



Clinical trial results:

A Phase 3, Randomized, Placebo-controlled, Parallel-group, Multicenter, Double-blind Study to Evaluate the Efficacy and Safety of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome not Adequately Controlled by Somatostatin Analog (SSA) Therapy

Summary

EudraCT number	2012-003460-47
Trial protocol	GB DE NL ES IT BE FR
Global end of trial date	21 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	LX1606-301-CS
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01677910
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	21 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to confirm that at least 1 or more treatment groups of telotristat ethyl compared with placebo was effective in reducing the number of BMs/day from Baseline averaged over the 12-week DBT Period of the study in patients not adequately controlled by current SSA therapy.

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	08 January 2013
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: 6
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 38
Worldwide total number of subjects	136
EEA total number of subjects	83

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	73
From 65 to 84 years	62
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 48 investigative sites in Australia, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Spain, Sweden, United Kingdom, and the United States from 08 January 2013 to 21 March 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 36 week open-label extension period.

Pre-assignment period milestones

Number of subjects started	136
Number of subjects completed	135

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Subject Randomized twice: 1
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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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Following a 3 to 4-week run-in period on stable-dose SSA therapy (octreotide or lanreotide) participants were randomized to receive two placebo-matching telotristat etiprate tablets administered three times daily for 12 weeks in the double-blind treatment period, followed by a 36 week open-label extension period.

Arm type	Placebo
Investigational medicinal product name	placebo-matching telotristat etiprate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

placebo-matching telotristat etiprate tablet(s) administered three times daily.

Arm title	250 mg Telotristat Etiprate
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Arm description:

Following a 3 to 4-week run-in period on stable-dose somatostatin analog (SSA) therapy (octreotide or lanreotide) participants were randomized to receive one 250 mg telotristat etiprate tablet plus one placebo-matching telotristat etiprate tablet administered three times daily for 12 Weeks in the double-blind treatment period, followed by a 36 week open-label extension period.

Arm type	Experimental
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Investigational medicinal product name	placebo-matching telotristat etiprate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: placebo-matching telotristat etiprate tablet(s) administered three times daily.	
Investigational medicinal product name	telotristat etiprate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: telotristat etiprate tablet(s) administered 3 times daily for 12 weeks	
Arm title	500 mg Telotristat Etiprate
Arm description: Following a 3 to 4-week run-in period on stable-dose SSA therapy (octreotide or lanreotide) participants were randomized to receive, one telotristat etiprate 250 mg plus one placebo-matching telotristat etiprate tablet administered 3 times daily for 1 week, followed by two telotristat etiprate (250 mg) tablets administered three times daily for 11 weeks in the double-blind treatment period, followed by a 36 week open-label extension period.	
Arm type	Experimental
Investigational medicinal product name	telotristat etiprate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: telotristat etiprate tablet(s) administered 3 times daily for 12 weeks	
Investigational medicinal product name	placebo-matching telotristat etiprate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: placebo-matching telotristat etiprate tablet(s) administered three times daily.	

Number of subjects in period 1^[1]	Placebo	250 mg Telotristat Etiprate	500 mg Telotristat Etiprate
Started	45	45	45
Completed	38	42	38
Not completed	7	3	7
Physician decision	-	-	1
Adverse event, non-fatal	6	2	3
Other	-	1	-
Withdrawal of consent	1	-	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One patient was randomized twice and is not included in the baseline period.

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
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Arm description:

Patients previously assigned to 250 mg or 500 mg three times daily of telotristat etiprate were administered 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	telotristat etiprate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

telotristat etiprate tablet(s) administered 3 times daily.

Investigational medicinal product name	placebo-matching telotristat etiprate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

placebo-matching telotristat etiprate tablet(s) administered three times daily.

Number of subjects in period 2^[2]	Telotristat Etiprate Open-Label Extension
Started	115
Completed	79
Not completed	36
Physician decision	4
Adverse event, non-fatal	15
Withdrawal of consent	9
Lost to follow-up	1
Lack of efficacy	5
Other not specified	2

Notes:

[2] - 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 subjects who participated in the double-blind treatment period participated in the open-label extension.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Following a 3 to 4-week run-in period on stable-dose SSA therapy (octreotide or lanreotide) participants were randomized to receive two placebo-matching telotristat etiprate tablets administered three times daily for 12 weeks in the double-blind treatment period, 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 on stable-dose somatostatin analog (SSA) therapy (octreotide or lanreotide) participants were randomized to receive one 250 mg telotristat etiprate tablet plus one placebo-matching telotristat etiprate tablet administered three times daily for 12 Weeks in the double-blind treatment period, 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 on stable-dose SSA therapy (octreotide or lanreotide) participants were randomized to receive, one telotristat etiprate 250 mg plus one placebo-matching telotristat etiprate tablet administered 3 times daily for 1 week, followed by two telotristat etiprate (250 mg) tablets administered three times daily for 11 weeks in the 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	45	45	45
Age categorical			
Units: Subjects			
<65 years	25	26	22
≥65 years	20	19	23
Age continuous			
Units: years			
arithmetic mean	63.3	62.4	64.9
standard deviation	± 8.67	± 9.12	± 9.06
Gender categorical			
Units: Subjects			
Female	21	24	20
Male	24	21	25
Ethnicity			
Ethnicity data was not provided for 1 participant in France.			
Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	45	44	44
No data	0	1	0
Race			
Race data was not provided for 11 subjects in France.			
Units: Subjects			
White	40	41	40
Black or African American	1	0	0
Asian	0	0	0
American Indian or Alaska Native	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0

Other	0	0	1
No data	3	4	4
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	11	11	17
4-Week	34	34	28
SSA Therapy Name at Study Entry			
Units: Subjects			
Octreotide	30	40	33
Lanreotide	15	5	12
Childbearing Potential			
Units: Subjects			
Yes	3	0	0
No	18	24	20
Not Applicable	24	21	25
Urinary 5-HIAA at Randomization			
ULN=upper limit of normal			
Units: Subjects			
≤ULN	12	12	12
>ULN	26	26	26
Unknown	7	7	7
Country			
Units: Subjects			
USA	12	13	12
Australia	1	2	3
Belgium	1	0	0
Canada	3	2	2
France	3	4	4
Germany	5	8	6
Israel	2	0	0
Italy	1	4	3
Netherlands	2	3	3
Spain	4	3	1
Sweden	3	3	3
United Kingdom	8	3	8
Region			
North America includes USA and Canada; Europe includes Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, and United Kingdom; Rest of the World includes Australia and Israel.			
Units: Subjects			
North America	15	15	14
Europe	27	28	28
Rest of the World	3	2	3
Weight			
Weight data was available for 131 subjects; N=43 subjects in the Placebo arm, N=44 subjects in the 250 mg telotristat etiprate arm and N=44 subjects in the 500 mg telotristat etiprate arm.			
Units: kg			
arithmetic mean	70.87	70.05	73.44
standard deviation	± 13.94	± 14.832	± 19.971
Height			

Height data was available for 120 subjects; N=39 subjects in the Placebo arm, N=41 subjects in the 250 mg Telotristat Etiprate arm and N=40 subjects in the 500 mg Telotristat Etiprate arm.			
Units: cm			
arithmetic mean	168.8	169.32	169.93
standard deviation	± 10.707	± 9.607	± 10.436
Baseline BMI			
Body Mass Index (BMI) data was available for 118 subjects; N=38 subjects in the Placebo arm, N=41 subjects in the 250 mg Telotristat Etiprate arm and N=39 subjects in the 500 mg Telotristat Etiprate arm.			
Units: kg/m ²			
arithmetic mean	25.13	24.26	25.24
standard deviation	± 4.79	± 4.702	± 5.352

Reporting group values	Total		
Number of subjects	135		
Age categorical			
Units: Subjects			
<65 years	73		
≥65 years	62		
Age continuous			
Units: years			
arithmetic mean	-		
standard deviation			
Gender categorical			
Units: Subjects			
Female	65		
Male	70		
Ethnicity			
Ethnicity data was not provided for 1 participant in France.			
Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	133		
No data	1		
Race			
Race data was not provided for 11 subjects in France.			
Units: Subjects			
White	121		
Black or African American	1		
Asian	0		
American Indian or Alaska Native	1		
Native Hawaiian or Other Pacific Islander	0		
Other	1		
No data	11		
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	39		
4-Week	96		
SSA Therapy Name at Study Entry			

Units: Subjects			
Octreotide	103		
Lanreotide	32		
Childbearing Potential			
Units: Subjects			
Yes	3		
No	62		
Not Applicable	70		
Urinary 5-HIAA at Randomization			
ULN=upper limit of normal			
Units: Subjects			
≤ULN	36		
>ULN	78		
Unknown	21		
Country			
Units: Subjects			
USA	37		
Australia	6		
Belgium	1		
Canada	7		
France	11		
Germany	19		
Israel	2		
Italy	8		
Netherlands	8		
Spain	8		
Sweden	9		
United Kingdom	19		
Region			
North America includes USA and Canada; Europe includes Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, and United Kingdom; Rest of the World includes Australia and Israel.			
Units: Subjects			
North America	44		
Europe	83		
Rest of the World	8		
Weight			
Weight data was available for 131 subjects; N=43 subjects in the Placebo arm, N=44 subjects in the 250 mg telotristat etiprate arm and N=44 subjects in the 500 mg telotristat etiprate arm.			
Units: kg			
arithmetic mean			
standard deviation	-		
Height			
Height data was available for 120 subjects; N=39 subjects in the Placebo arm, N=41 subjects in the 250 mg Telotristat Etiprate arm and N=40 subjects in the 500 mg Telotristat Etiprate arm.			
Units: cm			
arithmetic mean			
standard deviation	-		
Baseline BMI			
Body Mass Index (BMI) data was available for 118 subjects; N=38 subjects in the Placebo arm, N=41 subjects in the 250 mg Telotristat Etiprate arm and N=39 subjects in the 500 mg Telotristat Etiprate arm.			
Units: kg/m ²			
arithmetic mean			

standard deviation	-		
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Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Population includes all participants who received any fraction of a dose of study drug during the study.

Reporting group values	Safety Population		
Number of subjects	135		
Age categorical Units: Subjects			
<65 years			
≥65 years			
Age continuous Units: years arithmetic mean standard deviation	63.5 ± 8.94		
Gender categorical Units: Subjects			
Female	65		
Male	70		
Ethnicity			
Ethnicity data was not provided for 1 participant in France.			
Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	133		
No data	1		
Race			
Race data was not provided for 11 subjects in France.			
Units: Subjects			
White	121		
Black or African American	1		
Asian	0		
American Indian or Alaska Native	1		
Native Hawaiian or Other Pacific Islander	0		
Other	1		
No data	11		
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	39		
4-Week	96		
SSA Therapy Name at Study Entry			

Units: Subjects			
Octreotide	103		
Lanreotide	32		
Childbearing Potential			
Units: Subjects			
Yes	3		
No	62		
Not Applicable	70		
Urinary 5-HIAA at Randomization			
ULN=upper limit of normal			
Units: Subjects			
≤ULN	36		
>ULN	78		
Unknown	21		
Country			
Units: Subjects			
USA	37		
Australia	6		
Belgium	1		
Canada	7		
France	11		
Germany	19		
Israel	2		
Italy	8		
Netherlands	8		
Spain	8		
Sweden	9		
United Kingdom	19		
Region			
North America includes USA and Canada; Europe includes Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, and United Kingdom; Rest of the World includes Australia and Israel.			
Units: Subjects			
North America	44		
Europe	83		
Rest of the World	8		
Weight			
Weight data was available for 131 subjects; N=43 subjects in the Placebo arm, N=44 subjects in the 250 mg telotristat etiprate arm and N=44 subjects in the 500 mg telotristat etiprate arm.			
Units: kg			
arithmetic mean	71.46		
standard deviation	± 16.419		
Height			
Height data was available for 120 subjects; N=39 subjects in the Placebo arm, N=41 subjects in the 250 mg Telotristat Etiprate arm and N=40 subjects in the 500 mg Telotristat Etiprate arm.			
Units: cm			
arithmetic mean	169.35		
standard deviation	± 10.175		
Baseline BMI			
Body Mass Index (BMI) data was available for 118 subjects; N=38 subjects in the Placebo arm, N=41 subjects in the 250 mg Telotristat Etiprate arm and N=39 subjects in the 500 mg Telotristat Etiprate arm.			
Units: kg/m ²			
arithmetic mean	24.87		

standard deviation	± 4.931		
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End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Following a 3 to 4-week run-in period on stable-dose SSA therapy (octreotide or lanreotide) participants were randomized to receive two placebo-matching telotristat etiprate tablets administered three times daily for 12 weeks in the double-blind treatment period, 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 on stable-dose somatostatin analog (SSA) therapy (octreotide or lanreotide) participants were randomized to receive one 250 mg telotristat etiprate tablet plus one placebo-matching telotristat etiprate tablet administered three times daily for 12 Weeks in the double-blind treatment period, 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 on stable-dose SSA therapy (octreotide or lanreotide) participants were randomized to receive, one telotristat etiprate 250 mg plus one placebo-matching telotristat etiprate tablet administered 3 times daily for 1 week, followed by two telotristat etiprate (250 mg) tablets administered three times daily for 11 weeks in the 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 administered 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.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Population includes all participants who received any fraction of a dose of study drug during the study.	

Primary: 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 were included in the analyses.	
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	45	45	45	
Units: counts/day				
arithmetic mean (standard deviation)	-0.623 (\pm 0.8275)	-1.433 (\pm 1.3652)	-1.455 (\pm 1.3098)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Primary analysis used a blocked 2-sample Wilcoxon rank sum statistic stratified by the urinary 5-HIAA stratification at randomization.	
Mean difference is calculated as LX1606-Placebo	
Comparison groups	250 mg Telotristat Etiprate v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank sum
Parameter estimate	Mean difference (net)
Point estimate	-0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.283
upper limit	0.337

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Primary analysis used a blocked 2-sample Wilcoxon rank sum statistic stratified by the urinary 5-HIAA stratification at randomization.	
Mean difference is calculated as LX1606-Placebo	
Comparison groups	Placebo v 500 mg Telotristat Etiprate
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank sum
Parameter estimate	Mean difference (net)
Point estimate	-0.833
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.292
upper limit	-0.374

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]
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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 subjects who received at least one dose of study drug was used for analysis.

End point type	Primary
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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 17.6 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 analyses are 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	45	45	45	
Units: Participants	39	37	42	

Statistical analyses

No statistical analyses for this end point

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]
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End point description:

An 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 subjects who received at least one dose of study drug was used for analysis.

End point type	Primary
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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 54.3 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 analyses are reported for this endpoint.

End point values	Telotristat Etiprate Open- Label Extension			
Subject group type	Reporting group			
Number of subjects analysed	115			
Units: Participants	110			

Statistical analyses

No statistical analyses for this end point

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

End point title	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 u5-HIAA data available at Baseline and Week 12 were included in the analyses.	
End point type	Secondary
End point timeframe: Baseline and Week 12	

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	30	32	31	
Units: mg/24 hours				
arithmetic mean (standard deviation)	11.35 (± 35.0346)	-40.134 (± 84.7663)	-57.519 (± 82.3273)	

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 were included in the analyses.	
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	45	45	45	
Units: counts/day				
arithmetic mean (standard deviation)	-0.164 (\pm 1.1572)	-0.296 (\pm 1.3097)	-0.525 (\pm 1.3413)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Change form Baseline in Abdominal Pain Averaged Across all Time-Points
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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 available data were included in the analyses.

End point type	Secondary
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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	45	45	45	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.226 (\pm 1.1601)	-0.489 (\pm 1.4423)	-0.333 (\pm 1.1784)	

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 72.2 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Following a 3 to 4-week run-in period on stable-dose SSA therapy (octreotide or lanreotide) participants were randomized to receive two placebo-matching telotristat etiprate tablets administered three times daily for 12 weeks in the double-blind treatment period.

Reporting group title	250 mg Telotristat Etiprate
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Reporting group description:

Following a 3 to 4-week run-in period on stable-dose somatostatin analog (SSA) therapy (octreotide or lanreotide) participants were randomized to receive one 250 mg telotristat etiprate tablet plus one placebo-matching telotristat etiprate tablet administered three times daily for 12 Weeks in the double-blind treatment period.

Reporting group title	500 mg Telotristat Etiprate
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Reporting group description:

Following a 3 to 4-week run-in period on stable-dose SSA therapy (octreotide or lanreotide) participants were randomized to receive, one 250 mg telotristat etiprate tablet plus one placebo-matching telotristat etiprate tablet administered 3 times daily for 1 week, followed by two 250 mg telotristat etiprate tablets administered three times daily for 11 weeks in the double-blind treatment period.

Reporting group title	Telotristat Etiprate Open-Label Extension
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Reporting group description:

Patients previously assigned to 250 mg or 500 mg three times daily of telotristat etiprate were administered 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	7 / 45 (15.56%)	7 / 45 (15.56%)	8 / 45 (17.78%)
number of deaths (all causes)	3	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoid tumour			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pancreatic neuroendocrine tumour metastatic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tumour pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Breast cancer			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Neuroendocrine tumour			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Superior vena cava syndrome			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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			
Skin neoplasm excision			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	0 / 45 (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
Radiotherapy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Chemotherapy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Gastrostomy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Nephrostomy tube placement			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Surgery			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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			
Disease progression			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	0 / 45 (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
General physical health deterioration			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Multi-organ failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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			
Dyspnoea			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	0 / 45 (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
Psychiatric disorders			
Confusional state			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Investigation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood potassium decreased			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Cholangiogram			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Transaminases increased			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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			
Muscle injury			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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 embolisation syndrome alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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			
Carcinoid heart disease			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Cardiovascular disorder alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	0 / 45 (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
Acute myocardial infarction alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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 failure alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Supraventricular tachycardia			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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			
Sensory disturbance			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Epilepsy			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Presyncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Blood and lymphatic system disorders			
Anaemia of malignant disease			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	0 / 45 (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
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	0 / 45 (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
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Faecaloma				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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	
Diarrhoea				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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 haemorrhage				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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	
Haematemesis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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	
Ileal perforation				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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	
Large intestine perforation				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Peritoneal adhesions			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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 obstruction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Subileus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Colonic stenosis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	0 / 45 (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
Cholestasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Cholecystitis acute alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 45 (0.00%) 0 / 0 0 / 0	0 / 45 (0.00%) 0 / 0 0 / 0	0 / 45 (0.00%) 0 / 0 0 / 0
Renal and urinary disorders Haematuria alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 45 (0.00%) 0 / 0 0 / 0	1 / 45 (2.22%) 0 / 1 0 / 0	0 / 45 (0.00%) 0 / 0 0 / 0
Renal failure acute alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 45 (0.00%) 0 / 0 0 / 0	1 / 45 (2.22%) 0 / 1 0 / 0	0 / 45 (0.00%) 0 / 0 0 / 0
Haemorrhage urinary tract subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 45 (0.00%) 0 / 0 0 / 0	0 / 45 (0.00%) 0 / 0 0 / 0	0 / 45 (0.00%) 0 / 0 0 / 0
Nephrolithiasis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 45 (0.00%) 0 / 0 0 / 0	0 / 45 (0.00%) 0 / 0 0 / 0	0 / 45 (0.00%) 0 / 0 0 / 0
Renal failure alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 45 (0.00%) 0 / 0 0 / 0	0 / 45 (0.00%) 0 / 0 0 / 0	0 / 45 (0.00%) 0 / 0 0 / 0
Endocrine disorders Carcinoid syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 45 (0.00%) 0 / 0 0 / 0	0 / 45 (0.00%) 0 / 0 0 / 0	1 / 45 (2.22%) 0 / 3 0 / 0

Musculoskeletal and connective tissue disorders			
Flank pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	0 / 45 (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
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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			
Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Catheter site infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Meningitis bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Pyonephrosis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Septic shock			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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			
Hypokalemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	0 / 45 (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
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	0 / 45 (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
Hyponatraemia			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (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	37 / 115 (32.17%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoid tumour			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pancreatic neuroendocrine tumour metastatic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 115 (1.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine tumour			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Skin neoplasm excision			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radiotherapy			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 115 (2.61%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Chemotherapy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrostomy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrostomy tube placement			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Surgery				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
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 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Disease progression				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 115 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	3 / 115 (2.61%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Fatigue				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Investigation			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 115 (3.48%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Blood potassium decreased			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangiogram			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Muscle injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post embolisation syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Carcinoid heart disease			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiovascular disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 115 (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 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Sensory disturbance				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 115 (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 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				

subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia of malignant disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 115 (4.35%)		
occurrences causally related to treatment / all	5 / 7		
deaths causally related to treatment / all	0 / 0		
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
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	0 / 115 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 115 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 115 (1.74%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			

Haematemesis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileal perforation				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Peritoneal adhesions				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
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	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subileus				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colonic stenosis				

subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stenosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholestasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Haemorrhage urinary tract			

subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Carcinoid syndrome			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Flank pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Peritonitis			
subjects affected / exposed	2 / 115 (1.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Catheter site infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyonephrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Hypokalemia alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 115 (0.00%) 0 / 0 0 / 0			
Cachexia alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 115 (0.00%) 0 / 0 0 / 0			
Dehydration alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 115 (0.87%) 0 / 1 0 / 1			
Hyponatraemia alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 115 (0.87%) 3 / 4 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	39 / 45 (86.67%)	37 / 45 (82.22%)	42 / 45 (93.33%)
Investigations Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	4 / 45 (8.89%) 5	4 / 45 (8.89%) 4
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 45 (2.22%) 1	3 / 45 (6.67%) 4
Blood alkaline phosphatase increased			

subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	0 / 45 (0.00%) 0	3 / 45 (6.67%) 3
Vascular disorders Flushing alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Hypertension alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 2 / 45 (4.44%) 2 0 / 45 (0.00%) 0	 3 / 45 (6.67%) 4 0 / 45 (0.00%) 0	 3 / 45 (6.67%) 4 0 / 45 (0.00%) 0
Nervous system disorders Headache alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Dizziness alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Memory impairment alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 2 / 45 (4.44%) 2 2 / 45 (4.44%) 2 3 / 45 (6.67%) 3	 5 / 45 (11.11%) 5 0 / 45 (0.00%) 0 0 / 45 (0.00%) 0	 5 / 45 (11.11%) 6 4 / 45 (8.89%) 6 1 / 45 (2.22%) 1
General disorders and administration site conditions Fatigue alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Asthenia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Oedema peripheral alternative assessment type: Non-systematic	 4 / 45 (8.89%) 4 3 / 45 (6.67%) 3	 4 / 45 (8.89%) 4 2 / 45 (4.44%) 2	 7 / 45 (15.56%) 7 1 / 45 (2.22%) 1

subjects affected / exposed	2 / 45 (4.44%)	3 / 45 (6.67%)	2 / 45 (4.44%)
occurrences (all)	2	3	2
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	3 / 45 (6.67%)	0 / 45 (0.00%)
occurrences (all)	2	4	0
General physical health deterioration			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 45 (11.11%)	6 / 45 (13.33%)	14 / 45 (31.11%)
occurrences (all)	10	8	19
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 45 (17.78%)	5 / 45 (11.11%)	10 / 45 (22.22%)
occurrences (all)	10	5	10
Vomiting			
subjects affected / exposed	4 / 45 (8.89%)	2 / 45 (4.44%)	5 / 45 (11.11%)
occurrences (all)	5	2	8
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	3 / 45 (6.67%)	5 / 45 (11.11%)
occurrences (all)	0	3	7
Abdominal distension			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)	2 / 45 (4.44%)	1 / 45 (2.22%)
occurrences (all)	3	2	1
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)	3 / 45 (6.67%)	0 / 45 (0.00%)
occurrences (all)	3	3	0
Flatulence			
alternative assessment type: Non-systematic			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspepsia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 45 (2.22%)</p> <p>1</p> <p>3 / 45 (6.67%)</p> <p>3</p> <p>0 / 45 (0.00%)</p> <p>0</p>	<p>3 / 45 (6.67%)</p> <p>3</p> <p>1 / 45 (2.22%)</p> <p>1</p> <p>0 / 45 (0.00%)</p> <p>0</p>	<p>2 / 45 (4.44%)</p> <p>2</p> <p>1 / 45 (2.22%)</p> <p>1</p> <p>0 / 45 (0.00%)</p> <p>0</p>
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Dyspnoea</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 45 (0.00%)</p> <p>0</p> <p>1 / 45 (2.22%)</p> <p>1</p> <p>0 / 45 (0.00%)</p> <p>0</p>	<p>2 / 45 (4.44%)</p> <p>2</p> <p>1 / 45 (2.22%)</p> <p>1</p> <p>0 / 45 (0.00%)</p> <p>0</p>	<p>5 / 45 (11.11%)</p> <p>5</p> <p>3 / 45 (6.67%)</p> <p>4</p> <p>3 / 45 (6.67%)</p> <p>3</p>
<p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 45 (6.67%)</p> <p>3</p>	<p>0 / 45 (0.00%)</p> <p>0</p>	<p>1 / 45 (2.22%)</p> <p>1</p>
<p>Psychiatric disorders</p> <p>Depression</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Depressed mood</p> <p>alternative assessment type: Non-systematic</p>	<p>3 / 45 (6.67%)</p> <p>3</p>	<p>2 / 45 (4.44%)</p> <p>2</p>	<p>7 / 45 (15.56%)</p> <p>7</p>

subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Decreased interest			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 45 (2.22%)	2 / 45 (4.44%)	3 / 45 (6.67%)
occurrences (all)	1	2	3
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	3
Urinary tract infection			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Decreased appetite alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	3 / 45 (6.67%) 3	7 / 45 (15.56%) 7
Hypokalaemia subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	3 / 45 (6.67%) 3	5 / 45 (11.11%) 6

Non-serious adverse events	Telotristat Etiprate Open-Label Extension		
Total subjects affected by non-serious adverse events subjects affected / exposed	110 / 115 (95.65%)		
Investigations Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	9 / 115 (7.83%) 9 0 / 115 (0.00%) 0 0 / 115 (0.00%) 0		
Vascular disorders Flushing alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Hypertension alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	7 / 115 (6.09%) 11 6 / 115 (5.22%) 7		
Nervous system disorders Headache alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Dizziness	12 / 115 (10.43%) 13		

<p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>0 / 115 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Memory impairment</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>0 / 115 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>General disorders and administration site conditions</p> <p>Fatigue</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>13 / 115 (11.30%)</p> <p>occurrences (all)</p> <p>13</p> <p>Asthenia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>11 / 115 (9.57%)</p> <p>occurrences (all)</p> <p>14</p> <p>Oedema peripheral</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>10 / 115 (8.70%)</p> <p>occurrences (all)</p> <p>12</p> <p>Pyrexia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>8 / 115 (6.96%)</p> <p>occurrences (all)</p> <p>9</p> <p>General physical health deterioration</p> <p>subjects affected / exposed</p> <p>8 / 115 (6.96%)</p> <p>occurrences (all)</p> <p>9</p>			
<p>Gastrointestinal disorders</p> <p>Nausea</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>27 / 115 (23.48%)</p> <p>occurrences (all)</p> <p>41</p> <p>Abdominal pain</p> <p>alternative assessment type: Non-systematic</p>			

subjects affected / exposed	35 / 115 (30.43%)		
occurrences (all)	50		
Vomiting			
subjects affected / exposed	16 / 115 (13.91%)		
occurrences (all)	23		
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 115 (11.30%)		
occurrences (all)	14		
Abdominal distension			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 115 (11.30%)		
occurrences (all)	17		
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 115 (9.57%)		
occurrences (all)	17		
Flatulence			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 115 (9.57%)		
occurrences (all)	11		
Dyspepsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 115 (0.00%)		
occurrences (all)	0		
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 115 (6.96%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 115 (6.09%)		
occurrences (all)	7		

Cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 115 (0.00%) 0		
Epistaxis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 115 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 115 (0.00%) 0		
Psychiatric disorders Depression alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	10 / 115 (8.70%) 13		
Depressed mood alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	9 / 115 (7.83%) 9		
Decreased interest alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	7 / 115 (6.09%) 8		
Insomnia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	6 / 115 (5.22%) 6		
Musculoskeletal and connective tissue disorders Back pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	9 / 115 (7.83%) 13		

<p>Arthralgia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 115 (6.96%)</p> <p>9</p>		
<p>Muscle spasms</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 115 (5.22%)</p> <p>7</p>		
<p>Infections and infestations</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pneumonia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urinary tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 115 (5.22%)</p> <p>7</p> <p>0 / 115 (0.00%)</p> <p>0</p> <p>10 / 115 (8.70%)</p> <p>12</p>		
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypokalaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>13 / 115 (11.30%)</p> <p>13</p> <p>8 / 115 (6.96%)</p> <p>9</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2012	<p>Amendment 1:</p> <ol style="list-style-type: none">1. Added 2 exclusion criteria for the purposes of screening patients who may not have had carcinoid syndrome (CS)-related diarrhea. Specifically, exclusion criteria #15 and #16 were revised to clarify that only clinically significant findings that would compromise patient safety or the outcome of the study were to result in patient exclusion2. Modified text to clarify how patients with missing or uninterpretable urinary 5-hydroxyindoleacetic acid (u5-HIAA) results would be stratified3. Modified text regarding the use of concomitant medications to clarify the use of over-the-counter antidiarrheal therapy, bile acid sequestrants, and pancreatic enzymes4. Added text to clarify that select study visits may have been performed outside of investigative site at the discretion of the Investigator and Sponsor5. Added stool sampling to the Screening laboratory assessments6. Added text to specify that additional information was collected if episodes of adverse events of special interest (AESIs) occurred7. Defined central nervous system (CNS) events to include any clinically significant changes in mood, physical affect, or exacerbation of preexisting CNS conditions (eg, depression, migraine headaches) as AESIs8. Revised the analysis section to clarify that the Run-in and DBT Periods of the study were to be reported separately from the OLE Period
11 April 2013	<p>Amendment 2:</p> <ol style="list-style-type: none">1. Modified the secondary endpoint describing durability and additional endpoints for changes in bowel movement (BM) frequency to reflect a 30% change in response of desired criteria. Based on review of new data from completed Phase 2 studies by key opinion leaders in the field, a 30% change in response criteria was considered clinically relevant. The leaders had cited precedent for this proportion of change in prior studies of medications to control diarrhea2. Added information on patient symptomatology and clinical relevance of symptom improvement through semi-structured patient interviews3. Increased the number of study sites anticipated to participate to 704. Added definition of childbearing potential to the inclusion criteria5. Added information regarding benefit/risk assessment to the Introduction Section6. Added text to specify that a Data Safety Monitoring Board (DSMB) may have terminated the study if warranted7. Revised text to remove reference to the interactive voice response system as only a web-based system (IWRS) was to be utilized for this study8. Revised treatment compliance text to include criteria for defining a missed dose; specifically, "A dose outside of a 3-hour window should have been considered missed"9. Added restrictions for grapefruit just for 2-3 hours before and following dosing in the study10. Added text to allow rescreening of patients at the discretion of the Medical Monitor who were excluded during the Screening Period11. Added text to describe the patient Exit Interview Substudy12. Added a section to provide guidance to Investigators when monitoring/evaluating hepatic function13. Modified instructions on how blood pressure, height, and weight measurements should have been collected14. Updated safety reporting information15. Added additional details regarding pharmacokinetic (PK) sampling

06 September 2013	<p>Amendment 3:</p> <ol style="list-style-type: none"> 1. Revised the wording of the primary endpoint to correctly reflect that the planned analysis was to evaluate individual treatment groups versus placebo for a reduction of bowel movements (BMs) from an initial Baseline value 2. Secondary endpoints were revised to align with the clinical importance of additional pathological and physical manifestations of carcinoid syndrome (CS). The other efficacy objectives were adjusted to accommodate changes to the planned analysis 3. Replaced the term "refractory" with the term "not adequately controlled" for the patient population expected to participate. Although early signs of tachyphylaxis were exhibited in the planned patient population, patients who were eligible to participate in this study may have experienced some benefit from their background somatostatin analog therapy and, thus, were no longer adequately controlled 4. Allowed patients who had undergone tumor-directed therapies and experienced little or no reduction in BMs to participate 5. Increased the number of study sites anticipated to participate to 100 6. Clarified the PK objective and clarified that details of the population PK analyses were to be prepared in a separate document 7. Provided updated information on new and completed studies 8. Provided additional information for the withdrawal of patients 9. Added text to require capturing individual missed doses 10. Added assessment of a patient's clotting profile via prothrombin time and international normalized ratio laboratory values at Screening 11. Added parameters for depression detection and quality of sleep assessment during the DBT Period 12. Provided clarification that patients who become pregnant should have been discontinued from study treatment immediately 13. Clarified sample size calculations and statistical testing
17 April 2014	<p>Amendment 4:</p> <ol style="list-style-type: none"> 1. Modified portions of the statistical methodology to ensure consistency between the protocol and the Statistical Analysis Plan (SAP). Specifically, updates were made in order to describe which population was used in the sensitivity analyses of the primary efficacy endpoint, as well as to provide clarification on the summary of plasma concentration and pharmacokinetic (PK) parameters for the data collected from patients with intensive PK assessments 2. The name of the study drug (active metabolite and ethyl ester prodrug of the active metabolite) was modified throughout to correctly represent the adoption of the United States Adopted Name naming convention, and additional text was added to clarify that the identified dose of each tablet is representative of free base (ie, the ethyl ester prodrug) 3. Clarified the expected frequency of the Data Safety Monitoring Board (DSMB) meetings 4. Updated safety reporting text regarding relation to study drug and definition of an SAE 5. Statistical text was modified to describe disposition of AEs identified as adverse events of special interest (AESI) 6. Clarified the minimum dose requirement of SSA therapy in regards to inclusion criterion number 5 7. Added restrictions for both food and drink containing grapefruit to 2 to 3 hours before and after dosing
20 January 2015	<p>Amendment 5:</p> <ol style="list-style-type: none"> 1. Modified the exclusion criterion to remove the corrected QT interval using Fridericia's formula (QTcF) limitation of 450 msec 2. Clarified AESIs 3. Clarified the manner in which responses to questions designed to detect early signs of depression were to be managed 4. Clarified definition of AEs not related to study drug 5. Included a fifth classification for AEs, entitled "unlikely related" 6. Further defined the criteria for reporting a hospitalization as an SAE 7. Further defined how primary and secondary endpoints were to be analyzed and 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: