Clinical trial results:
A Phase 2, Open-Label, Multi-Center, Serial Ascending-Dose, Dose Finding Study to Evaluate the Safety and Tolerability of LX1606 in Subjects with Symptomatic Carcinoid Syndrome

Summary

EudraCT number	2009-016973-13
Trial protocol	DE GB
Global end of trial date	12 February 2014

Results information

Result version number	v1 (current)
This version publication date	22 December 2016
First version publication date	22 December 2016

Trial information

Trial identification

Sponsor protocol code	LX1606.1-203-CS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01104415
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lexicon Pharmaceuticals, Inc.
Sponsor organisation address	8800 Technology Forest Place, The Woodlands, TX , United States, 77381-1160
Public contact	Pablo Lapuerta, MD, Lexicon Pharmaceuticals, Inc., 281 863-3000,
Scientific contact	Pablo Lapuerta, MD , Lexicon Pharmaceuticals, Inc. , 281 863-3000,

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 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2014
Global end of trial reached?	Yes
Global end of trial date	12 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety and tolerability of orally administered LX1606 in subjects with symptomatic carcinoid syndrome.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles derived from the Declaration of Helsinki and with GCP as required by the International Council for Harmonisation (ICH) guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products.

Background therapy:

The majority of subjects (86.7%) received antigrowth hormones (lanreotide, octreotide) during the study.

Evidence for comparator:

No comparators were used in the study.

Actual start date of recruitment	15 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Germany: 9
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	10
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After signing the informed consent form, patients who satisfied inclusion/exclusion criteria were entered into the study on Day 1 (start of study drug) and were considered enrolled at that time. Sixteen patients were screened; however, 15 patients were enrolled with the 16th patient identified as a screen failure prior to enrollment.

Period 1

Period 1 title	Core Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Telotristat etiprate - Core Phase

Arm description:

Efficacy Full Analysis Set- all patients who received at least 1 dose of study drug and had at least 1 post-Baseline efficacy assessment. For daily diary data, patients were included in the evaluation at a time point if they had 80% of the data points available for the interval.

Arm type	Experimental
Investigational medicinal product name	telotristat etiprate
Investigational medicinal product code	
Other name	LX1606 Hippurate
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients participated in a 2-week Run-in Period to establish Baseline symptoms.
Following the Run-in Period, all patients were given telotristat etiprate oral capsules at a starting dosage of 150 mg 3 times daily (tid) for 14 days. Dose escalations occurred serially every 14 days, up to a maximum dosage of telotristat etiprate 500 mg (as free base) tid, as guided by specific clinical criteria for dose escalation.

Number of subjects in period 1	Telotristat etiprate - Core Phase
Started	15
Completed	14
Not completed	1
Consent withdrawn by subject	1

Period 2

Period 2 title	Extension Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Telotristat etiprate - Extension Period

Arm description:

Full Analysis Set – all patients who entered the 124-week Extension Period, received at least 1 dose of study drug, and had at least 1 post-Baseline efficacy assessment.

Arm type	Experimental
Investigational medicinal product name	telotristat etiprate
Investigational medicinal product code	
Other name	LX1606 Hippurate
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients received their highest tolerated dose (250 mg or 500 mg tid) during the Extension Period

Number of subjects in period 2[1]	Telotristat etiprate - Extension Period
Started	11
Completed	0
Not completed	11
Physician decision	1
Death	1
Transition to Study LX1606.302	4
Heart surgery/feeling miserable	1
Progressive disease	4

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Upon completion of the Core Phase, 11 patients were eligible to enter the Extension Period. Of those that were not eligible, 1 patient withdrew consent after completion of the Core Phase; 2 patients completed the Core Phase prior to the optional Extension Period being available.

Baseline characteristics

Reporting groups	
Reporting group title	Core Phase
Reporting group description:	
All enrolled subjects.	

Reporting group values	Core Phase	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
Adults (18-64 years)	10	10	
From 65-84 years	5	5	
Age continuous Units: years			
arithmetic mean	61.1		
full range (min-max)	43 to 80	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	8	8	

End points

End points reporting groups

Reporting group title	Telotristat etiprate - Core Phase

Reporting group description:

Efficacy Full Analysis Set- all patients who received at least 1 dose of study drug and had at least 1 post-Baseline efficacy assessment. For daily diary data, patients were included in the evaluation at a time point if they had 80% of the data points available for the interval.

Reporting group title	Telotristat etiprate - Extension Period

Reporting group description:

Full Analysis Set – all patients who entered the 124-week Extension Period, received at least 1 dose of study drug, and had at least 1 post-Baseline efficacy assessment.

Subject analysis set title	Core Phase - Pharmacodynamic Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who had received at least 1 dose of study drug, had a valid Baseline PD assessment, and at least 1 valid post- Baseline PD assessment (whole blood 5-HT or u5-HIAA). Pharmacodynamic data presentation and analyses were to be based upon total number of patients in this analysis set.

Subject analysis set title	Extension Period - Pharmacodynamic Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who had received at least 1 dose of study drug, had a valid Baseline PD assessment, and had at least 1 valid post-Baseline PD assessment in the Extension Period (whole blood 5-HT or u5-HIAA).

Primary: Safety and tolerability of telotristat etiprate

End point title	Safety and tolerability of telotristat etiprate[1]

End point description:

End point type	Primary

End point timeframe:

Core Phase: up to Week 12
Extension Period: up to 120 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 were conducted for the primary endpoint.

End point values	Telotristat etiprate - Core Phase	Telotristat etiprate - Extension Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	11		
Units: Number of subjects with TEAEs	15	11		

Attachments (see zip file)	Summary of Safety/Table 1 - Summary of Safety - LX1606.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline - Number of daily bowel movements

End point title	Change from Baseline - Number of daily bowel movements

End point description:

End point type	Secondary

End point timeframe:

Core Phase: Weeks 9 - 12
Extension Period: Week 24

End point values	Telotristat etiprate - Core Phase	Telotristat etiprate - Extension Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: number of bowel movements per day				
arithmetic mean (standard deviation)	-2.6 (± 1.381)	-2.85 (± 1.64)		

Attachments (see zip file)	Figure 1 - Mean Number of Bowel Movements - Core Phase -

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline - Stool Form/consistency

End point title	Change from Baseline - Stool Form/consistency

End point description:

End point type	Secondary

End point timeframe:

Core Phase = Weeks 9 - 12
Extension Phase = Week 24

End point values	Telotristat etiprate - Core Phase	Telotristat etiprate - Extension Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: mean stool form 6-point scale				
arithmetic mean (standard deviation)	-0.79 (± 0.707)	-1.31 (± 0.666)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline - Sensation of urgency to defecate

End point title	Change from Baseline - Sensation of urgency to defecate

End point description:

Endpoint for Weeks 9 - 12: Proportion of Days (%) with Sensation of Urgency to Defecate
Endpoint for Week 24: Summary of Weekly Sensation of Urgency to Defecate (Mean Urgency/Day)

End point type	Secondary

End point timeframe:

Core Phase = Weeks 9 - 12
Extension Period = Week 24

End point values	Telotristat etiprate - Core Phase	Telotristat etiprate - Extension Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: Proportion of days - urgency to defecate				
arithmetic mean (standard deviation)	-11.32 (± 36.66)	-22.79 (± 49.546)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline - Sensation/severity of nausea

End point title	Change from Baseline - Sensation/severity of nausea

End point description:

Core Phase endpoint - mean VAS value during Weeks 9 - 12
Extension Period endpoint - weekly mean VAS value for Week 24

End point type	Secondary

End point timeframe:

Core Phase = Weeks 9 - 12
Extension Phase = Week 24

End point values	Telotristat etiprate - Core Phase	Telotristat etiprate - Extension Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: Visual Analog Scale (0-100 mm)				
arithmetic mean (standard deviation)	-2.43 (± 5.208)	-5.71 (± 8.797)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjective global assessment of symptoms of carcinoid syndrome

End point title	Subjective global assessment of symptoms of carcinoid syndrome

End point description:

End point type	Secondary

End point timeframe:

Core Phase = Weeks 9 - 12
Extension Period = Week 24

End point values	Telotristat etiprate - Core Phase	Telotristat etiprate - Extension Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: Number of patients with improvement	10	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline - Number of cutaneous flushing episodes

End point title	Change from Baseline - Number of cutaneous flushing episodes

End point description:

End point type	Secondary

End point timeframe:

Core Phase = Weeks 9 - 12
Extension Phase = Week 24

End point values	Telotristat etiprate - Core Phase	Telotristat etiprate - Extension Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: Daily number of flushing episodes				
arithmetic mean (standard deviation)	-0.88 (± 1.205)	-1.55 (± 1.784)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically meaningful symptom reduction

End point title	Clinically meaningful symptom reduction

End point description:

Meaningful symptom reduction is defined as either a) an average of < 4 bowel movements per day over 15 consecutive days, b) a 50% reduction from baseline in the number of bowel movements, c) a positive response to the question regarding adequate relief, or d) a 50% reduction from baseline in the number of daily flushing episodes. Baseline value is defined as values prior to the initial administration of study drug. Post-baseline values are calculated for each study interval, Weeks 1-12.

End point type	Secondary

End point timeframe:

Core Phase = Week 12

End point values	Telotristat etiprate - Core Phase			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: number of subjects	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline - Urinary 5-HIAA

End point title	Change from Baseline - Urinary 5-HIAA

End point description:

End point type	Secondary

End point timeframe:

Core Phase = Week 12
Extension Period = Week 20/21

End point values	Core Phase - Pharmacodynamic Analysis Set	Extension Period - Pharmacodynamic Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	7		
Units: mg/24 hours				
arithmetic mean (standard deviation)	-97.26 (± 164.995)	7 (± 32.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline - Severity of abdominal pain or discomfort

End point title	Change from Baseline - Severity of abdominal pain or discomfort

End point description:

Core Phase endpoint - mean VAS value during Weeks 9 - 12
Extension Period endpoint - weekly mean VAS value for Week 24

End point type	Secondary

End point timeframe:

Core Phase: Weeks 9 - 12
Extension Period: Week 24

End point values	Telotristat etiprate - Core Phase	Telotristat etiprate - Extension Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Visual Analog Scale (0 - 100 mm)				
arithmetic mean (standard deviation)	-8.66 (± 18.724)	-24.11 (± 19.643)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Core Phase = Weeks 1-12
Extension Period = through 120 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Telotristat etiprate - Core Phase

Reporting group description:

All subjects who received telotristat etiprate at any time during the Core Phase.

Reporting group title	Telotristat etiprate - Extension Period

Reporting group description:

All subjects who received telotristat etiprate at any time during the Extension Period.

Serious adverse events	Telotristat etiprate - Core Phase	Telotristat etiprate - Extension Period	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)	7 / 11 (63.64%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Surgical and medical procedures			
Cardiac operation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia repair			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Therapeutic embolisation			
subjects affected / exposed	0 / 15 (0.00%)	2 / 11 (18.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Carcinoid heart disease			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
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	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Carcinoid syndrome			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
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 - Core Phase	Telotristat etiprate - Extension Period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	11 / 11 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pain			

subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 15 (13.33%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Flushing			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Lymphoedema			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Thrombophlebitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 15 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Fatigue			
subjects affected / exposed	2 / 15 (13.33%)	3 / 11 (27.27%)	
occurrences (all)	2	3	
Oedema peripheral			
subjects affected / exposed	0 / 15 (0.00%)	3 / 11 (27.27%)	
occurrences (all)	0	3	
Influenza like illness			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Chest discomfort			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Genital haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 15 (13.33%)	4 / 11 (36.36%)	
occurrences (all)	2	4	
Cough			
subjects affected / exposed	0 / 15 (0.00%)	3 / 11 (27.27%)	
occurrences (all)	0	4	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	4	
Nasal congestion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Sleep disorder			

subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 15 (6.67%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Hepatic enzyme increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Blood potassium increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Blood chromogranin A increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Vitamin D decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Body temperature increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Arthropod bite			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Radius fracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Post embolisation syndrome			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Procedural pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Arthropod sting			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Cardiac disorders			
Carcinoid heart disease			
subjects affected / exposed	0 / 15 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Sinus bradycardia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 15 (33.33%)	0 / 11 (0.00%)	
occurrences (all)	7	0	
Lethargy			
subjects affected / exposed	2 / 15 (13.33%)	1 / 11 (9.09%)	
occurrences (all)	2	2	
Dysgeusia			
subjects affected / exposed	1 / 15 (6.67%)	3 / 11 (27.27%)	
occurrences (all)	1	4	
Migraine			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Headache			

subjects affected / exposed	4 / 15 (26.67%)	1 / 11 (9.09%)	
occurrences (all)	4	2	
Orthostatic intolerance			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Polyneuropathy			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Ocular hyperaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 15 (40.00%)	2 / 11 (18.18%)	
occurrences (all)	8	3	
Diarrhoea			
subjects affected / exposed	3 / 15 (20.00%)	4 / 11 (36.36%)	
occurrences (all)	3	6	
Abdominal pain upper			
subjects affected / exposed	2 / 15 (13.33%)	2 / 11 (18.18%)	
occurrences (all)	2	3	
Flatulence			
subjects affected / exposed	2 / 15 (13.33%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	2 / 15 (13.33%)	2 / 11 (18.18%)	
occurrences (all)	3	2	
Vomiting			

subjects affected / exposed	2 / 15 (13.33%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Ascites			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Brunner's gland hyperplasia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Colonic polyp			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Diverticulum			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Small intestinal obstruction			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Hyperhidrosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Night sweats			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

Renal and urinary disorders Polyuria subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 11 (0.00%) 0	
Endocrine disorders Carcinoid syndrome subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 11 (18.18%) 2	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 2 / 15 (13.33%) 2 0 / 15 (0.00%) 0 1 / 15 (6.67%) 2 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0	 1 / 11 (9.09%) 1 3 / 11 (27.27%) 3 1 / 11 (9.09%) 2 1 / 11 (9.09%) 1 1 / 11 (9.09%) 2	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Oral candidiasis	 2 / 15 (13.33%) 2 2 / 15 (13.33%) 2 0 / 15 (0.00%) 0	 4 / 11 (36.36%) 6 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1	

subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	2	
Staphylococcal infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Infected bites			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Tooth abscess			
subjects affected / exposed	1 / 15 (6.67%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Escherichia infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Post procedural infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	0 / 15 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2010	Amendment #1: 1. Inclusion criteria were revised to require patients of childbearing potential to agree to use a highly effective method of contraception (defined as having a failure rate of <1% per year). 2. Dose-limiting toxicities were revised to include the definition for a minimum intolerable dose.
10 January 2011	Amendment #2: 1. Study design was modified to allow for an optional 24-week, Open-label Extension Period treatment in which eligible patients who completed the initial 4-week Treatment Period could continue to receive treatment. 2. Inclusion criterion was modified to include all carcinoid tumors. 3. Study population was modified to reflect an increase in the number of study sites (from 8 to 15).
13 June 2011	Amendment #3: 1. Pregnancy section was modified to reflect the change in the extension requirement of contraceptive use and monitoring for both males and females.
08 August 2011	Amendment #4: 1. Study design was modified to allow for an optional 72-week, Open-label Extension Period in which eligible patients who completed the initial 4-week Treatment Period could continue to receive treatment. 2. Exclusion criterion for liver function values was revised to reflect the increase in the allowable ALP levels from ≥1.5 to ≥3 × ULN.
18 July 2012	Amendment #5: Study design was modified to reflect that patients had to be able to tolerate dose regimens of 250 mg tid or 500 mg tid to enroll into the optional Extension Period of the study as the 50-mg capsule strength would no longer be manufactured.
13 November 2012	Amendment #6: 1. Study design was modified to allow for an optional 124-week, Open-label Extension Period in which eligible patients who completed the initial 12-week Treatment Period could continue to receive treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported