Clinical trial results:
A Phase 3, Randomized, Placebo-controlled, Multicenter, Double-blind Study to Evaluate the Safety and Efficacy of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome

Summary

EudraCT number	2013-001543-31
Trial protocol	BE DE SE NL ES
Global end of trial date	29 March 2016

Results information

Result version number	v1 (current)
This version publication date	27 January 2018
First version publication date	27 January 2018

Trial information

Trial identification

Sponsor protocol code	LX1606.1-303-CS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02063659
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lexicon Pharmaceuticals, Inc.
Sponsor organisation address	8800 Technology Forest Place, The Woodlands, United States, 77381-1160
Public contact	Pablo Lapuerta, MD, Executive Vice President and Chief Medical Officer, Lexicon Pharmaceuticals, Inc., +1 (908) 360-4774, plapuerta@lexpharma.com
Scientific contact	Pablo Lapuerta, MD, Executive Vice President and Chief Medical Officer, Lexicon Pharmaceuticals, Inc., +1 (908) 360-4774, plapuerta@lexpharma.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 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to evaluate the effect of telotristat etiprate versus placebo on the incidence of treatment-emergent adverse events and on 5-hydroxyindoleacetic acid (5-HIAA) levels.

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	11 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	76
EEA total number of subjects	44

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)	41
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 31 investigative sites in Australia, Belgium, Canada, France, Germany, Israel, Netherlands, Spain, Sweden, United Kingdom, and the United States from 11 Mar 2014 to 29 Mar 2016.

Pre-assignment

Screening details:

Participants with Carcinoid Syndrome not adequately controlled by somatostatin analog (SSA) therapy were randomly assigned in a 1:1:1 ratio to receive placebo, 250 mg or 500 mg telotristat etiprate (LX1606) in the double-blind treatment period and were eligible to receive 500 mg telotristat etiprate in the open-label extension period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Following a 3 to 4-week run-in period, participants were randomized to receive two placebo-matching telotristat eptiprate tablets administered three times daily for 12 weeks, followed by a 36 week open-label extension 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:

After a 3 to 4-week run-in period, participants were randomized to receive two placebo-matching telotristat eptiprate tablets administered three times daily for 12 weeks.

Arm title	250 mg Telotristat Etiprate

Arm description:

Following a 3 to 4-week run-in period, participants were randomized to receive one 250 mg telotristat etiprate tablet and one placebo-matching telotristat etiprate tablet administered three times daily for 12 Weeks, followed by a 36 week open-label extension period.

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

Dosage and administration details:

One placebo-matching telotristat etiprate tablet administered three times daily for 12 Weeks.

Investigational medicinal product name	Telotristat etiprate
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

After a 3 to 4-week run-in period, participants were randomized to receive one telotristat etiprate (250 mg) tablet.

Arm title	500 mg Telotristat Etiprate

Arm description:

Following a 3 to 4-week run-in period, participants were randomized to receive one 250 mg telotristat etiprate tablet and one placebo-matching telotristat etiprate tablet administered three times daily for one week, followed by two 250 mg telotristat etiprate tablets administered three times daily for 11 weeks in the 12 Week double-blind treatment period, followed by a 36 week open-label extension period.

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

Dosage and administration details:

One placebo-matching telotristat etiprate tablet administered three times daily for one week.

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

Dosage and administration details:

After a 3 to 4-week run-in period, participants were randomized to receive one telotristat etiprate (250 mg) tablet administered three times daily for one week, followed by two telotristat etiprate (250 mg) tablets administered three times daily for 11 weeks.

Number of subjects in period 1	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate
Started	26	25	25
Completed	24	22	22
Not completed	2	3	3
Physician decision	1	-	-
Adverse event, non-fatal	1	2	-
Withdrawal of consent	-	1	3

Period 2

Period 2 title	Open-Label Extension Period (OLE)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Telotristat Etiprate Open-Label Extension

Arm description:

Patients previously assigned to 250 mg or 500 mg three times daily of telotristat etiprate were adminstered two 250 mg telotristat etiprate tablets three times daily in a 36 week open-label extension (OLE) period. Patients previously assigned to placebo were administered one 250 mg telotristat etiprate tablet plus one placebo-matching tablet three times daily for one week, followed by two 250 mg telotristat etiprate tablets three times daily for 35 weeks.

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

Dosage and administration details:

One placebo-matching telotristat etiprate tablet administered three times daily for one week.

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

Dosage and administration details:

One telotristat etiprate (250) mg administered three times daily for one week, followed by two 250 mg telotristat etiprate tablets three times daily in a 36-week open-label extension period.

Number of subjects in period 2[1]	Telotristat Etiprate Open-Label Extension
Started	67
Completed	47
Not completed	20
Physician decision	1
Adverse event, non-fatal	7
Withdrawal of consent	9
Reason not specified	2
Lack of efficacy	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not all participants who participated in the double-blind treatment period participated in the open-label extension period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Following a 3 to 4-week run-in period, participants were randomized to receive two placebo-matching telotristat eptiprate tablets administered three times daily for 12 weeks, followed by a 36 week open-label extension period.	
Reporting group title	250 mg Telotristat Etiprate
Reporting group description:	
Following a 3 to 4-week run-in period, participants were randomized to receive one 250 mg telotristat etiprate tablet and one placebo-matching telotristat etiprate tablet administered three times daily for 12 Weeks, followed by a 36 week open-label extension period.	
Reporting group title	500 mg Telotristat Etiprate
Reporting group description:	
Following a 3 to 4-week run-in period, participants were randomized to receive one 250 mg telotristat etiprate tablet and one placebo-matching telotristat etiprate tablet administered three times daily for one week, followed by two 250 mg telotristat etiprate tablets administered three times daily for 11 weeks in the 12 Week double-blind treatment period, followed by a 36 week open-label extension period.	

Reporting group values	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate
Number of subjects	26	25	25
Age categorical Units: Subjects			
<65 years	12	14	15
≥65 years	14	11	10
Age continuous Units: years			
arithmetic mean	62.2	63.6	62.7
standard deviation	± 10.32	± 12.62	± 11.97
Gender categorical Units: Subjects			
Female	13	11	10
Male	13	14	15
Ethnicity			
Ethnicity data is missing for 1 subject.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	25	25	25
No data	1	0	0
Race			
Race data is not available for 1 subject.			
Units: Subjects			
White	25	25	23
Black or African American	0	0	1
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	1

No data	1	0	0
Somatostatin Analog (SSA) Therapy Schedule at Study Entry			
Patients who were on a 2-week SSA therapy or receiving SSA therapy via a subcutaneous continuous infusion pump are included in the "4-week" category.			
Units: Subjects			
3-Week	6	7	9
4-Week	20	15	11
Not on SSA	0	3	5
SSA Therapy Name at Study Entry Units: Subjects			
Octreotide	12	17	16
Lanreotide	14	5	3
Unknown	0	0	1
Not applicable	0	3	5
Childbearing Potential Units: Subjects			
Yes	2	4	1
No	11	7	9
Not Applicable	13	14	15
Urinary 5-HIAA at Randomization			
ULN=upper limit of normal.			
Units: Subjects			
≤ULN	9	5	8
>ULN	17	18	17
Unknown	0	2	0
Country Units: Subjects			
USA	4	5	7
Australia	4	0	3
Belgium	1	2	2
Canada	0	1	1
France	1	0	0
Germany	3	2	2
Israel	2	3	2
Netherlands	3	2	1
Spain	1	5	4
Sweden	0	2	0
United Kingdom	7	3	3
Region			
North America includes USA and Canada; Europe includes Belgium, France, Germany, Netherlands, Spain, Sweden, and United Kingdom; Rest of the World includes Australia and Israel.			
Units: Subjects			
North America	4	6	8
Europe	16	16	12
Rest of the World	6	3	5
Weight Units: kg			
arithmetic mean	76.38	74.74	76.69
standard deviation	± 16.959	± 17.839	± 26.188
Height Units: cm			

arithmetic mean	169.48	169.74	170.08
standard deviation	± 9.765	± 10.025	± 8.525
Baseline BMI			
BMI=body mass index.			
Units: kg/m2			
arithmetic mean	26.28	25.96	26.21
standard deviation	± 4.364	± 5.258	± 9.213

Reporting group values	Total		
Number of subjects	76		
Age categorical			
Units: Subjects			
<65 years	41		
≥65 years	35		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	34		
Male	42		
Ethnicity			
Ethnicity data is missing for 1 subject.			
Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	75		
No data	1		
Race			
Race data is not available for 1 subject.			
Units: Subjects			
White	73		
Black or African American	1		
Asian	0		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	0		
Other	1		
No data	1		
Somatostatin Analog (SSA) Therapy Schedule at Study Entry			
Patients who were on a 2-week SSA therapy or receiving SSA therapy via a subcutaneous continuous infusion pump are included in the "4-week" category.			
Units: Subjects			
3-Week	22		
4-Week	46		
Not on SSA	8		
SSA Therapy Name at Study Entry			
Units: Subjects			
Octreotide	45		
Lanreotide	22		
Unknown	1		

Not applicable	8		
Childbearing Potential Units: Subjects			
Yes	7		
No	27		
Not Applicable	42		
Urinary 5-HIAA at Randomization			
ULN=upper limit of normal.			
Units: Subjects			
≤ULN	22		
>ULN	52		
Unknown	2		
Country Units: Subjects			
USA	16		
Australia	7		
Belgium	5		
Canada	2		
France	1		
Germany	7		
Israel	7		
Netherlands	6		
Spain	10		
Sweden	2		
United Kingdom	13		
Region			
North America includes USA and Canada; Europe includes Belgium, France, Germany, Netherlands, Spain, Sweden, and United Kingdom; Rest of the World includes Australia and Israel.			
Units: Subjects			
North America	18		
Europe	44		
Rest of the World	14		
Weight Units: kg arithmetic mean standard deviation	 -		
Height Units: cm arithmetic mean standard deviation	 -		
Baseline BMI			
BMI=body mass index.			
Units: kg/m2 arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Following a 3 to 4-week run-in period, participants were randomized to receive two placebo-matching telotristat eptiprate tablets administered three times daily for 12 weeks, followed by a 36 week open-label extension period.	
Reporting group title	250 mg Telotristat Etiprate
Reporting group description:	
Following a 3 to 4-week run-in period, participants were randomized to receive one 250 mg telotristat etiprate tablet and one placebo-matching telotristat etiprate tablet administered three times daily for 12 Weeks, followed by a 36 week open-label extension period.	
Reporting group title	500 mg Telotristat Etiprate
Reporting group description:	
Following a 3 to 4-week run-in period, participants were randomized to receive one 250 mg telotristat etiprate tablet and one placebo-matching telotristat etiprate tablet administered three times daily for one week, followed by two 250 mg telotristat etiprate tablets administered three times daily for 11 weeks in the 12 Week double-blind treatment period, followed by a 36 week open-label extension period.	
Reporting group title	Telotristat Etiprate Open-Label Extension
Reporting group description:	
Patients previously assigned to 250 mg or 500 mg three times daily of telotristat etiprate were adminstered two 250 mg telotristat etiprate tablets three times daily in a 36 week open-label extension (OLE) period. Patients previously assigned to placebo were administered one 250 mg telotristat etiprate tablet plus one placebo-matching tablet three times daily for one week, followed by two 250 mg telotristat etiprate tablets three times daily for 35 weeks.	

Primary: Number of Participants with Treatment-Emergent Adverse Events (TEAEs) in the Double-Blind Period

End point title	Number of Participants with Treatment-Emergent Adverse Events (TEAEs) in the Double-Blind Period[1]
End point description:	
An adverse event (AE) was defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A TEAE was an AE reported after the first dose of randomized treatment on Day 1. Safety population, defined as all participants who received at least one dose of study drug, was used for analysis.	
End point type	Primary
End point timeframe:	
First dose of study drug to within 30 days of last dose of study drug in the Double-Blind Period (Up to 17.1 Weeks)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is reported for this endpoint.

End point values	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	25	25	
Units: participants	21	25	22	

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change from Baseline in Urinary 5-hydroxyindoleacetic Acid (u5-HIAA) Levels

End point title	Percent Change from Baseline in Urinary 5-hydroxyindoleacetic Acid (u5-HIAA) Levels

End point description:

u5-HIAA is a standard test used in clinical practice to assess neuroendocrine tumor (NET) activity and is collected as a 24-hour urine specimen. A negative change from Baseline indicates improvement. Participants from the Intent-to-treat population, all randomized participants, with data available for this endpoint were included in the analysis.

End point type	Primary

End point timeframe:

Baseline and 12 Weeks

End point values	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	17	19	
Units: mg/24 hours				
arithmetic mean (standard deviation)	97.721 (± 397.0107)	-33.164 (± 58.4754)	-76.466 (± 17.3714)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The primary analysis used a blocked 2-sample Wilcoxon rank sum statistic stratified by the u5-HIAA at randomization.
Mean difference is calculated as LX1606-Placebo.

Comparison groups	Placebo v 250 mg Telotristat Etiprate
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank sum
Parameter estimate	Hodges-Lehman estimator of difference
Point estimate	-53.955

Confidence interval	
level	95 %
sides	2-sided
lower limit	-84.955
upper limit	-25.119

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The primary analysis used a blocked 2-sample Wilcoxon rank sum statistic stratified by the u5-HIAA at randomization.
Mean difference is calculated as LX1606-Placebo.

Comparison groups	Placebo v 500 mg Telotristat Etiprate
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank sum
Parameter estimate	Hodges-Lehman estimator of difference
Point estimate	-89.662
Confidence interval	
level	95 %
sides	2-sided
lower limit	-113.104
upper limit	-63.863

Primary: Number of Participants with TEAEs in the Open-Label Extension Period

End point title	Number of Participants with TEAEs in the Open-Label Extension Period[2]

End point description:

End point type	Primary

End point timeframe:

First dose of study drug to within 30 days of last dose of study drug in the Open-Label Extension Period (Up to 52.6 Weeks)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is reported for this endpoint.

End point values	Telotristat Etiprate Open-Label Extension			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: participants	61			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Number of Bowel Movements (BMs) per Day Averaged over 12 Weeks

End point title	Change from Baseline in the Number of Bowel Movements (BMs) per Day Averaged over 12 Weeks

End point description:

Participants recorded the number of bowel movements per day in a daily diary. The total number of BMs per day were averaged over the 12-week period. A negative change from Baseline indicates improvement.
Participants from the Intent-to-treat population, all randomized participants, with data available for this endpoint were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and 12 Weeks

End point values	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	25	
Units: counts/day				
arithmetic mean (standard deviation)	0.05 (± 0.3263)	-0.452 (± 0.694)	-0.595 (± 0.724)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Stool Form/Consistency Averaged Across all Time-Points

End point title	Change from Baseline in Stool Form/Consistency Averaged Across all Time-Points

End point description:

Participants assessed stool form/consistency of a BM using the Bristol Stool Form Scale where: 1=hard lumps to 7=watery liquid. The daily scores were averaged over the 12-week period. A negative change indicates improvement.
Participants from the Intent-to-treat population, all randomized participants, with data available for this endpoint were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and 12 Weeks

End point values	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	25	
Units: score on a scale				
arithmetic mean (standard deviation)	0.006 (± 0.4127)	-0.196 (± 0.7012)	-0.597 (± 0.8605)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Number of Daily Cutaneous Flushing Episodes Averaged Across all Time-Points

End point title	Change from Baseline in the Number of Daily Cutaneous Flushing Episodes Averaged Across all Time-Points

End point description:

Participants recorded the number daily flushing episodes per day in a daily diary. The total number of flushing episodes per day were averaged over the 12-week period. A negative change from Baseline indicates improvement.
Participants from the Intent-to-treat population, all randomized participants, with data available for this endpoint were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and 12 Weeks

End point values	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	25	
Units: counts/day				
arithmetic mean (standard deviation)	-0.333 (± 1.2203)	-0.061 (± 0.9754)	0.114 (± 2.0992)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Abdominal Pain Averaged Across all Time-Points

End point title	Change from Baseline in Abdominal Pain Averaged Across all Time-Points

End point description:

Participants recorded abdominal pain in a daily diary. Participants evaluated the level of any abdominal pain using an 11-point numeric rating scale, where: 0=no pain to 10=worst pain ever experienced. The average daily abdominal pain was averaged over the 12-week period. A negative change from Baseline indicates improvement.

Participants from the Intent-to-treat population, all randomized participants, with data available for this endpoint were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and 12 Weeks

End point values	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	25	
Units: score on a scale				
arithmetic mean (standard deviation)	-0.063 (± 0.7823)	-0.234 (± 0.9697)	0.025 (± 0.7744)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Frequency of Rescue Short-acting, Somatostatin Analog (SSA) used to Treat Carcinoid Syndrome Symptoms Averaged Across all Time-Points

End point title	Change in the Frequency of Rescue Short-acting, Somatostatin Analog (SSA) used to Treat Carcinoid Syndrome Symptoms Averaged Across all Time-Points

End point description:

The frequency (the number of times) the participant used rescue with SSA to control symptoms was recorded in a daily diary. The daily number of rescue treatments with SSA was averaged over the 12-week period. A negative change from Baseline (less use of SSA) indicates improvement.
Participants from the Intent-to-treat population, all randomized participants, with data available for this endpoint were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and 12 Weeks

End point values	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	25	
Units: counts/day				
arithmetic mean (standard deviation)	-0.013 (± 0.1359)	-0.065 (± 0.3542)	0.006 (± 0.103)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Number of Daily BMs Averaged over the 12-week DBT Period, among Participants who were not Receiving SSA Therapy at Baseline

End point title	Change from Baseline in the Number of Daily BMs Averaged over the 12- week DBT Period, among Participants who were not Receiving SSA Therapy at Baseline[3]

End point description:

Participants recorded the number of bowel movements per day in a daily diary. The total number of BMs per day were averaged over the 12-week period. A negative change from Baseline indicates improvement.
Participants from the Intent-to-treat population, all randomized participants, with data available for this endpoint were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and 12 Weeks

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The Placebo arm is not included because all participants in the Placebo arm were receiving SSA therapy at Baseline.

End point values	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: counts/day				
arithmetic mean (standard deviation)	-0.906 (± 0.5925)	-0.98 (± 1.154)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug to within 30 days of last dose of study drug (Up to 77.7 Weeks)

Adverse event reporting additional description:

Data for the double-blind treatment period and the open-label extension period were analyzed separately. In the Non-Serious Adverse Event section, a result of "0" for a preferred term means that there are no participants in that arm above the 5% threshold.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

After a 3 to 4-week run-in period, participants were randomized to receive two placebo-matching telotristat eptiprate tablets administered three times daily for 12 weeks.

Reporting group title	250 mg Telotristat Etiprate

Reporting group description:

Following a 3 to 4-week run-in period, participants were randomized to receive one 250 mg telotristat etiprate tablet and one placebo-matching telotristat etiprate tablet administered three times daily for 12 Weeks.

Reporting group title	500 mg Telotristat Etiprate

Reporting group description:

Following a 3 to 4-week run-in period, participants were randomized to receive one 250 mg telotristat etiprate tablet and one placebo-matching telotristat etiprate tablet administered three times daily for one week, followed by two 250 mg telotristat etiprate tablets administered three times daily for 11 weeks.

Reporting group title	Telotristat Etiprate Open-Label Extension

Reporting group description:

Patients previously assigned to 250 mg or 500 mg three times daily of telotristat etiprate were adminstered two 250 mg telotristat etiprate tablets three times daily in a 36 week open-label extension (OLE) period. Patients previously assigned to placebo were administered one 250 mg telotristat etiprate tablet plus one placebo-matching tablet three times daily for one week, followed by two 250 mg telotristat etiprate tablets three times daily for 35 weeks.

Serious adverse events	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 26 (19.23%)	1 / 25 (4.00%)	3 / 25 (12.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 26 (3.85%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic neoplasm			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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			
Diagnostic procedure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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			
Femur fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Post procedural bile leak			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Wound secretion			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Congenital, familial and genetic disorders			
Atrial septal defect			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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			
Mitral valve incompetence			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	0 / 25 (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
Acute myocardial infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Surgical and medical procedures			
Urethral stent insertion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	0 / 25 (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
Hepatectomy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Small intestinal resection			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Antibiotic prophylaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Therapeutic embolisation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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			
Transient ischaemic attack			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	0 / 25 (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			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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			
Ascites			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Ileus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Lower gastrointestinal haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Small intestinal haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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

Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	0 / 25 (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
Sleep apnoea syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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			
Escherichia bacteraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Herpes zoster ophthalmic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (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

Serious adverse events	Telotristat Etiprate Open-Label Extension		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 67 (25.37%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic neoplasm			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine tumour			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Diagnostic procedure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural bile leak			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Wound secretion				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Atrial septal defect				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Mitral valve incompetence				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 67 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Urethral stent insertion				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatectomy				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal resection				

alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Antibiotic prophylaxis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Therapeutic embolisation				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Transient ischaemic attack				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 67 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
alternative assessment type: Non-systematic				
subjects affected / exposed	3 / 67 (4.48%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Ascites				

alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
alternative assessment type: Non-systematic				
subjects affected / exposed	3 / 67 (4.48%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hiatus hernia				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal haemorrhage				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sleep apnoea syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Escherichia bacteraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster ophthalmic			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 26 (80.77%)	25 / 25 (100.00%)	22 / 25 (88.00%)
Investigations			
Gamma-glutamyltransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 26 (7.69%)	3 / 25 (12.00%)	0 / 25 (0.00%)
occurrences (all)	2	3	0
Nervous system disorders			
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 26 (11.54%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	3	0	2
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Presyncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 26 (7.69%)	3 / 25 (12.00%)	2 / 25 (8.00%)
occurrences (all)	2	3	2
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	2	1	0
Oedema peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	1 / 25 (4.00%)
occurrences (all)	0	3	1
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	3 / 25 (12.00%)	0 / 25 (0.00%)
occurrences (all)	0	5	0
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 26 (15.38%)	8 / 25 (32.00%)	1 / 25 (4.00%)
occurrences (all)	5	11	1
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 26 (19.23%)	4 / 25 (16.00%)	2 / 25 (8.00%)
occurrences (all)	5	4	2
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 26 (15.38%)	3 / 25 (12.00%)	2 / 25 (8.00%)
occurrences (all)	6	4	2
Constipation			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 26 (3.85%)	4 / 25 (16.00%)	3 / 25 (12.00%)
occurrences (all)	1	5	3
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 26 (11.54%)	1 / 25 (4.00%)	2 / 25 (8.00%)
occurrences (all)	3	2	2
Abdominal distension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	3 / 25 (12.00%)	1 / 25 (4.00%)
occurrences (all)	0	3	1
Dyspepsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 26 (7.69%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	2	2	0
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	2	1	0
Oropharyngeal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Night sweats			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	1 / 25 (4.00%)
occurrences (all)	0	2	1
Psychiatric disorders			
Depressed mood			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	3	1	0
Depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	2	1	1
Musculoskeletal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	3 / 25 (12.00%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Influenza			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2

Non-serious adverse events	Telotristat Etiprate Open-Label Extension		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 67 (91.04%)		
Investigations			
Gamma-glutamyltransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
Weight decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Vascular disorders			
Flushing			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	12		
Nervous system disorders			
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences (all)	0		
Headache			

alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	6		
Presyncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	7		
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	7		
Oedema peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	13		
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 67 (17.91%)		
occurrences (all)	15		
Diarrhoea			

alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	12		
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 67 (20.90%)		
occurrences (all)	20		
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	9		
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	6		
Abdominal distension			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Dyspepsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences (all)	0		
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
Oropharyngeal pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 67 (0.00%)		
occurrences (all)	0		
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Night sweats			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depressed mood			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences (all)	0		
Depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	9		
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences (all)	0		
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Arthralgia			
alternative assessment type: Non-systematic			

subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Infections and infestations			
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences (all)	0		
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 67 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Decreased appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2013	Amendment 1: 1. Clarified the objectives of the study 2. Removed pharmacokinetic (PK) sampling 3. Modified study design to include dose titrations at Week 1 of the Double-blind Treatment (DBT) Period and at Week 13 of the Open-label Extension (OLE) Period to improve tolerability during the study period transitions 4. Revised study population to clarify eligible patients 5. Revised Inclusion Criterion 4 to clarify stool form/consistency entry requirement 6. Added exclusion criterion to require that patients provide a stool sample for examination for enteric pathogens, pathogenic ova or parasites, or clostridium difficile 7. Removed exclusion criterion 19 8. Added discontinuation for pregnancy to criteria for stopping treatment/study withdrawal 9. Revised criteria for termination of the study to reflect that the data safety monitoring board (DSMB) may have terminated the study if warranted 10. Revised treatment compliance to include criteria for defining a missed dose 11. Added stool sampling to the screening laboratory assessments 12. Revised serious adverse event (SAE) reporting to include an email address in case of fax failure and to remove a duplicate email address for sites outside of North America 13. Revised safety reporting of pregnancy to indicate that any patient who became pregnant during the study was to be discontinued from study drug immediately and followed through delivery or termination of the pregnancy 14. Revised efficacy analyses to reflect changes from baseline in bowel movements (BMs) for the regression models being used
01 February 2014	Amendment 2: 1. Revised wording of the primary endpoint to correctly reflect that planned analysis was to evaluate individual dose groups versus placebo for a percent change in u5-HIAA from an initial baseline value and incidence of TEAEs 2. Increased the number of study sites anticipated to participate in the study 3. Clarified entry criteria and data disposition of patients who previously failed screening for LX1606.1-301-CS 4. Provided updated information on new, ongoing, and completed studies 5. Removed the requirements of capturing individual missed doses 6. Included Depression and Sleep Assessments at each visit during the DBT Period 7. Included contact information for reporting of SAEs in Israel and Brazil 8. Updated study management to reflect that current guidance documents were to be used to conduct the study 9. Updated statistical methodology to support protocol revisions
14 January 2015	Amendment 3: 1. Modified the eligibility criteria in order to remove the QTcF exclusion criterion 2. Clarified that patients must have been taking a stable dose of SSA therapy if receiving therapy at study entry 3. Clarified the allocation of tablets and doses given during the blinded transition period to the OLE Period 4. Clarified Adverse Events of Special Interest (AESIs) 5. Clarified the manner in which responses to questions designed to detect early signs of depression were to be managed 6. Clarified definitions of AEs not related to study drug 7. Included a fifth classification for AEs: "unlikely related" 8. Further defined the criteria for reporting hospitalization as a SAE 9. Further defined how the study was to be reported

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

During the open-label extension there was no placebo control, so safety results should be interpreted with caution.

Notes: