	1	-	3
Adverse Event or SAE	36	45	16
Randomised and never dispensed drug	-	1	-
Protocol deviation	3	4	4

Baseline characteristics

Reporting groups

Reporting group title	Eluxadoline 75 mg
Reporting group description: Eluxadoline 75 mg tablets, orally, twice daily for up to 52 weeks period.	
Reporting group title	Eluxadoline 100 mg
Reporting group description: Eluxadoline 100 mg tablets, orally, twice daily for up to 52 weeks period.	
Reporting group title	Placebo
Reporting group description: Eluxadoline placebo matching tablets, orally, twice daily for up to 52 weeks period.	

Reporting group values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo
Number of subjects	429	426	427
Age, Customized Units: Subjects			
18-40 years	173	166	159
41-64 years	227	225	217
≥65 years	29	35	51
Age Continuous Units: years			
arithmetic mean	44.5	44.4	45.8
standard deviation	± 13.18	± 13.91	± 14.10
Gender, Male/Female Units: Subjects			
Female	278	283	277
Male	151	143	150
Race/Ethnicity, Customized Units: Subjects			
White	374	368	370
Black	46	48	46
Asian	3	3	4
American Indian or Alaska Native	1	2	1
Native Hawaiian or Other Pacific Islander	0	1	0
Other	5	4	6
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	119	117	125
Not Hispanic or Latino	310	309	302
Body Mass Index (BMI) Units: kg/m ²			
arithmetic mean	30.70	31.22	30.63
standard deviation	± 7.421	± 7.858	± 7.253

Reporting group values	Total		
Number of subjects	1282		

Age, Customized Units: Subjects			
18-40 years	498		
41-64 years	669		
≥65 years	115		
Age Continuous Units: years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	838		
Male	444		
Race/Ethnicity, Customized Units: Subjects			
White	1112		
Black	140		
Asian	10		
American Indian or Alaska Native	4		
Native Hawaiian or Other Pacific Islander	1		
Other	15		
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	361		
Not Hispanic or Latino	921		
Body Mass Index (BMI) Units: kg/m ² arithmetic mean standard deviation	-		

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 52 weeks period.	
Reporting group title	Eluxadoline 100 mg
Reporting group description: Eluxadoline 100 mg tablets, orally, twice daily for up to 52 weeks period.	
Reporting group title	Placebo
Reporting group description: Eluxadoline placebo matching tablets, orally, twice daily for up to 52 weeks 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: participant who met daily response criteria for at least 50% of 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 $\geq 30\%$ compared to baseline. 2) Daily stool consistency response: Bristol Stool Scale (BSS) score < 5 or absence of a bowel movement if accompanied by $\geq 30\%$ improvement in worst abdominal pain compared to baseline pain. 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, 7 = watery with no solid pieces. Intent to Treat (ITT) analysis set included all participants who were randomised into treatment group 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	427	426	427	
Units: percentage of participants				
number (not applicable)	23.4	29.3	19.0	

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	854
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.112 ^[1]
Method	Chi-square test statistic

Notes:

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

Statistical analysis title	Statistical analysis 2
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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	853
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
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End point description:

Composite responders: a participant 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 $\geq 30\%$ compared to baseline. 2) Daily stool consistency response: Bristol Stool Scale (BSS) score < 5 or the absence of a bowel movement if accompanied by $\geq 30\%$ improvement in worst abdominal pain compared to baseline pain. BSS was 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
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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	427	426	427	
Units: percentage of participants				
number (not applicable)	23.9	25.1	17.1	

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	854
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.014 ^[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	853
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004 ^[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 are defined as participants who met the daily pain response criteria (ie, the worst abdominal pain score in the past 24 hours improved by $\geq 30\%$ 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	427	426	427	
Units: percentage of participants				
number (not applicable)				
Responders during Weeks 1-12	42.4	43.2	39.6	
Responders during Weeks 1-26	45.2	46.5	43.3	
Responders during Weeks 1-4	40.5	44.4	37.5	
Responders during Weeks 5-8	44.5	47.2	45.4	
Responders during Weeks 9-12	44.5	45.8	43.8	
Responders during Weeks 13-16	44.3	44.1	45.4	
Responders during Weeks 17-20	44.7	43.2	41.5	
Responders during Weeks 21-24	44.7	42.0	38.4	

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:	
<p>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 $\geq 30\%$ 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.</p>	
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	427	426	427	
Units: percentage of participants				
number (not applicable)				
Responders during Weeks 1-12	30.0	34.3	22.0	

Responders during Weeks 1-26	28.1	34.0	24.1	
Responders during Weeks 1-4	28.8	31.5	19.0	
Responders during Weeks 5-8	31.1	35.2	24.1	
Responders during Weeks 9-12	29.0	35.2	24.6	
Responders during Weeks 13-16	27.6	32.9	24.4	
Responders during Weeks 17-20	31.9	31.5	23.7	
Responders during Weeks 21-24	30.2	30.3	24.4	

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
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End point description:

IBS-d global symptom responders are 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 is 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
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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	427	426	427	
Units: percentage of participants				
number (not applicable)				
Responders during Weeks 1-12	35.1	34.7	28.8	
Responders during Weeks 1-26	36.3	37.1	32.3	
Responders during Weeks 1-4	32.6	31.9	26.9	
Responders during Weeks 5-8	37.0	38.7	32.8	
Responders during Weeks 9-12	35.6	36.6	34.0	
Responders during Weeks 13-16	35.8	35.9	35.4	
Responders during Weeks 17-20	37.5	36.4	33.3	
Responders during Weeks 21-24	36.8	35.2	29.5	

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
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End point description:

IBS-QoL responders are 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
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End point timeframe:

Weeks 4, 8, 12, 18, 26, 36, 44, and 52 (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	427	426	427	
Units: percentage of participants				
number (not applicable)				
Responders at Week 4	42.6	44.1	37.0	
Responders at Week 8	43.8	49.8	41.7	
Responders at Week 12	44.3	48.1	44.0	
Responders at Week 18	44.5	45.1	43.3	
Responders at Week 26	45.4	45.1	40.0	
Responders at Week 36	41.0	43.2	39.6	
Responders at Week 44	39.6	40.1	37.5	
Responders at Week 52/EOT	49.4	54.9	47.8	

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
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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 are 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	427	426	427	
Units: percentage of participants				
number (not applicable)				
Responders during Weeks 1-12	52.9	54.2	43.8	
Responders during Weeks 1-26	45.7	49.5	40.0	

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	427	426	427	
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 4 (n= 392, 381, 401)	-2.24 (± 2.204)	-2.41 (± 2.326)	-2.01 (± 2.156)	
Change at Week 12 (n= 338, 335, 335)	-2.75 (± 2.534)	-2.97 (± 2.526)	-2.61 (± 2.444)	
Change at Week 26 (n= 264, 262, 264)	-3.27 (± 2.578)	-3.52 (± 2.543)	-3.00 (± 2.579)	

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 randomized into a treatment group and presents data for participants according to their randomization 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	427	426	427	
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 4 (n= 330, 318, 329)	-1.84 (± 2.303)	-2.03 (± 2.333)	-1.72 (± 2.303)	
Change at Week 12 (n= 277, 272, 274)	-2.42 (± 2.616)	-2.49 (± 2.533)	-2.16 (± 2.544)	
Change at Week 26 n= 209, 210, 210)	-2.76 (± 2.823)	-2.94 (± 2.576)	-2.47 (± 2.562)	

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	427	426	427	
Units: number of bowel movements				
arithmetic mean (standard deviation)				
Week 4 (n= 392, 381, 401)	3.20 (± 2.090)	3.20 (± 2.236)	3.72 (± 2.100)	
Week 12 (n= 338, 335, 335)	3.12 (± 2.143)	3.09 (± 2.318)	3.44 (± 1.987)	
Week 26 (n= 264, 262, 264)	2.83 (± 2.158)	2.79 (± 2.270)	3.12 (± 1.831)	

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	427	426	427	
Units: incontinence episodes				
arithmetic mean (standard deviation)				
Week 4 (n= 392, 381, 401)	0.74 (± 1.603)	0.72 (± 1.534)	0.93 (± 2.140)	
Week 12 (n= 338, 335, 335)	0.63 (± 1.542)	0.71 (± 1.663)	0.94 (± 3.612)	
Week 26 (n= 264, 262, 264)	0.46 (± 1.298)	0.58 (± 1.358)	0.69 (± 1.500)	

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 is one where the participant reports zero incontinence episodes. The number of incontinence free days for a participant is 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	427	426	427	
Units: days				
arithmetic mean (standard deviation)				
Week 4 (n= 392, 381, 401)	4.83 (± 2.745)	4.95 (± 2.618)	4.63 (± 2.741)	
Week 12 (n= 338, 335, 335)	4.96 (± 2.672)	4.79 (± 2.671)	4.64 (± 2.704)	
Week 26 (n= 264, 262, 264)	4.39 (± 2.465)	4.35 (± 2.449)	4.00 (± 2.539)	

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	427	426	427	
Units: episode				
arithmetic mean (standard deviation)				
Week 4 (n= 392, 381, 401)	1.75 (± 1.840)	1.74 (± 1.879)	2.19 (± 2.082)	
Week 12 (n= 338, 335, 335)	1.55 (± 1.777)	1.60 (± 1.995)	1.81 (± 1.883)	
Week 26 (n= 264, 262, 264)	1.25 (± 1.773)	1.45 (± 2.113)	1.55 (± 1.853)	

Statistical analyses

No statistical analyses for this end point

Secondary: IBS-QoL Total Scores

End point title	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. 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, 8, 12, 18, 26, 36, 44, and 52 (EOT)	

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	427	426	427	
Units: score on a scale				
arithmetic mean (standard deviation)				
Responders at Week 4 (n= 384, 371, 392)	62.37 (± 23.747)	64.34 (± 24.049)	57.13 (± 24.318)	
Responders at Week 8 (n= 354, 354, 360)	66.22 (± 23.919)	67.73 (± 23.421)	59.46 (± 24.323)	
Responders at Week 12 (n= 339, 330, 342)	66.80 (± 24.131)	68.93 (± 23.938)	61.72 (± 25.545)	
Responders at Week 18 (n= 315, 312, 315)	68.75 (± 23.902)	70.05 (± 23.662)	63.60 (± 24.618)	
Responders at Week 26 (n= 288, 291 , 290)	70.74 (± 23.312)	71.34 (± 23.106)	64.83 (± 24.380)	
Responders at Week 36 (n= 277, 272, 278)	70.53 (± 23.043)	72.37 (± 23.246)	66.47 (± 24.034)	
Responders at Week 44 (n= 267, 261, 271)	70.30 (± 24.408)	72.15 (± 24.398)	65.59 (± 25.045)	
Responders at Week 52/EOT (n= 351, 353, 362)	68.85 (± 24.754)	71.02 (± 24.294)	63.93 (± 26.359)	

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, 36, 44, and 52/EOT	

End point values	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	427	426	427	
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 4 (n= 382, 371, 392)	16.49 (± 20.693)	17.86 (± 20.191)	13.25 (± 18.475)	
Change at Week 8 (n= 353, 354 , 360)	19.88 (± 21.855)	21.08 (± 21.347)	15.76 (± 19.398)	
Change at Week 12 (n= 337, 330, 342)	20.26 (± 23.412)	22.76 (± 22.592)	17.76 (± 21.523)	
Change at Week 18 (n= 313, 312, 315)	23.09 (± 23.846)	24.18 (± 23.025)	19.80 (± 22.368)	
Change at Week 26 (n= 288, 291, 290)	25.28 (± 23.679)	25.80 (± 23.998)	20.62 (± 22.306)	
Change at Week 36 (n= 277, 272, 278)	25.37 (± 24.603)	27.18 (± 24.201)	22.64 (± 23.414)	
Change at Week 44 (n= 267, 261, 271)	25.13 (± 24.948)	26.64 (± 25.017)	21.77 (± 23.977)	
Change at Week 52/EOT (n= 349, 353, 362)	23.30 (± 23.959)	25.86 (± 23.854)	20.66 (± 23.956)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 54 weeks

Adverse event reporting additional description:

Safety Analysis Set included participants who were enrolled in the study and received at least one dose of study drug and presents data for participants according to the actual treatment received. The number of participants in the 100-mg eluxadoline group was more than the participants who started this group due to the systematic misallocations.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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Reporting groups

Reporting group title	Eluxadoline 75 mg
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Reporting group description:

Eluxadoline 75 mg tablets, orally, twice daily for up to 52 weeks period.

Reporting group title	Eluxadoline 100 mg
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Reporting group description:

Eluxadoline 100 mg tablets, orally, twice daily for up to 52 weeks period.

Reporting group title	Placebo
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Reporting group description:

Eluxadoline placebo matching tablets, orally, twice daily for up to 52 weeks period.

Serious adverse events	Eluxadoline 75 mg	Eluxadoline 100 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 428 (5.84%)	27 / 479 (5.64%)	16 / 427 (3.75%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid neoplasm			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Liposarcoma			
subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteriosclerosis			

subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Hematoma			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Hypertension			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Hypertensive crisis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontanea			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Asthma			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 428 (0.00%)	2 / 479 (0.42%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conversion disorder			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Depression			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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

Hepatic enzyme increased subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Injury, poisoning and procedural complications			
Ankle fracture subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Procedural complication subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Road traffic accident subjects affected / exposed	1 / 428 (0.23%)	2 / 479 (0.42%)	0 / 427 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Spinal compression fracture subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Subdural hematoma			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Angina pectoris			
subjects affected / exposed	1 / 428 (0.23%)	2 / 479 (0.42%)	0 / 427 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Coronary artery disease			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Myocardial infarction			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Stress cardiomyopathy			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intracranial pressure increased			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Presyncope			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Primary progressive multiple sclerosis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Syncope			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Syncope vasovagal			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Eye disorders			
Papilloedema			
subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 428 (0.23%)	3 / 479 (0.63%)	0 / 427 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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

Colitis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal hemorrhagic			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Hemorrhoids			
subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Irritable bowel syndrome			
subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 428 (0.23%)	1 / 479 (0.21%)	0 / 427 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 428 (0.23%)	2 / 479 (0.42%)	0 / 427 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholecystitis chronic			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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			
Hydronephrosis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Back pain			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Musculoskeletal pain			
subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 428 (0.47%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 428 (0.23%)	1 / 479 (0.21%)	0 / 427 (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
Cellulitis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Diverticulitis			
subjects affected / exposed	2 / 428 (0.47%)	1 / 479 (0.21%)	0 / 427 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Influenza			
subjects affected / exposed	2 / 428 (0.47%)	0 / 479 (0.00%)	0 / 427 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	1 / 428 (0.23%)	0 / 479 (0.00%)	0 / 427 (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
Pneumonia			

subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Rectal abscess			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 428 (0.00%)	1 / 479 (0.21%)	0 / 427 (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
Obesity			
subjects affected / exposed	0 / 428 (0.00%)	0 / 479 (0.00%)	1 / 427 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Eluxadoline 100 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 428 (19.63%)	89 / 479 (18.58%)	47 / 427 (11.01%)
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	27 / 428 (6.31%)	44 / 479 (9.19%)	12 / 427 (2.81%)
occurrences (all)	31	53	12
Nausea			
subjects affected / exposed	34 / 428 (7.94%)	31 / 479 (6.47%)	19 / 427 (4.45%)
occurrences (all)	36	42	21
Vomiting			

subjects affected / exposed occurrences (all)	22 / 428 (5.14%) 22	19 / 479 (3.97%) 21	7 / 427 (1.64%) 8
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	14 / 428 (3.27%) 17	25 / 479 (5.22%) 32	15 / 427 (3.51%) 18

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2012	<ul style="list-style-type: none">• Duration of electronic diary collection from 12 weeks to 26 weeks was changed• Duration of electronic diary notifications for constipation, excess rescue medication usage, and participants compliance from 12 weeks to 26 weeks was changed• Daily assessment of abdominal discomfort to electronic diary collection was added• Clinic visits were scheduled for Weeks 20 and 28 to Weeks 18 and 26, respectively• Exclusion criteria for lactose intolerance and gastrointestinal infection was added• Triglycerides evaluation at Baseline was added and clarified lipase and triglyceride evaluations should be completed for any participant with confirmed or suspected pancreatitis• Clarification for use of rescue medication (loperamide extended from 12 weeks to 26 weeks), prohibited medications (added tramadol to the list), and concomitant medications (extended prohibition of concomitant medications that could interfere with the study from 12 weeks to 26 weeks)
24 August 2012	<ul style="list-style-type: none">• Eligibility criteria was updated and microscopic colitis as an example of an excluded inflammatory bowel disease was added• The pregnancy reporting requirement from the start of the study to the time of the first dose of study drug was changed to be consistent with the inclusion criteria
30 October 2012	<ul style="list-style-type: none">• Eligibility criteria was clarified• Clarification 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• Investigators must re-verify the participants meets all inclusion/exclusion criteria at the time of randomisation• Instructions for participants to take their last dose of study drug the day before the end-of-treatment visit were added• Guidance in the event of elevation in liver enzymes, including the timing of repeat labs and the criteria for withdrawal from the study was added
04 December 2013	<ul style="list-style-type: none">• Clarified that to support a potential Marketing Authorisation Application (MAA) to the European Medicines Agency (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• Clarified that an extraction of data would occur once all participants had completed at least 26 weeks of treatment and at least 100 participants had completed 52 weeks of treatment. The protocol previously specified that an initial extraction of efficacy data would be conducted once all participants completed 12 weeks of treatment and an additional extraction of efficacy and safety data would occur when 100 participants completed 52 weeks of treatment. This change was made to minimize the number of data extractions and to eliminate any extraction prior to completion of all diary data collection in the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported