Clinical trial results:
A Phase 3, Prospective, Randomised, Double-blind, Multi-center Study of the Efficacy and Safety of Lanreotide Autogel/Depot 120 mg Plus BSC vs. Placebo Plus BSC for Tumour Control in Subjects With Well Differentiated, Metastatic and/or Unresectable, Typical or Atypical, Lung Neuroendocrine Tumours

Summary

EudraCT number	2015-004992-62
Trial protocol	GB ES DE NL DK PL IT
Global end of trial date	28 February 2020

Results information

Result version number	v1
This version publication date	16 October 2021
First version publication date	16 October 2021

Trial information

Trial identification

Sponsor protocol code	A-US-52030-328

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02683941
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Biopharmaceuticals, Inc.
Sponsor organisation address	106 Allen Road, Basking Ridge, United States, NJ 07920
Public contact	Medical Director, Ipsen Biopharmaceuticals, Inc., clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen Biopharmaceuticals, Inc., clinical.trials@ipsen.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	28 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to describe the antitumour efficacy of lanreotide 120 milligrams (mg) monotherapy plus best supportive care (BSC) every 28 days, in terms of progression free survival (PFS), measured by central review using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria, every 12 weeks, in subjects with unresectable and/or metastatic well differentiated, typical or atypical lung neuroendocrine tumours (NETs) in either the double-blind phase, or in the open-label treatment phase.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki of the World Medical Association (2013 version), in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice and in compliance with independent ethics committees/institutional review boards and informed consent regulations. In addition, the study adhered to all United States of America Food and Drug Administration (FDA), other local regulatory requirements, and relevant company policies.

Background therapy: -

Evidence for comparator:

Placebo plus BSC was chosen as the control arm because, at the time of study initiation, there were no definitive, well-controlled studies demonstrating the efficacy and safety of somatostatin analogues (SSAs) in this setting.

Actual start date of recruitment	06 March 2017
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	Canada: 5
Country: Number of subjects enrolled	United States: 13
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	77
EEA total number of subjects	54

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)	24
From 65 to 84 years	50
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 37 investigation sites in adult subjects with well differentiated, metastatic and/or unresectable, typical or atypical bronchopulmonary (BP) NETs who did not require SSA treatment for symptom control.

Pre-assignment

Screening details:

This study consisted of two phases: the double-blind phase, and the open-label phase. 77 subjects were randomised to receive study treatment until disease progression, unacceptable toxicity, withdrawal for any reason, or up to 18 months after the last subject was randomised. Subjects were randomised 2:1 to either lanreotide or placebo plus BSC.

Period 1

Period 1 title	Double-blind phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Lanreotide

Arm description:

Subjects received deep subcutaneous (SC) injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and continue to receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the double-blind phase or open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Arm type	Experimental
Investigational medicinal product name	Lanreotide
Investigational medicinal product code	
Other name	LAN
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lanreotide Autogel/Depot 120 mg was administered by deep SC injection in the superior, external quadrant of the buttock at a dose of 120 mg, every 28 days (Q4 weeks).

Arm title	Placebo

Arm description:

Subjects received deep SC injections of placebo (saline solution 0.9%) Q4 weeks plus BSC in the double-blind phase. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo (saline solution 0.9%) was administered by deep SC injection in the superior, external quadrant of the buttock at a dose of 120 mg, every 28 days (Q4 weeks).

Number of subjects in period 1	Lanreotide	Placebo
Started	51	26
Completed	41	21
Not completed	10	5
Consent withdrawn by subject	4	2
Disease progression	5	2
Adverse event, non-fatal	-	1
Lost to follow-up	1	-

Period 2

Period 2 title	Open-Label Treatment Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lanreotide

Arm description:

Subjects received deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and continue to receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the double-blind phase or open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Arm type	Experimental
Investigational medicinal product name	Lanreotide
Investigational medicinal product code	
Other name	LAN
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lanreotide Autogel/Depot 120 mg was administered by deep SC injection in the superior, external quadrant of the buttock at a dose of 120 mg, every 28 days (Q4 weeks).

Arm title	Placebo

Arm description:

Subjects received deep SC injections of placebo (saline solution 0.9%) Q4 weeks plus BSC in the double-blind phase. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Arm type	Placebo
Investigational medicinal product name	Lanreotide
Investigational medicinal product code	
Other name	LAN
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lanreotide Autogel/Depot 120 mg was administered by deep SC injection in the superior, external quadrant of the buttock at a dose of 120 mg, every 28 days (Q4 weeks).

Number of subjects in period 2[1]	Lanreotide	Placebo
Started	21	19
Completed	1	6
Not completed	20	13
Consent withdrawn by subject	-	2
Disease progression	1	2
Study termination by the sponsor	18	9
Unspecified	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Prior to protocol amendment #5, subjects qualified for the option to continue into the open-label treatment phase if they met the following additional inclusion criteria:
Subjects have central review confirmed/documented disease progression;
There was a request from the subject to receive open-label lanreotide plus BSC;
Subjects were randomised in the placebo plus BSC arm.
Following protocol amendment #5, the open-label treatment phase remained optional for all subjects.

Period 3

Period 3 title	Open-Label Follow-up Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No

Arm title	Lanreotide

Arm description:

Subjects received deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and continue to receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the double-blind phase or open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo

Arm description:

Subjects received deep SC injections of placebo (saline solution 0.9%) Q4 weeks plus BSC in the double-blind phase. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Lanreotide	Placebo
Started	18	8
Completed	0	0
Not completed	18	8
Consent withdrawn by subject	3	3
Study termination by the sponsor	6	4
Unspecified	8	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Lanreotide
Reporting group description:	
Subjects received deep subcutaneous (SC) injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and continue to receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the double-blind phase or open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).	
Reporting group title	Placebo
Reporting group description:	
Subjects received deep SC injections of placebo (saline solution 0.9%) Q4 weeks plus BSC in the double-blind phase. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).	

Reporting group values	Lanreotide	Placebo	Total
Number of subjects	51	26	77
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	66.4	65.8	
standard deviation	± 11.94	± 13.89	-
Gender categorical Units: Subjects			
Female	23	12	35
Male	28	14	42
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	9	4	13
Missing	42	22	64
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	0	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	35	19	54
More than one race	0	0	0
Unknown or Not Reported	12	7	19

End points reporting groups

Reporting group title	Lanreotide

Reporting group description:

Subjects received deep subcutaneous (SC) injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and continue to receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the double-blind phase or open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Reporting group title	Placebo

Reporting group description:

Subjects received deep SC injections of placebo (saline solution 0.9%) Q4 weeks plus BSC in the double-blind phase. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Reporting group title	Lanreotide

Reporting group description:

Subjects received deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and continue to receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the double-blind phase or open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Reporting group title	Placebo

Reporting group description:

Subjects received deep SC injections of placebo (saline solution 0.9%) Q4 weeks plus BSC in the double-blind phase. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Reporting group title	Lanreotide

Reporting group description:

Subjects received deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and continue to receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the double-blind phase or open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Reporting group title	Placebo

Reporting group description:

Subjects received deep SC injections of placebo (saline solution 0.9%) Q4 weeks plus BSC in the double-blind phase. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Subject analysis set title	Overall Study: Lanreotide
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the double-blind phase or open-label treatment phase they entered the open-label follow-up phase. The follow-up phase ended at the same time as the open-label treatment phase (18 months after the last subject randomised).

Subject analysis set title	Double-Blind Phase: Lanreotide
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and continue to receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the double-blind phase they entered the open-label follow-up phase.

Subject analysis set title	Double-Blind Phase: Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received deep SC injections of placebo (saline solution 0.9%) Q4 weeks plus BSC in the double-blind phase. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC.

Subject analysis set title	Open-Label Treatment Phase: All Subjects
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the open-label treatment phase they entered the open-label follow-up phase.

Primary: Median PFS Time in Subjects Randomised to Lanreotide in the Double-Blind Phase or Open-Label Treatment Phase, Assessed by Central Review

End point title	Median PFS Time in Subjects Randomised to Lanreotide in the Double-Blind Phase or Open-Label Treatment Phase, Assessed by Central Review[1]

End point description:

PFS for subjects randomised in the lanreotide group, assessed by central review using Response Evaluation Criteria In Solid Tumours Version 1.1 (RECIST v1.1) criteria every 12 weeks, defined as the time from randomisation to disease progression or death from any causes during either the double-blind phase, or the open-label treatment phase. The distribution of PFS times were estimated using the Kaplan-Meier product limit method. The intention to treat (ITT) Population included all randomised subjects. Subjects were analysed as randomised, regardless of the treatment received. One subject randomised to lanreotide should have been censored in the PFS analysis for treatment discontinuation for toxicity or other reasons, however the baseline central radiological assessment was performed prior to the randomisation date, therefore the subject was excluded from the analysis.

End point type	Primary

End point timeframe:

Up to a maximum of 33 months

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 additional statistical analysis was prespecified for this endpoint.

End point values	Overall Study: Lanreotide			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: months				
median (confidence interval 95%)	16.6 (12.8 to 21.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median PFS Time in the Double-Blind Phase, Assessed by Central Review

End point title	Median PFS Time in the Double-Blind Phase, Assessed by Central Review

End point description:

PFS was assessed by central review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomisation to disease progression or death from any causes during the double-blind phase. The distribution of PFS times were estimated using the Kaplan-Meier product limit method. The ITT Population included all randomised subjects. Subjects were analysed as randomised, regardless of the treatment received. One subject in the double-blind phase: lanreotide arm should have been censored in the PFS analysis for treatment discontinuation for toxicity or other reasons, however the baseline central radiological assessment was performed prior to the randomisation date, therefore the subject was excluded from the analysis. '99999' denotes the upper confidence interval (CI) was not calculable due to insufficient progression events.

End point type	Secondary

End point timeframe:

Up to a maximum of 15 months

End point values	Double-Blind Phase: Lanreotide	Double-Blind Phase: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	26		
Units: months				
median (confidence interval 95%)	16.6 (11.3 to 21.9)	13.6 (8.3 to 99999)		

Statistical analyses

Statistical analysis title	Lanreotide versus (vs) Placebo

Statistical analysis description:

The hazard ratio and the 95% CI were estimated using a Cox proportional hazards model, stratified for interactive web response system (IWRS) tumour subtype (typical vs atypical) using the exact method for ties. P-value of stratified log rank test comparing lanreotide to placebo with strata based on the IWRS tumour subtype (typical vs atypical) stratification factor.

Comparison groups	Double-Blind Phase: Lanreotide v Double-Blind Phase: Placebo

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.88

Secondary: Median PFS Time in the Double-Blind Phase, Assessed by Local Review

End point title	Median PFS Time in the Double-Blind Phase, Assessed by Local Review

End point description:

PFS was assessed by local review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomisation to disease progression or death from any causes during the double-blind phase. The distribution of PFS times were estimated using the Kaplan-Meier product limit method. The ITT population included all randomised subjects. Subjects were analysed as randomised, regardless of the treatment received. Two subjects should have been censored in the PFS analysis, however the baseline central radiological assessment was performed prior to the randomisation date, therefore the subjects were excluded from the analysis. '99999' denotes the upper CI was not calculable due to insufficient progression events.

End point type	Secondary

End point timeframe:

Up to a maximum of 15 months

End point values	Double-Blind Phase: Lanreotide	Double-Blind Phase: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	25		
Units: months				
median (confidence interval 95%)	16.6 (11.1 to 99999)	13.6 (8.3 to 99999)		

Statistical analyses

Statistical analysis title	Lanreotide vs Placebo

Statistical analysis description:

The hazard ratio and the 95% CI were estimated using a Cox proportional hazards model, stratified for IWRS tumour subtype (typical vs atypical) using the exact method for ties. P-value of stratified log rank test comparing lanreotide to placebo with strata based on the IWRS tumour subtype (typical vs atypical) stratification factor.

Comparison groups	Double-Blind Phase: Lanreotide v Double-Blind Phase: Placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.671
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.76

Secondary: Objective Response Rate (ORR) in the Double-Blind Phase

End point title	Objective Response Rate (ORR) in the Double-Blind Phase

End point description:

ORR was assessed by central review and local review using RECIST v1.1 criteria every 12 weeks, defined as the percentage of subjects who achieved a best overall response of complete response or partial response in the double-blind phase. The ITT population included all randomised subjects. Subjects were analysed as randomised, regardless of the treatment received. Two subjects were excluded from the analysis as they had no best response recorded in the raw data.

End point type	Secondary

End point timeframe:

Up to a maximum of 15 months

End point values	Double-Blind Phase: Lanreotide	Double-Blind Phase: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	25		
Units: percentage of subjects				
number (confidence interval 95%)				
Central review	14.00 (5.82 to 26.74)	0.00 (0.00 to 13.72)		
Local review	6.00 (1.25 to 16.55)	4.00 (0.10 to 20.35)		

Statistical analyses

Statistical analysis title	Lanreotide vs Placebo (Central Review)

Statistical analysis description:

The treatment difference compares lanreotide to placebo (central review). The 95% exact unconditional CI was used for ORR difference

Comparison groups	Double-Blind Phase: Lanreotide v Double-Blind Phase: Placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage difference
Point estimate	14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.97
upper limit	37.86

Statistical analysis title	Lanreotide vs Placebo (Local Review)

Statistical analysis description:

The treatment difference compares lanreotide to placebo (local review). The 95% exact unconditional CI was used for ORR difference

Comparison groups	Double-Blind Phase: Lanreotide v Double-Blind Phase: Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.69
upper limit	26.53

Secondary: Time to Treatment Failure (TTF) in the Double-Blind Phase

End point title	Time to Treatment Failure (TTF) in the Double-Blind Phase

End point description:

TTF was defined as the time from randomisation to disease progression using RECIST v1.1, death, consent withdrawn, an adverse event, protocol deviations, lost to follow-up, the appearance of carcinoid syndrome or other hormone related syndrome necessitating the initiation of SSAs (rescue octreotide and/or long-acting release SSA), or initiation of anticancer treatment in the double-blind phase. The distribution of TTF times were estimated using the Kaplan-Meier product limit method. The ITT Population included all randomised subjects. Subjects were analysed as randomised, regardless of the treatment received.

End point type	Secondary

End point timeframe:

Up to a maximum of 15 months

End point values	Double-Blind Phase: Lanreotide	Double-Blind Phase: Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	26		
Units: months				
median (confidence interval 95%)	13.3 (5.6 to 14.1)	9.8 (5.4 to 13.6)		

Statistical analyses

Statistical analysis title	Lanreotide vs Placebo

Statistical analysis description:

The hazard ratio and the 95% CI were estimated using a Cox proportional hazards model, stratified for IWRS tumour subtype (typical vs atypical) using the exact method for ties. P-value of stratified log rank test comparing lanreotide to placebo with strata based on the IWRS tumour subtype (typical vs atypical) stratification factor.

Comparison groups	Double-Blind Phase: Lanreotide v Double-Blind Phase: Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.582
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.5

Secondary: Mean Changes From Baseline in the Biomarker Chromogranin A (CgA) in the Double-Blind Phase and Open-Label Treatment Phase

End point title	Mean Changes From Baseline in the Biomarker Chromogranin A (CgA) in the Double-Blind Phase and Open-Label Treatment Phase

End point description:

Blood samples were collected to determine plasma CgA. Baseline was defined as the last non-missing measurement collected prior to the first dose of study treatment (lanreotide). The x of the upper limit of nornal (ULN) was calculated as raw value/ULN. Double-blind phase: The ITT Population included all randomised subjects with non-missing measurements. Subjects were analysed as randomised, regardless of the treatment received. Open-label phase: The open-label ITT Population included all ITT subjects with non-missing measurements entering the open-label phase who received at least one injection of lanreotide autogel/depot in the open-label phase. 'n' denotes number of subjects analysed at each specified time point; '9999' denotes no subjects were analysed.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 12, 24, and 48, and post-treatment in the double-blind phase (a maximum of 15 months); Baseline, Weeks 12, 24, and 48, and post-treatment in the the open-label treatment phase (a maximum of 33 months)

End point values	Double-Blind Phase: Lanreotide	Double-Blind Phase: Placebo	Open-Label Treatment Phase: All Subjects	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38	22	33	
Units: x of ULN				
arithmetic mean (standard deviation)				
Week 8 (n = 38, 22, 0)	-213.63 (± 1293.111)	0.09 (± 2.578)	9999 (± 9999)	
Week 12 (n = 38, 20, 33)	-214.49 (± 1344.401)	5.73 (± 15.519)	-28.27 (± 149.110)	
Week 24 (n = 33, 19, 30)	-3.42 (± 14.122)	60.41 (± 193.327)	-1.42 (± 8.338)	
Week 48 (n = 24, 11, 7)	-4.07 (± 8.066)	1.24 (± 2.969)	-1.66 (± 0.925)	
Post-treatment (n = 33, 14, 31)	12.22 (± 64.053)	160.11 (± 596.759)	-31.59 (± 167.515)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Decrease of CgA ≥30% From Baseline at Week 8 in the Double-Blind Phase and Open-Label Treatment Phase

End point title	Percentage of Subjects With a Decrease of CgA ≥30% From Baseline at Week 8 in the Double-Blind Phase and Open-Label Treatment Phase

End point description:

Measured in subjects with an elevated CgA at baseline (≥2 x ULN). Blood samples were collected to determine plasma CgA. Baseline was defined as the last non-missing measurement collected prior to the first dose of study treatment (lanreotide). Double-blind phase: The ITT Population included all randomised subjects with non-missing measurements and elevated CgA at baseline. Subjects were analysed as randomised, regardless of the treatment received. Open-label phase: The open-label ITT Population included all ITT subjects with non-missing measurements and elevated CgA at baseline entering the open-label phase who received at least one injection of lanreotide autogel/depot in the open-label phase.

End point type	Secondary

End point timeframe:

Baseline and Week 8 in the double-blind phase; Baseline and Week 8 in the open-label treatment phase

End point values	Double-Blind Phase: Lanreotide	Double-Blind Phase: Placebo	Open-Label Treatment Phase: All Subjects	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	13	19	
Units: percentage of subjects				
number (confidence interval 95%)	63.3 (43.9 to	7.7 (0.2 to	73.7 (48.8 to	

80.1)	36.0)	90.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes From Baseline in Quality of Life (QoL), as Assessed by the European Organisation for Research and Treatment of Cancer QoL Questionnaire Core-30 (EORTC QLQ-C30) Global Health Status (GHS)/QoL Score

End point title	Mean Changes From Baseline in Quality of Life (QoL), as Assessed by the European Organisation for Research and Treatment of Cancer QoL Questionnaire Core-30 (EORTC QLQ-C30) Global Health Status (GHS)/QoL Score

End point description:

The EORTC QLQ-C30 (Version 3.0) consisted of 30 questions. The final 2 questions were related to GHS/QoL, with responses requested on a 7-point scale from 1 ('Very poor') to 7 ('Excellent'). The GHS/QoL scale ranges in score from 0 to 100. A high score for the GHS/QoL scale represents a high QoL, thus, an increase in score represents an increase in QoL. 95% Clopper-Pearson CIs were estimated using the exact method for binomial distributions. Baseline was defined as the last non-missing measurement collected prior to the first dose of study treatment (lanreotide).

End point type	Secondary

End point timeframe:

Baseline and post-treatment in the double-blind phase (a maximum of 15 months); Baseline and post-treatment in the open-label treatment phase (a maximum of 33 months)

End point values	Double-Blind Phase: Lanreotide	Double-Blind Phase: Placebo	Open-Label Treatment Phase: All Subjects	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	3	34	
Units: score on a scale				
arithmetic mean (standard deviation)	-2.7 (± 18.27)	-19.4 (± 17.33)	0.0 (± 19.67)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Experienced QoL Deterioration

End point title	Percentage of Subjects Who Experienced QoL Deterioration

End point description:

QoL deterioration was defined by a decrease from baseline in EORTC QLQ-C30 GHS/QoL Score of at least 10 points. The EORTC QLQ-C30 (V3.0) consisted of 30 questions. The final 2 questions were related to GHS/QoL, with responses requested on a 7-point scale from 1 ('Very poor') to 7 ('Excellent'). The GHS/QoL scale ranges in score from 0 to 100. A high score for the GHS/QoL scale represents a high QoL, thus, an increase in score represents an increase in QoL. 95% Clopper-Pearson CIs were estimated

using the exact method for binomial distributions. Baseline was defined as the last non-missing measurement collected prior to the first dose of study treatment (lanreotide). Double-blind phase: The ITT population. Open-label phase: The open-label ITT population.

End point type	Secondary

End point timeframe:

Baseline and post-treatment in the double-blind phase (a maximum of 15 months); Baseline and post-treatment in the open-label treatment phase (a maximum of 33 months)

End point values	Double-Blind Phase: Lanreotide	Double-Blind Phase: Placebo	Open-Label Treatment Phase: All Subjects	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	3	34	
Units: percentage of subjects				
number (confidence interval 95%)	32.0 (14.9 to 53.5)	66.7 (9.4 to 99.2)	23.5 (10.7 to 41.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes From Baseline in Urinary 5-hydroxyindoleacetic Acid (5-HIAA) Levels in the Double-Blind Phase and Open-Label Treatment Phase

End point title	Mean Changes From Baseline in Urinary 5-hydroxyindoleacetic Acid (5-HIAA) Levels in the Double-Blind Phase and Open-Label Treatment Phase

End point description:

Measured in subjects with an elevated 5-HIAA at baseline (≥2 x ULN). The assessment of urinary 5-HIAA required subjects to collect their urine for the 24 hour period prior to the study visit. Baseline was defined as the last non-missing measurement collected prior to the first dose of study treatment (lanreotide). The x of ULN was calculated as raw value/ULN. Double-blind phase: The ITT Population included all randomised subjects with non-missing measurements and elevated 5-HIAA at baseline. Subjects were analysed as randomised, regardless of the treatment received. Open-label phase: The open-label ITT Population included all ITT subjects with non-missing measurements and elevated 5-HIAA at baseline entering the open-label phase who received at least one injection of lanreotide autogel/depot in the open-label phase. 'n' denotes number of subjects analysed at each specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 12, 24, and 48, and post-treatment in the double-blind phase (a maximum of 15 months); Baseline, Weeks 12, 24, and 48, and post-treatment in the the open-label treatment phase (a maximum of 33 months)

End point values	Double-Blind Phase: Lanreotide	Double-Blind Phase: Placebo	Open-Label Treatment Phase: All Subjects	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	4[2]	3[3]	
Units: x of ULN				
arithmetic mean (standard deviation)				
Week 8 (n = 7, 4, 0)	-2.90 (± 5.368)	2.78 (± 4.215)	9999 (± 9999)	
Week 12 (n = 5, 3, 2)	0.21 (± 1.904)	5.38 (± 4.342)	-0.47 (± 1.886)	
Week 24 (n = 5, 2, 3)	0.15 (± 3.041)	-1.40 (± 2.734)	-4.84 (± 10.019)	
Week 48 (n = 4, 1, 1)	-3.00 (± 8.900)	1.13 (± 99999)	-2.47 (± 99999)	
Post-treatment (n = 5, 2, 2)	-1.27 (± 7.007)	-5.13 (± 11.597)	0.60 (± 3.583)	

Notes:

[2] - '99999' denotes standard deviation was not calculable as only 1 subject was analysed.

[3] - '9999' denotes no subjects were analysed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days after the last study treatment administration/early termination, approximately 33 months

Adverse event reporting additional description:

The safety population included all subjects who received at least one injection of study treatment. Subjects were analysed as treated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Double-Blind Phase: Lanreotide

Reporting group description:

Subjects received deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and continue to receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the double-blind phase they entered the open-label follow-up phase.

Reporting group title	Open-Label Follow-Up Phase: All Subjects

Reporting group description:

If the subject received lanreotide autogel/depot and progressed during the double-blind phase or open-label treatment phase, the subject entered the follow-up phase of the open-label extension phase and was followed for QoL/survival and all subsequent anticancer treatments received. No intervention was received in the open-label follow-up phase.

Reporting group title	Open-Label Treatment Phase: All Subjects

Reporting group description:

Subjects received deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC. If a subject progressed during the open-label treatment phase they entered the open-label follow-up phase.

Reporting group title	Double-Blind Phase: Placebo

Reporting group description:

Subjects received deep SC injections of placebo (saline solution 0.9%) Q4 weeks plus BSC in the double-blind phase. Following protocol amendment #5 (28 Jan 2019), all ongoing subjects in the double-blind phase, who had not yet progressed (assessed locally and confirmed centrally) were offered to enter the open-label treatment phase and receive deep SC injections of lanreotide autogel/depot 120 mg Q4 weeks plus BSC.

Serious adverse events	Double-Blind Phase: Lanreotide	Open-Label Follow-Up Phase: All Subjects	Open-Label Treatment Phase: All Subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 51 (19.61%)	0 / 26 (0.00%)	1 / 40 (2.50%)
number of deaths (all causes)	2	7	0
number of deaths resulting from adverse events	1	0	0
Injury, poisoning and procedural complications			
Femoral neck fracture			

subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Atrioventricular block complete			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Myocardial infarction			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Nervous system disorders			
Vagus nerve disorder			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Diarrhoea			

subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (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
Gastritis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (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
Inguinal hernia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (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
Pancreatitis acute			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Subileus			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (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			
Biliary dilatation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Cholecystitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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

Dyspnoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Pneumothorax			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (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 distress			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Confusional state			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (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
Mental status changes			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (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
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (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			
Pneumocystis jirovecii infection			

subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (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
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-Blind Phase: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 26 (26.92%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Vagus nerve disorder			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Subileus			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcohol withdrawal syndrome			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumocystis jirovecii infection			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Double-Blind Phase: Lanreotide	Open-Label Follow-Up Phase: All Subjects	Open-Label Treatment Phase: All Subjects
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 51 (94.12%)	0 / 26 (0.00%)	26 / 40 (65.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Basal cell carcinoma			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Cancer pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Squamous cell carcinoma			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Tumour pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Flushing			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	2
Hypertension			
subjects affected / exposed	5 / 51 (9.80%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	14	0	0
Hypotension			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Varicose vein			

subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 51 (21.57%)	0 / 26 (0.00%)	2 / 40 (5.00%)
occurrences (all)	19	0	10
Chest discomfort			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	2
Chest pain			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	5	0	1
Chills			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	13 / 51 (25.49%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	20	0	1
General physical health deterioration			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	4 / 51 (7.84%)	0 / 26 (0.00%)	2 / 40 (5.00%)
occurrences (all)	5	0	2
Injection site pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Injection site reaction			
subjects affected / exposed	3 / 51 (5.88%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	5	0	0
Non-cardiac chest pain			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	3	0	1
Oedema			

subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	5 / 51 (9.80%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	10	0	1
Pyrexia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	2	0	2
Xerosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Contrast media reaction			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Drug hypersensitivity			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Vaginal discharge			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal dryness			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Asthma			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Asthma-chronic obstructive			

pulmonary disease overlap syndrome			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	3 / 51 (5.88%)	0 / 26 (0.00%)	2 / 40 (5.00%)
occurrences (all)	4	0	4
Atelectasis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	6 / 51 (11.76%)	0 / 26 (0.00%)	2 / 40 (5.00%)
occurrences (all)	8	0	3
Dyspnoea exertional			
subjects affected / exposed	5 / 51 (9.80%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	6	0	2
Emphysema			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Interstitial lung disease			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Mediastinal fibrosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1

Productive cough			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	3	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	2	0	1
Confusional state			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	3 / 51 (5.88%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Insomnia			
subjects affected / exposed	4 / 51 (7.84%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	5	0	0
Irritability			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Investigations			
Amylase increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blood albumin increased			

subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 51 (5.88%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	3	0	2
Blood bilirubin increased			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Blood cholesterol increased			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	2	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Blood glucose increased			
subjects affected / exposed	4 / 51 (7.84%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood potassium increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blood sodium decreased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood triglycerides increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			

subjects affected / exposed	3 / 51 (5.88%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	3	0	1
Intestinal transit time increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Lipase increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	4 / 51 (7.84%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	5	0	1
Weight increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Fall			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	2	0	1
Joint dislocation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Procedural nausea			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Scar			

subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Atrioventricular block			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Atrioventricular block second degree			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Bradycardia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Cardiac failure			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Cardiovascular disorder			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Nervous system disorders			
Carotid arteriosclerosis			

subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Cognitive disorder			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Cervicobrachial syndrome			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Coordination abnormal			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Dementia Alzheimer's type			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	8 / 51 (15.69%)	0 / 26 (0.00%)	2 / 40 (5.00%)
occurrences (all)	15	0	2
Dysgeusia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	4 / 51 (7.84%)	0 / 26 (0.00%)	4 / 40 (10.00%)
occurrences (all)	5	0	5
Head discomfort			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Lacunar infarction			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Memory impairment			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Neuralgia			

subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Parkinsonism			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Hyperleukocytosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Anaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Leukocytosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Vertigo			

subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	3 / 40 (7.50%)
occurrences (all)	3	0	4
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Eye haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Glaucoma			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Lacrimation increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Swelling of eyelid			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	5 / 51 (9.80%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	14	0	1
Abdominal pain			
subjects affected / exposed	10 / 51 (19.61%)	0 / 26 (0.00%)	4 / 40 (10.00%)
occurrences (all)	21	0	4
Abdominal pain upper			
subjects affected / exposed	5 / 51 (9.80%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	5	0	0
Anal incontinence			

subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Ascites			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	32 / 51 (62.75%)	0 / 26 (0.00%)	9 / 40 (22.50%)
occurrences (all)	61	0	13
Constipation			
subjects affected / exposed	8 / 51 (15.69%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	9	0	1
Dry mouth			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Dyschezia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Dysphagia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	7 / 51 (13.73%)	0 / 26 (0.00%)	2 / 40 (5.00%)
occurrences (all)	12	0	2
Erosive duodenitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Glycogenic acanthosis			

subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Hiatus hernia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Impaired gastric emptying			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	6 / 51 (11.76%)	0 / 26 (0.00%)	3 / 40 (7.50%)
occurrences (all)	17	0	5
Pancreatic failure			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Paraesthesia oral			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Rectal tenesmus			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Steatorrhoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Stomatitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	7 / 51 (13.73%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	8	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

Hepatomegaly			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Actinic keratosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 26 (0.00%)	2 / 40 (5.00%)
occurrences (all)	3	0	2
Dry skin			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Melanoderma			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Pruritus			

subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Rash			
subjects affected / exposed	3 / 51 (5.88%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Skin induration			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Nocturia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Polyuria			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

Renal mass			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Urinary tract discomfort			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Renal pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Endocrine disorders			
Carcinoid syndrome			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Hyperthyroidism			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 51 (11.76%)	0 / 26 (0.00%)	2 / 40 (5.00%)
occurrences (all)	8	0	2
Arthritis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	5 / 51 (9.80%)	0 / 26 (0.00%)	3 / 40 (7.50%)
occurrences (all)	6	0	3
Bursitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Joint swelling			

subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	2	0	1
Musculoskeletal chest pain			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	2	0	1
Muscular weakness			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	4	0	2
Myalgia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Rotator cuff syndrome			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Synovial cyst			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Bronchitis			
subjects affected / exposed	5 / 51 (9.80%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	6	0	0
Candida infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Conjunctivitis bacterial			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	4 / 51 (7.84%)	0 / 26 (0.00%)	2 / 40 (5.00%)
occurrences (all)	6	0	4
Pneumonia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Paronychia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Postoperative wound infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Skin infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1

Tinea pedis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Tooth abscess			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Tooth infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	3 / 51 (5.88%)	0 / 26 (0.00%)	3 / 40 (7.50%)
occurrences (all)	3	0	6
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	6 / 51 (11.76%)	0 / 26 (0.00%)	3 / 40 (7.50%)
occurrences (all)	7	0	4
Dehydration			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Hyperglycaemia			
subjects affected / exposed	4 / 51 (7.84%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	5	0	3
Hyperkalaemia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Hypernatraemia			

subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	2
Hypoglycaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	3 / 40 (7.50%)
occurrences (all)	1	0	3
Vitamin D deficiency			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Double-Blind Phase: Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 26 (96.15%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Basal cell carcinoma			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Cancer pain			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Tumour pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Flushing			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Varicose vein			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	11		
Chest discomfort			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Chest pain			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	10 / 26 (38.46%)		
occurrences (all)	10		
General physical health deterioration			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Injection site reaction			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Oedema			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Xerosis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
Immune system disorders			

Contrast media reaction subjects affected / exposed occurrences (all) Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0 1 / 26 (3.85%) 3		
Reproductive system and breast disorders Breast tenderness subjects affected / exposed occurrences (all) Vaginal discharge subjects affected / exposed occurrences (all) Vulvovaginal dryness subjects affected / exposed occurrences (all)	 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Aphonia subjects affected / exposed occurrences (all) Asthma subjects affected / exposed occurrences (all) Asthma-chronic obstructive pulmonary disease overlap syndrome subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Atelectasis subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all)	 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 3 / 26 (11.54%) 3 1 / 26 (3.85%) 1 0 / 26 (0.00%) 0		

Dyspnoea				
subjects affected / exposed	4 / 26 (15.38%)			
occurrences (all)	4			
Dyspnoea exertional				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Emphysema				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Interstitial lung disease				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Haemoptysis				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Mediastinal fibrosis				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Nasal congestion				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Oropharyngeal pain				
subjects affected / exposed	3 / 26 (11.54%)			
occurrences (all)	3			
Productive cough				
subjects affected / exposed	3 / 26 (11.54%)			
occurrences (all)	3			
Rhinorrhoea				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Sleep apnoea syndrome				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Upper-airway cough syndrome				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			

Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Confusional state			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Irritability			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Investigations			
Amylase increased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood albumin increased			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood cholesterol increased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Blood creatinine increased				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Blood glucose increased				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Blood lactate dehydrogenase increased				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Blood potassium increased				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Blood sodium decreased				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	2			
Blood triglycerides increased				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Intestinal transit time increased				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Lipase increased				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Weight decreased				
subjects affected / exposed	3 / 26 (11.54%)			
occurrences (all)	3			
Weight increased				

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Joint dislocation			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Procedural nausea			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Scar			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Atrial fibrillation			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Atrioventricular block			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Atrioventricular block second degree			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Bradycardia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Cardiac failure			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Cardiovascular disorder			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Left ventricular hypertrophy			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Carotid arteriosclerosis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Cognitive disorder			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Cervicobrachial syndrome			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Coordination abnormal			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Dementia Alzheimer's type			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		

Dizziness				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Dysgeusia				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Headache				
subjects affected / exposed	4 / 26 (15.38%)			
occurrences (all)	4			
Head discomfort				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Hypoaesthesia				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Lacunar infarction				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Memory impairment				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Neuralgia				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Neuropathy peripheral				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Sciatica				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Parkinsonism				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Syncope				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			

Blood and lymphatic system disorders			
Hyperleukocytosis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Iron deficiency anaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Leukocytosis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Lymphadenopathy			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Eye haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Glaucoma			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Lacrimation increased			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Swelling of eyelid			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	4		
Anal incontinence			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Ascites			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	8 / 26 (30.77%)		
occurrences (all)	12		
Constipation			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	4		
Dry mouth			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Dyschezia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		

Dyspepsia				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Dysphagia				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Flatulence				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Erosive duodenitis				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Frequent bowel movements				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Glycogenic acanthosis				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Haemorrhoids				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Hiatus hernia				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Impaired gastric emptying				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	4 / 26 (15.38%)			
occurrences (all)	4			
Pancreatic failure				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			

Paraesthesia oral			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Rectal tenesmus			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Steatorrhoea			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hepatomegaly			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Actinic keratosis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Dry skin			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Melanoderma			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Rash maculo-papular			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Skin induration			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Skin lesion			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			

Chronic kidney disease			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Nocturia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Polyuria			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Renal mass			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Urinary tract discomfort			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Renal pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Carcinoid syndrome			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hyperthyroidism			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Arthritis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Bursitis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
Flank pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Joint swelling			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Myalgia			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Osteoporosis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Rotator cuff syndrome			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Synovial cyst			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Candida infection			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Conjunctivitis bacterial			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		

Gastroenteritis				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Nasopharyngitis				
subjects affected / exposed	4 / 26 (15.38%)			
occurrences (all)	4			
Pneumonia				
subjects affected / exposed	1 / 26 (3.85%)			
occurrences (all)	1			
Paronychia				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Postoperative wound infection				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Respiratory tract infection				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Skin infection				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Tinea pedis				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Tooth abscess				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Tooth infection				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				
subjects affected / exposed	2 / 26 (7.69%)			
occurrences (all)	2			
Urinary tract infection				
subjects affected / exposed	0 / 26 (0.00%)			
occurrences (all)	0			

Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	6 / 26 (23.08%)		
occurrences (all)	7		
Dehydration			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	11		
Hyperkalaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypernatraemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Iron deficiency			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Vitamin D deficiency			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2015	Taking into consideration the recently presented results of the RADIANT IV study and feedback from key thought leaders, it was decided to amend the A-US-52030-328 Protocol in order to: • Extend the patient population; • Modify the primary criteria; • Add a stratification factor; • Include European sites; • Change from a Phase 2 to a Phase 3 study.
20 April 2016	• To align the protocol with the Investigational Brochure and SmPC, as requested by the French Ministry of Health (ANSM) and French Ethic Committee (CPP Ile de France 8); • To align the protocol with the guidelines for assessing EORTC QoL in clinical trials; • To provide a more accurate definition of the treatment failure; • To align the protocol with the biobanking standard guidance; • To harmonise the language (English US to English UK) and correct minor inconsistencies.
13 June 2016	• Somatostatin receptor imaging (SRI) Clarification on the evaluation method for one type of SRI (Ga-PET) (update electronic case report form page); • Protocol clarifications/re-wording.
05 October 2016	Main changes of the protocol amendment #4 are linked to requests from Regulatory European authorities and ethics committees (ECs) and from the FDA: • Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) removed (as requested by the French EC) as it is a general questionnaire not specifically validated in oncology and not developed for use in randomised controlled trial. This questionnaire mainly used to assess subjects' satisfaction either in symptomatic diseases or when the administration mode differs from one arm to another. Given the asymptomatic nature of the disease studied, it is expected that the questions in the TSQM 9 are not appropriate; • Study objective and endpoints re-ordered & sensitivity analysis added to follow the FDA requests; • Inclusion & exclusion criteria reviewed taking into account the German Competent Authority request; • Several subjects receive Chemotherapy upfront in daily practice – to allow these subjects to be included in the study the exclusion criterion was adapted (up to 2 lines of chemotherapy prior to the study entry); • Commercial product provided to the subject if they still benefit of it at the end of the study (request from the research EC in UK and from the Central EC in Italy).
28 January 2019	• Administrative changes; • Changes of the objectives, endpoints and study design due to the premature stop of the recruitment; • Changes in Biobanking and pharmacokinetics (PK) (location of samples; PK modelling removed due to lack of subjects).

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.

National Comprehensive Cancer Network & European Neuroendocrine Tumor Society guidelines (2015/2016) led to prescription of SSAs in this setting, thereby limiting recruitment.

Notes: