



Clinical trial results:

A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606)

Summary

EudraCT number	2013-002596-18
Trial protocol	DE GB ES SE IT BE
Global end of trial date	12 September 2018

Results information

Result version number	v1 (current)
This version publication date	01 March 2019
First version publication date	01 March 2019

Trial information

Trial identification

Sponsor protocol code	LX1606.1-302-CS
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02026063
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lexicon Pharmaceuticals, Inc.
Sponsor organisation address	8800 Technology Forest Place, The Woodlands, Texas, United States, 73301
Public contact	Shanna Jackson, Lexicon Pharmaceuticals, Inc., 001 281 863 3484, sjackson@lexpharma.com
Scientific contact	Shanna Jackson, Lexicon Pharmaceuticals, Inc., 001 281 863 3484, sjackson@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	12 September 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the long-term safety and tolerability of orally administered telotristat etiprate.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 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	Netherlands: 9
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Israel: 7
Worldwide total number of subjects	124
EEA total number of subjects	73

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)	65
From 65 to 84 years	57
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects whose participation was ongoing in 1 of the following studies [LX1606.1-202-CS (NCT00853047), LX1606.1-203-CS (NCT01104415), LX1606.1-301-CS (NCT01677910), LX1606.1-303-CS (NCT02063659)] were eligible to enrol in this long-term safety study at the same dose received in the previous (parent) study.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Telotristat Etiprate 250 mg

Arm description:

Subjects were treated with telotristat etiprate in a previous study for 9 to 46 months. Subjects received one telotristat etiprate (250 mg) tablet three times daily (tid) up to an additional 228 weeks in this long-term extension study.

Arm type	Experimental
Investigational medicinal product name	Telotristat Etiprate
Investigational medicinal product code	
Other name	LX1606
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Telotristat etiprate tablet administered tid orally in this long-term extension study.

Arm title	Telotristat Etiprate 500 mg
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Arm description:

Subjects were treated with telotristat etiprate in a previous study for 9 to 46 months. Subjects received two telotristat etiprate (250 mg) tablet tid up to an additional 204 weeks in this long-term extension study.

Arm type	Experimental
Investigational medicinal product name	Telotristat Etiprate
Investigational medicinal product code	
Other name	LX1606
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Telotristat etiprate tablet administered tid orally in this long-term extension study.

Number of subjects in period 1	Telotristat Etiprate 250 mg	Telotristat Etiprate 500 mg
Started	22	102
Completed	13	53
Not completed	9	49
Physician decision	-	10
Adverse event	5	20
Noncompliance with study drug	1	1
Withdrawal of consent	1	6
Reason not specified	2	7
Lost to follow-up	-	1
Lack of efficacy	-	4

Baseline characteristics

Reporting groups

Reporting group title	Telotristat Etiprate 250 mg
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Reporting group description:

Subjects were treated with telotristat etiprate in a previous study for 9 to 46 months. Subjects received one telotristat etiprate (250 mg) tablet three times daily (tid) up to an additional 228 weeks in this long-term extension study.

Reporting group title	Telotristat Etiprate 500 mg
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Reporting group description:

Subjects were treated with telotristat etiprate in a previous study for 9 to 46 months. Subjects received two telotristat etiprate (250 mg) tablet tid up to an additional 204 weeks in this long-term extension study.

Reporting group values	Telotristat Etiprate 250 mg	Telotristat Etiprate 500 mg	Total
Number of subjects	22	102	124
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	64.5 ± 7.60	63.4 ± 10.33	-
Gender categorical Units: Subjects			
Female	14	41	55
Male	8	61	69
Ethnicity			
Here, Unknown= Ethnicity information not provided.			
Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	22	100	122
Unknown	0	1	1
Race Units: Subjects			
White	22	93	115
Black or African American	0	2	2
American Indian or Alaska Native	0	1	1
Other	0	6	6

End points

End points reporting groups

Reporting group title	Telotristat Etiprate 250 mg
Reporting group description: Subjects were treated with telotristat etiprate in a previous study for 9 to 46 months. Subjects received one telotristat etiprate (250 mg) tablet three times daily (tid) up to an additional 228 weeks in this long-term extension study.	
Reporting group title	Telotristat Etiprate 500 mg
Reporting group description: Subjects were treated with telotristat etiprate in a previous study for 9 to 46 months. Subjects received two telotristat etiprate (250 mg) tablet tid up to an additional 204 weeks in this long-term extension study.	
Subject analysis set title	Telotristat Etiprate (All subjects)
Subject analysis set type	Per protocol
Subject analysis set description: Subjects were treated with telotristat etiprate in a previous study for 9 to 46 months. Telotristat etiprate (250 or 500 mg) tablet administered tid up to an additional 228 weeks (250 mg) and an additional 204 weeks (500 mg) in this long-term extension study.	

Primary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) ^[1]
End point description: An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs or symptoms occurring in any phase of the clinical study whether or not considered related to the study medication. Safety Population included all subjects who received any fraction of a dose of telotristat etiprate during the study.	
End point type	Primary
End point timeframe: First dose of study drug (Day 1) up to 15 days post last dose (approximately up to 236 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: Statistical analyses were not planned for this endpoint.	

End point values	Telotristat Etiprate 250 mg	Telotristat Etiprate 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	102		
Units: Number of Subjects				
number (not applicable)				
TEAE	22	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and

Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) Score at Each Visit

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) Score at Each Visit
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End point description:

QLQ-C30 is a standardized 30-item scale used to assess HR-QOL and is composed of both multi-item scales and single-item measures. These included 5 functional scales physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning; 3 symptom scales (fatigue, nausea and vomiting, and pain); a global health status (GHS) /quality of life (QOL) scale; and 6 single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). Minimum and maximum values are 0 and 100 respectively. Higher score indicated higher response level. Per-Protocol (PP) population included subjects who received telotristat etiprate and had no major protocol deviations that would interfere with collection or interpretation of efficacy data. "n" is number of subjects with evaluable data at the given time-point. Subjects were combined for efficacy endpoint as the subjects received dose adjustment per investigator's discretion.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 24, 48, 72 and 84

End point values	Telotristat Etiprate (All subjects)			
Subject group type	Subject analysis set			
Number of subjects analysed	124			
Units: Score on a scale				
arithmetic mean (standard deviation)				
GHS/QOL, Baseline (n=118)	60.664 (± 17.4627)			
GHS/QOL, Change at Week 24 (n=102)	-0.980 (± 17.9878)			
GHS/QOL, Change at Week 48 (n=88)	-4.261 (± 17.3239)			
GHS/QOL, Change at Week 72 (n=77)	-1.840 (± 17.0795)			
GHS/QOL, Change at Week 84 (n=54)	0.309 (± 14.5660)			
Physical functioning, Baseline (n=120)	79.958 (± 20.3109)			
Physical functioning, Change at Week 24 (n=103)	-2.670 (± 13.6888)			
Physical functioning, Change at Week 48 (n=90)	-2.667 (± 13.2129)			
Physical functioning, Change at Week 72 (n=78)	-3.077 (± 14.8758)			
Physical functioning, Change at Week 84 (n=55)	-1.939 (± 9.8275)			
Role functioning, Baseline (n=119)	73.810 (± 26.9766)			
Role functioning, Change at Week 24 (n=102)	-4.248 (± 23.9965)			
Role functioning, Change at Week 48 (n=89)	-5.431 (± 27.1518)			
Role functioning, Change at Week 72 (n=77)	-4.329 (± 23.9399)			
Role functioning, Change at Week 84 (n=54)	-1.543 (± 21.5414)			

Emotional functioning, Baseline (n=118)	75.683 (\pm 21.6630)			
Emotional functioning, Change at Week 24 (n=102)	-1.552 (\pm 17.5010)			
Emotional functioning, Change at Week 48 (n=88)	-0.852 (\pm 17.5549)			
Emotional functioning, Change at Week 72 (n=77)	-1.623 (\pm 19.7313)			
Emotional functioning, Change at Week 84 (n=54)	3.858 (\pm 14.3621)			
Cognitive functioning, Baseline (n=118)	78.955 (\pm 21.7283)			
Cognitive functioning, Change at Week 24 (n=102)	0.000 (\pm 18.1668)			
Cognitive functioning, Change at Week 48 (n=88)	-1.515 (\pm 16.8830)			
Cognitive functioning, Change at Week 72 (n=77)	-1.299 (\pm 22.2568)			
Cognitive functioning, Change at Week 84 (n=54)	3.086 (\pm 18.0478)			
Social functioning, Baseline (n=118)	74.011 (\pm 24.1220)			
Social functioning, Change at Week 24 (n=102)	-1.797 (\pm 21.2258)			
Social functioning, Change at Week 48 (n=88)	-4.167 (\pm 24.5327)			
Social functioning, Change at Week 72 (n=77)	-1.732 (\pm 26.0151)			
Social functioning, Change at Week 84 (n=54)	-0.617 (\pm 20.7215)			
Fatigue, Baseline (n=120)	33.981 (\pm 24.7530)			
Fatigue, Change at Week 24 (n=103)	4.800 (\pm 21.3903)			
Fatigue, Change at Week 48 (n=90)	7.284 (\pm 20.9473)			
Fatigue, Change at Week 72 (n=78)	6.054 (\pm 19.3320)			
Fatigue, Change at Week 84 (n=55)	4.444 (\pm 17.8394)			
Nausea and vomiting, Baseline (n=119)	9.104 (\pm 13.3312)			
Nausea and vomiting, Change at Week 24 (n=103)	1.618 (\pm 15.0371)			
Nausea and vomiting, Change at Week 48 (n=90)	0.556 (\pm 14.8757)			
Nausea and vomiting, Change at Week 72 (n=78)	2.137 (\pm 20.3432)			
Nausea and vomiting, Change at Week 84 (n=55)	-1.212 (\pm 15.3339)			
Pain, Baseline (n=120)	26.528 (\pm 25.0579)			
Pain, Change at Week 24 (n=103)	3.722 (\pm 21.8845)			
Pain, Change at Week 48 (n=90)	6.481 (\pm 22.9930)			
Pain, Change at Week 72 (n=78)	1.709 (\pm 26.5351)			
Pain, Change at Week 84 (n=55)	-4.848 (\pm 22.3774)			
Dyspnea, Baseline (n=120)	18.611 (\pm 24.7474)			

Dyspnea, Change at Week 24 (n=103)	1.294 (± 19.7602)			
Dyspnea, Change at Week 48 (n=89)	5.618 (± 22.0399)			
Dyspnea, Change at Week 72 (n=78)	2.564 (± 21.3331)			
Dyspnea, Change at Week 84 (n=55)	6.667 (± 16.2288)			
Insomnia, Baseline (n=120)	26.389 (± 28.6307)			
Insomnia, Change at Week 24 (n=103)	3.560 (± 26.3679)			
Insomnia, Change at Week 48 (n=90)	3.704 (± 27.1144)			
Insomnia, Change at Week 72 (n=78)	2.564 (± 24.4827)			
Insomnia, Change at Week 84 (n=55)	0.000 (± 21.2762)			
Appetite loss, Baseline (n=119)	13.165 (± 21.3563)			
Appetite loss, Change at Week 24 (n=102)	3.595 (± 26.0772)			
Appetite loss, Change at Week 48 (n=89)	3.745 (± 21.5780)			
Appetite loss, Change at Week 72 (n=78)	10.256 (± 27.5543)			
Appetite loss, Change at Week 84 (n=55)	4.848 (± 22.6061)			
Constipation, Baseline (n=118)	7.345 (± 16.3854)			
Constipation, Change at Week 24 (n=102)	3.595 (± 18.7079)			
Constipation, Change at Week 48 (n=88)	0.379 (± 17.8645)			
Constipation, Change at Week 72 (n=77)	4.762 (± 20.7423)			
Constipation, Change at Week 84 (n=54)	3.086 (± 19.7134)			
Diarrhea, Baseline (n=118)	42.090 (± 33.3128)			
Diarrhea, Change at Week 24 (n=102)	1.961 (± 29.9701)			
Diarrhea, Change at Week 48 (n=88)	5.682 (± 34.7300)			
Diarrhea, Change at Week 72 (n=76)	3.947 (± 32.1879)			
Diarrhea, Change at Week 84 (n=53)	0.000 (± 31.3513)			
Financial difficulties, Baseline (n=118)	18.079 (± 28.1240)			
Financial difficulties, Change at Week 24 (n=102)	-0.327 (± 15.9034)			
Financial difficulties, Change at Week 48 (n=87)	1.533 (± 19.6270)			
Financial difficulties, Change at Week 72 (n=77)	0.433 (± 25.0692)			
Financial difficulties, Change at Week 84 (n=54)	-1.235 (± 19.3857)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Gastrointestinal Symptoms of Carcinoid Neuroendocrine Tumors (GI.NET21) Score at Each Visit

End point title	Change From Baseline in Gastrointestinal Symptoms of Carcinoid Neuroendocrine Tumors (GI.NET21) Score at Each Visit
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End point description:

GI.NET21 is a standardized 21-item scale composed of both multi-item scales and single-item measures. These included 5 functional scales gastrointestinal (GI), endocrine, treatment-related, social functioning, and disease related worries scale (DRWS), and 4 single items (muscle and bone pain symptom (BPS), sexual functioning, communication function (CF), body image and information about the disease). The minimum and maximum values are 1 and 4, respectively. A higher score indicated worst outcome. PP population included the subjects who received telotristat etiprate and had no major protocol deviations that would interfere with the collection or interpretation of the efficacy data. "n" is the number of subjects with evaluable data at the given time-point.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 24, 48, 72 and 84

End point values	Telotristat Etiprate (All subjects)			
Subject group type	Subject analysis set			
Number of subjects analysed	124			
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Endocrine scale, Baseline (n=120)	25.000 (± 20.6367)			
Endocrine scale, Change at Week 24 (n=103)	1.726 (± 15.8483)			
Endocrine scale, Change at Week 48 (n=90)	1.111 (± 17.0717)			
Endocrine scale, Change at Week 72 (n=78)	1.425 (± 19.8082)			
Endocrine scale, Change at Week 84 (n=54)	4.938 (± 21.2213)			
GI symptoms scale, Baseline (n=120)	25.014 (± 17.9343)			
GI symptoms scale, Change at Week 24 (n=103)	3.576 (± 14.9243)			
GI symptoms scale, Change at Week 48 (n=90)	3.759 (± 16.7890)			
GI symptoms scale, Change at Week 72 (n=78)	1.581 (± 19.0823)			
GI symptoms scale, Change at Week 84 (n=54)	-0.278 (± 17.3137)			
Treatment scale, Baseline (n=101)	10.176 (± 14.6370)			
Treatment scale, Change at Week 24 (n=80)	-0.486 (± 13.7849)			
Treatment scale, Change at Week 48 (n=66)	1.684 (± 14.0873)			
Treatment scale, Change at Week 72 (n=58)	0.575 (± 18.8668)			

Treatment scale, Change at Week 84 (n=35)	2.063 (± 20.4384)			
Social function scale, Baseline (n=120)	32.037 (± 22.8748)			
Social function scale, Change at Week 24 (n=103)	3.128 (± 16.4229)			
Social function scale, Change at Week 48 (n=90)	2.160 (± 22.4658)			
Social function scale, Change at Week 72 (n=77)	1.587 (± 21.3052)			
Social function scale, Change at Week 84 (n=54)	0.000 (± 18.4415)			
DRWS, Baseline (n=120)	36.713 (± 26.9224)			
DRWS, Change at Week 24 (n=103)	1.456 (± 20.4932)			
DRWS, Change at Week 48 (n=90)	-1.049 (± 22.5767)			
DRWS, Change at Week 72 (n=77)	-0.289 (± 26.5962)			
DRWS, Change at Week 84 (n=54)	-3.601 (± 22.4868)			
Muscle and BPS, Baseline (n=120)	30.833 (± 27.7250)			
Muscle and BPS, Change at Week 24 (n=102)	-3.268 (± 21.7546)			
Muscle and BPS, Change at Week 48 (n=90)	7.407 (± 31.9088)			
Muscle and BPS, Change at Week 72 (n=76)	-1.316 (± 25.2048)			
Muscle and BPS, Change at Week 84 (n=54)	2.469 (± 24.9543)			
Sexual function, Baseline (n=91)	30.769 (± 36.5928)			
Sexual function, Change at Week 24 (n=62)	2.151 (± 29.4893)			
Sexual function, Change at Week 48 (n=58)	-2.299 (± 24.0711)			
Sexual function, Change at Week 72 (n=51)	-3.922 (± 24.6280)			
Sexual function, Change at Week 84 (n=36)	-1.852 (± 19.4274)			
Information and CF, Baseline (n=120)	2.500 (± 9.8186)			
Information and CF, Change at Week 24 (n=103)	3.236 (± 17.1591)			
Information and CF, Change at Week 48 (n=90)	0.741 (± 13.1995)			
Information and CF, Change at Week 72 (n=77)	1.299 (± 13.7241)			
Information and CF, Change at Week 84 (n=54)	5.556 (± 25.6978)			
Body image, Baseline (n=119)	11.765 (± 21.5187)			
Body image, Change at Week 24 (n=100)	6.333 (± 24.4789)			
Body image, Change at Week 48 (n=89)	5.618 (± 23.1573)			
Body image, Change at Week 72 (n=76)	6.579 (± 28.8134)			
Body image, Change at Week 84 (n=53)	3.774 (± 27.4721)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adequate Relief as per Subjective Global Assessment Question

End point title	Percentage of Subjects with Adequate Relief as per Subjective Global Assessment Question
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End point description:

Subjects were asked to respond to the following question: "In the past 7 days, have you had adequate relief of your carcinoid syndrome bowel complaints such as diarrhea, urgent need to have a bowel movement, abdominal pain, or discomfort? The percentage of subjects reporting adequately (answered Yes) were reported. PP population included the subjects who received telotristat etiprate and had no major protocol deviations that would interfere with the collection or interpretation of the efficacy data. "n" is the number of subjects with evaluable data at the given time-point.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 12, 24, 36, 48, 60, 72 and 84	

End point values	Telotristat Etiprate (All subjects)			
Subject group type	Subject analysis set			
Number of subjects analysed	124			
Units: Percentage of subjects				
number (not applicable)				
Baseline (n=99)	61.6			
Week 12 (n=106)	64.2			
Week 24 (n=104)	52.9			
Week 36 (n=95)	57.9			
Week 48 (n=95)	61.1			
Week 60 (n=89)	55.1			
Week 72 (n=77)	58.4			
Week 84 (n=55)	67.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subjective Global Assessment of Carcinoid Syndrome Symptoms on 11-Point Numeric Scale at Each Visit

End point title	Change From Baseline in Subjective Global Assessment of
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End point description:

Subjects were asked the following question to assess global symptoms associated with carcinoid syndrome (CS) on an 11-point scale: "Rate the severity of your overall carcinoid symptoms over the past 7 days on a scale from 0 to 10, where 0=no symptoms and 10=worst symptoms ever experienced. A negative change from baseline indicated improvement. PP population included the subjects who received telotristat etiprate and had no major protocol deviations that would interfere with the collection or interpretation of the efficacy data. "n" is the number of subjects with evaluable data at the given time-point. Subjects were combined for efficacy endpoint as the majority of subjects received telotristat etiprate 500 mg.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 60, 72 and 84

End point values	Telotristat Etiprate (All subjects)			
Subject group type	Subject analysis set			
Number of subjects analysed	124			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=92)	3.022 (± 1.9214)			
Change at Week 12 (n=86)	0.558 (± 2.4428)			
Change at Week 24 (n=78)	0.654 (± 2.2553)			
Change at Week 36 (n=73)	0.630 (± 2.2944)			
Change at Week 48 (n=71)	1.056 (± 2.5684)			
Change at Week 60 (n=66)	0.576 (± 1.9773)			
Change at Week 72 (n=60)	0.483 (± 2.2661)			
Change at Week 84 (n=45)	0.644 (± 2.2172)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug (Day 1) up to 15 days post last dose (approximately up to 236 Weeks)

Adverse event reporting additional description:

Safety population included all subjects who received any fraction of a dose of telotristat etiprate during the study.

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	Telotristat Etiprate 250 mg
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Reporting group description:

Subjects were treated with telotristat etiprate in a previous study for 9 to 46 months. Subjects received one telotristat etiprate (250 mg) tablet tid up to an additional 228 weeks in this long-term extension study.

Reporting group title	Telotristat Etiprate 500 mg
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Reporting group description:

Subjects were treated with telotristat etiprate in a previous study for 9 to 46 months. Subjects received two telotristat etiprate (250 mg) tablet tid up to an additional 204 weeks in this long-term extension study.

Serious adverse events	Telotristat Etiprate 250 mg	Telotristat Etiprate 500 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 22 (54.55%)	54 / 102 (52.94%)	
number of deaths (all causes)	2	18	
number of deaths resulting from adverse events	2	18	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Investigation			
subjects affected / exposed	1 / 22 (4.55%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour			
subjects affected / exposed	2 / 22 (9.09%)	4 / 102 (3.92%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer			

subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to ovary			
subjects affected / exposed	1 / 22 (4.55%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to testicle			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic carcinoid tumour			

subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Radiotherapy			
subjects affected / exposed	0 / 22 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileocolectomy			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Disease progression			
subjects affected / exposed	2 / 22 (9.09%)	11 / 102 (10.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 6	
General physical health deterioration			
subjects affected / exposed	0 / 22 (0.00%)	3 / 102 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 22 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Complication of device insertion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 22 (4.55%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic enzyme increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laparoscopy			
subjects affected / exposed	1 / 22 (4.55%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral neck fracture			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 22 (4.55%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 22 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 22 (4.55%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 22 (4.55%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			

subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of chronic disease			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Visual impairment			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	6 / 102 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 22 (0.00%)	4 / 102 (3.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 22 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 22 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 22 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 22 (4.55%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Localised intraabdominal fluid collection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 22 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute hepatic failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cholangitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder perforation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 22 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Basedow's disease			
subjects affected / exposed	1 / 22 (4.55%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid crisis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondritis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm			
subjects affected / exposed	1 / 22 (4.55%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	3 / 102 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 22 (4.55%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal wall abscess			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perihepatic abscess			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 22 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 22 (4.55%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Telotristat Etiprate 250 mg	Telotristat Etiprate 500 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	100 / 102 (98.04%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroendocrine tumour			
subjects affected / exposed	2 / 22 (9.09%)	5 / 102 (4.90%)	
occurrences (all)	8	6	
Vascular disorders			
Flushing			
subjects affected / exposed	4 / 22 (18.18%)	13 / 102 (12.75%)	
occurrences (all)	8	18	
Hypertension			
subjects affected / exposed	1 / 22 (4.55%)	13 / 102 (12.75%)	
occurrences (all)	1	16	
Surgical and medical procedures			
Radiotherapy			
subjects affected / exposed	2 / 22 (9.09%)	2 / 102 (1.96%)	
occurrences (all)	10	6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 22 (18.18%)	28 / 102 (27.45%)	
occurrences (all)	4	37	
Pyrexia			
subjects affected / exposed	1 / 22 (4.55%)	20 / 102 (19.61%)	
occurrences (all)	1	25	
Disease progression			
subjects affected / exposed	2 / 22 (9.09%)	16 / 102 (15.69%)	
occurrences (all)	2	21	
Oedema periphera			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	17 / 102 (16.67%) 19	
Asthenia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	15 / 102 (14.71%) 26	
Chest discomfort subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	2 / 102 (1.96%) 2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3	11 / 102 (10.78%) 15	
Cough subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	10 / 102 (9.80%) 10	
Psychiatric disorders			
Depression subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 4	11 / 102 (10.78%) 14	
Depressed mood subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	9 / 102 (8.82%) 15	
Insomnia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	8 / 102 (7.84%) 8	
Investigations			
Weight decreased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	15 / 102 (14.71%) 18	
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3	3 / 102 (2.94%) 3	
Investigation subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 6	3 / 102 (2.94%) 7	
Blood glucose increased			

subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 4	1 / 102 (0.98%) 1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 22 (4.55%)	10 / 102 (9.80%)	
occurrences (all)	1	10	
Headache			
subjects affected / exposed	1 / 22 (4.55%)	10 / 102 (9.80%)	
occurrences (all)	1	13	
Syncope			
subjects affected / exposed	1 / 22 (4.55%)	10 / 102 (9.80%)	
occurrences (all)	1	13	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 22 (9.09%)	11 / 102 (10.78%)	
occurrences (all)	2	17	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 22 (40.91%)	35 / 102 (34.31%)	
occurrences (all)	16	73	
Nausea			
subjects affected / exposed	5 / 22 (22.73%)	36 / 102 (35.29%)	
occurrences (all)	19	49	
Abdominal pain			
subjects affected / exposed	3 / 22 (13.64%)	37 / 102 (36.27%)	
occurrences (all)	4	74	
Constipation			
subjects affected / exposed	3 / 22 (13.64%)	22 / 102 (21.57%)	
occurrences (all)	6	30	
Vomiting			
subjects affected / exposed	1 / 22 (4.55%)	24 / 102 (23.53%)	
occurrences (all)	6	32	
Abdominal pain upper			
subjects affected / exposed	2 / 22 (9.09%)	13 / 102 (12.75%)	
occurrences (all)	2	18	
Flatulence			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	7 / 102 (6.86%) 7	
Abdominal distension subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	6 / 102 (5.88%) 8	
Small intestinal obstruction subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	6 / 102 (5.88%) 9	
Glossodynia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 102 (0.00%) 0	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	8 / 102 (7.84%) 8	
Rash subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	6 / 102 (5.88%) 8	
Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 102 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	17 / 102 (16.67%) 18	
Arthralgia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	15 / 102 (14.71%) 18	
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	8 / 102 (7.84%) 9	
Flank pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	6 / 102 (5.88%) 7	
Pain in extremity			

subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	5 / 102 (4.90%) 5	
Neck pain subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3	4 / 102 (3.92%) 5	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 4	9 / 102 (8.82%) 14	
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	9 / 102 (8.82%) 10	
Influenza subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	8 / 102 (7.84%) 8	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	6 / 102 (5.88%) 6	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 4	13 / 102 (12.75%) 15	
Dehydration subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	7 / 102 (6.86%) 7	
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	6 / 102 (5.88%) 8	
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	6 / 102 (5.88%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2014	The following changes were made in the protocol amendment 1: 1. Study name modified to remove "symptoms" consistent with the secondary objective. 2. Modified text to specify that up to 100 subjects were expected to participate in this study. 3. Modified Synopsis and Treatments section. 4. Modified the Clinical Trials of TE in Humans section to reflect the most current data. 5. Modified Benefit/Risk section to clarify a reduction in serotonin, decreased the risk of carcinoid heart disease. 6. Modified Criteria for Stopping Treatment/Study Withdrawal section to clarify patient responsibilities. 7. Modified Dose Adjustment section to clarify dose adjustment. 8. Modified the Study Procedures to remove reference to study visits. 9. Modified the Efficacy Assessments section to indicate EORTC QLQ-C30 and GI.NET21 and the subjective global assessment were quality of life (QOL) measurements. 10. Modified Study Procedures, Depression Detection to include parameters for depression. 11. Revise definitions of AEs and SAEs. 12. Modified Ethical Standards, General Instructions section to reflect current guidance documents were used. 13. Modified Schedule of Assessments table to include weight with all physical examinations (including brief symptom oriented examinations); added urine pregnancy test to be conducted for females of childbearing potential at Weeks 12, 24, and 36; and added sleep and depression assessments to be captured at every visit, including the 2-Week Follow-up Visit.
08 October 2014	The following changes were made in the protocol amendment 2: 1. Modified Duration of Participation section in Synopsis to 86 weeks. 2. Modified Synopsis exclusion criterion (number 1) and Study Populations sections 3. Modified the Clinical Trials of Telotristat Etiprate in Humans section 4. Modified the Phase 1 and Phase 2 Studies section to reflect a recently completed Phase 1 and Phase 2 study. 5. Modified the Benefit/Risk Assessment section. 8. Modified the Study Population, Inclusion Criteria section. 9. Modified Study Population. 10. Modified Treatment – Concomitant Medication section. 11. Modified Study Procedures –Vital Sign Measurements section to remove the requirement to capture blood pressure measurement by using Sponsor-provided equipment. 12. Modified the Safety Reporting, SAE section bullet number 3, to include reference to a new section defining hospitalization as an SAE. 13. Inserted Safety Reporting. 14. Modified Statistical Methodology – Interim analysis section. 15. Modified Schedule of Assessments to show dispensation of LX1606 at Week 48; removal of EOS from Week 48; removal of serum pregnancy testing from the study; added urine pregnancy test to be conducted for females of childbearing potential at all study weeks; added Week 60, Week 72, and Week 84/EOS Visits; and updated the footnote to reflect the new EOS Visit. 16. Modified Appendix B, Amount of Blood to be Collected from Each subject to reflect the estimated volume of blood collected based upon changes in the Schedule of Assessments table.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported