



Clinical trial results:

Double blind, Randomised, Placebo Controlled Clinical Trial Investigating the Efficacy and Safety of Somatuline Depot (Lanreotide) Injection in the Treatment of Carcinoid Syndrome

Summary

EudraCT number	2010-019066-92
Trial protocol	CZ LV PL
Global end of trial date	15 December 2015

Results information

Result version number	v1 (current)
This version publication date	05 January 2018
First version publication date	05 January 2018

Trial information

Trial identification

Sponsor protocol code	2-55-52030-730
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00774930
WHO universal trial number (UTN)	-
Other trial identifiers	TR321: TR321

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma SAS
Sponsor organisation address	65 quai Georges Gorse, Boulogne Billancourt Cedex, France, 92100
Public contact	Medical Director, Oncology, Ipsen Pharma SAS, clinical.trials@ipsen.com
Scientific contact	Medical Director, Oncology, Ipsen Pharma SAS, 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	15 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2015
Global end of trial reached?	Yes
Global end of trial date	15 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of lanreotide Autogel (Somatuline Depot) subcutaneous (s.c.) injections administered every 4 weeks (\pm 3 days) for the control of symptoms associated with carcinoid syndrome (diarrhoea and/or flushing) as compared to placebo, measured by the usage of subcutaneous octreotide as rescue medication to control symptoms.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice. All national and local regulatory requirements were also adhered to.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 May 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 40
Country: Number of subjects enrolled	Latvia: 2
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Ukraine: 25
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	India: 8
Country: Number of subjects enrolled	Brazil: 18
Worldwide total number of subjects	115
EEA total number of subjects	6

Notes:

Subjects enrolled per age group

In utero	0
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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)	78
From 65 to 84 years	36
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients with a history of carcinoid syndrome were enrolled into this multi-site, 3 phase study from 26 May 2009. There was a 16 week double-blind phase, a 32 week open-label phase, and long-term open-label extension. The last patient completed the double-blind phase on 6 May 2013, and the open-label extension on 15 December 2015.

Pre-assignment

Screening details:

153 patients were screened, and 115 patients met all inclusion criteria and none of the exclusion criteria to be randomised to the double-blind phase.

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 Autogel

Arm description:

Patients were randomised to receive lanreotide Autogel 120 milligrams (mg) deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks).

Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.

Arm type	Active comparator
Investigational medicinal product name	Lanreotide Autogel
Investigational medicinal product code	Lanreotide Autogel 120 mg
Other name	Somatuline Depot
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients were administered lanreotide Autogel 120 mg deep s.c. injection every 4 weeks if randomised to receive this treatment in the double-blind phase, in the initial open-label phase and in the long-term open-label extension.

Arm title	Placebo
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Arm description:

Patients were randomised to receive placebo deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks).

Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.

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:

Patients were administered placebo deep s.c. injection every 4 weeks during the double-blind phase.

Placebo consisted of 0.9% saline solution administered in a similar volume to the lanreotide Autogel injection.

Number of subjects in period 1	Lanreotide Autogel	Placebo
Started	59	56
Completed	45	34
Not completed	14	22
Patient decision	1	5
Disease progression	1	1
Adverse event, non-fatal	1	2
Early rollover to open-label phase	11	12
Sponsor decision	-	1
Started non-protocol radiation therapy	-	1

Period 2

Period 2 title	Initial open-label phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lanreotide Autogel

Arm description:

Patients were randomised to receive lanreotide Autogel 120 milligrams (mg) deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks).

Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.

Arm type	Active comparator
Investigational medicinal product name	Lanreotide Autogel
Investigational medicinal product code	Lanreotide Autogel 120 mg
Other name	Somatuline Depot
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients were administered lanreotide Autogel 120 mg deep s.c. injection every 4 weeks if randomised to receive this treatment in the double-blind phase, in the initial open-label phase and in the long-term

open-label extension.

Arm title	Placebo
Arm description: Patients were randomised to receive placebo deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks). Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.	
Arm type	Placebo
Investigational medicinal product name	Lanreotide Autogel
Investigational medicinal product code	Lanreotide Autogel 120 mg
Other name	Somatuline Depot
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients were administered lanreotide Autogel 120 mg deep s.c. injection every 4 weeks if randomised to receive this treatment in the double-blind phase, in the initial open-label phase and in the long-term open-label extension.

Number of subjects in period 2^[1]	Lanreotide Autogel	Placebo
Started	45	33
Completed	43	37
Not completed	13	8
Patient decision	4	3
Disease progression	2	1
Adverse event, non-fatal	1	1
Not specified	1	-
Peptide Receptor Radionuclide Therapy	-	1
Investigator decision	3	2
Sponsor decision	1	-
Patient consumed prohibited medication	1	-
Joined	11	12
Early rollover to open-label phase	11	12

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: One patient in the placebo arm completed the double-blind treatment phase but did not enter the initial open-label phase.

Period 3

Period 3 title	Long-term open-label extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lanreotide Autogel

Arm description:

Patients were randomised to receive lanreotide Autogel 120 milligrams (mg) deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks).

Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.

Arm type	Active comparator
Investigational medicinal product name	Lanreotide Autogel
Investigational medicinal product code	Lanreotide Autogel 120 mg
Other name	Somatuline Depot
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients were administered lanreotide Autogel 120 mg deep s.c. injection every 4 weeks if randomised to receive this treatment in the double-blind phase, in the initial open-label phase and in the long-term open-label extension.

Arm title	Placebo
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Arm description:

Patients were randomised to receive placebo deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks).

Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.

Arm type	Placebo
Investigational medicinal product name	Lanreotide Autogel
Investigational medicinal product code	Lanreotide Autogel 120 mg
Other name	Somatuline Depot
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients were administered lanreotide Autogel 120 mg deep s.c. injection every 4 weeks if randomised to receive this treatment in the double-blind phase, in the initial open-label phase and in the long-term open-label extension.

Number of subjects in period 3^[2]	Lanreotide Autogel	Placebo
Started	32	25
Completed	17	8
Not completed	15	17
Patient decision	-	5
Disease progression	2	5

Adverse event, non-fatal	7	3
Proton Pump Inhibitor Dose Adjusted	-	1
Tumour Progression of Hepatic Metastases	-	1
Investigator decision	4	1
Sponsor decision	2	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The long-term open-label extension allowed for the continued provision of lanreotide Autogel to eligible patients in which lanreotide Autogel was not yet approved, as such not all patients who completed the initial open-label phase entered the long-term open-label extension.

Baseline characteristics

Reporting groups

Reporting group title	Lanreotide Autogel
Reporting group description:	
Patients were randomised to receive lanreotide Autogel 120 milligrams (mg) deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks).	
Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomised to receive placebo deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks).	
Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.	

Reporting group values	Lanreotide Autogel	Placebo	Total
Number of subjects	59	56	115
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	43	35	78
From 65-84 years	16	20	36
85 years and over	0	1	1
Age continuous			
Units: years			
arithmetic mean	57.9	59.3	-
standard deviation	± 10.6	± 11.6	-
Gender categorical			
Units: Subjects			
Female	32	35	67
Male	27	21	48
Race/Ethnicity, Customized			
Units: Subjects			
Asian	6	3	9
Black/African American	2	3	5
White	44	44	88
Multi-race	7	6	13

End points

End points reporting groups

Reporting group title	Lanreotide Autogel
Reporting group description: Patients were randomised to receive lanreotide Autogel 120 milligrams (mg) deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks). Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.	
Reporting group title	Placebo
Reporting group description: Patients were randomised to receive placebo deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks). Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.	
Reporting group title	Lanreotide Autogel
Reporting group description: Patients were randomised to receive lanreotide Autogel 120 milligrams (mg) deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks). Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.	
Reporting group title	Placebo
Reporting group description: Patients were randomised to receive placebo deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks). Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.	
Reporting group title	Lanreotide Autogel
Reporting group description: Patients were randomised to receive lanreotide Autogel 120 milligrams (mg) deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks). Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.	
Reporting group title	Placebo
Reporting group description: Patients were randomised to receive placebo deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks). Eligible patients then entered the initial open-label phase in which they received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks.	
Reporting group title	Lanreotide (Double-blind phase)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients were randomised to receive lanreotide Autogel 120 mg deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks).	
Reporting group title	Placebo (Double-blind phase)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients were randomised to receive placebo deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks).	
Subject analysis set title	Lanreotide (Initial Open-label phase)

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All eligible patients who continued into the initial open-label phase received lanreotide Autogel 120 mg deep s.c. every 4 weeks for 32 weeks. Analysis set includes patients who were randomised to either lanreotide or placebo in the double-blind phase.	
Subject analysis set title	Lanreotide (Long-term Open-label extension)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In the long-term open-label extension, eligible patients continued to receive lanreotide Autogel 120 mg deep s.c. every 4 weeks. Analysis set includes patients who were randomised to either lanreotide or placebo in the double-blind phase.	

Primary: Percentage of days with s.c. octreotide as rescue medication during the double-blind phase

End point title	Percentage of days with s.c. octreotide as rescue medication during the double-blind phase
End point description:	
Patients were required to record daily, using the Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS), the number of diarrhoea and/or flushing events per day as well as the use and dose of s.c. octreotide, if any, as rescue medication.	
The number of days in which s.c. octreotide was used as a rescue medication during the double-blind phase to control symptoms associated with carcinoid syndrome was determined as a measure of lanreotide efficacy. The least squares (LS) mean percentage of days with s.c. octreotide as rescue medication during the 16 week double-blind phase is presented.	
The Intention-to-Treat (ITT) population consisted of all randomised patients (regardless of whether the patients received or adhered to the allocated treatment group). Patients from the ITT population were analysed under the randomised treatment group.	
End point type	Primary
End point timeframe:	
Day 1 (Week 0) to end of Week 16.	

End point values	Lanreotide Autogel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	56		
Units: percentage of days				
least squares mean (confidence interval 95%)	33.72 (25.02 to 42.42)	48.49 (39.57 to 57.40)		

Statistical analyses

Statistical analysis title	Treatment difference (Lanreotide - Placebo)
Statistical analysis description:	
An Analysis of Covariance (ANCOVA) model was used to test whether there was a difference between the placebo and treatment groups in the usage of s.c. octreotide required to control symptoms associated with carcinoid syndrome. The ANCOVA model used 2 stratification variables at randomisation (study site, and prior somatostatin analogue therapy), and 2 baseline covariates (baseline average daily frequency of diarrhoea and flushing events).	
Comparison groups	Lanreotide Autogel v Placebo

Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0165
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-14.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.78
upper limit	-2.75

Secondary: Average daily frequency of diarrhoea events during the double-blind phase

End point title	Average daily frequency of diarrhoea events during the double-blind phase
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End point description:

The mean frequency of diarrhoea events (per day) during the 16 week double-blind phase based on patient IVRS/IWRS diary records is presented.

The ITT population consisted of all randomised patients (regardless of whether the patients received or adhered to the allocated treatment group). Patients from the ITT population were analysed under the randomised treatment group.

End point type	Secondary
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End point timeframe:

Day 1 (Week 0) to end of Week 16.

End point values	Lanreotide Autogel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	56		
Units: number of events				
arithmetic mean (standard deviation)	1.56 (± 1.83)	1.35 (± 1.45)		

Statistical analyses

Statistical analysis title	Treatment difference (Lanreotide - Placebo)
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Statistical analysis description:

An ANCOVA model adjusted for stratification factors and baseline average daily frequency of diarrhoea was used.

Comparison groups	Lanreotide Autogel v Placebo
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Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2544
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.15

Secondary: Average daily frequency of flushing events during the double-blind phase

End point title	Average daily frequency of flushing events during the double-blind phase
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End point description:

The mean frequency of flushing events (per day) during the 16 week double-blind phase based on patient IVRS/IWRS diary records is presented.

The ITT population consisted of all randomised patients (regardless of whether the patients received or adhered to the allocated treatment group). Patients from the ITT population were analysed under the randomised treatment group.

End point type	Secondary
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End point timeframe:

Day 1 (Week 0) to end of Week 16.

End point values	Lanreotide Autogel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	56		
Units: number of events				
arithmetic mean (standard deviation)	0.92 (± 1.45)	1.75 (± 2.26)		

Statistical analyses

Statistical analysis title	Treatment difference (Lanreotide - Placebo)
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Statistical analysis description:

An ANCOVA model adjusted for stratification factors and baseline average daily frequency of flushing events was used.

Comparison groups	Lanreotide Autogel v Placebo
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Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0229
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	-0.06

Secondary: Percentage of days of use of other rescue medication during the double-blind phase

End point title	Percentage of days of use of other rescue medication during the double-blind phase
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End point description:

Patients were required to record daily, using the IVRS/IWRS, the number of diarrhoea and/or flushing events per day as well as the use and dose of s.c. octreotide, if any, as well as the use of other concomitant rescue medications.

The number of days in which rescue medications other than s.c. octreotide were used during the double-blind phase to control symptoms associated with carcinoid syndrome was determined as a measure of lanreotide efficacy. The mean percentage of days with other rescue medication use during the 16 week double-blind phase is presented.

The ITT population consisted of all randomised patients (regardless of whether the patients received or adhered to the allocated treatment group). Patients from the ITT population were analysed under the randomised treatment group.

End point type	Secondary
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End point timeframe:

Day 1 (Week 0) to end of Week 16.

End point values	Lanreotide Autogel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	56		
Units: Percentage of days				
arithmetic mean (standard deviation)	8.86 (± 19.34)	6.25 (± 17.48)		

Statistical analyses

Statistical analysis title	Treatment difference (Lanreotide - Placebo)
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Statistical analysis description:

An ANCOVA model including baseline usage of other rescue medications and baseline average daily frequencies of diarrhoea and flushing events.

Comparison groups	Lanreotide Autogel v Placebo
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Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8627
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.68
upper limit	5.57

Secondary: Percentage of patients who rolled over into the initial open-label phase before completing the double-blind phase.

End point title	Percentage of patients who rolled over into the initial open-label phase before completing the double-blind phase.
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End point description:

The percentage of patients with an early rollover (ERO) into the initial open-label phase before completion of the 16 week double-blind phase is presented.

The ITT population consisted of all randomised patients (regardless of whether the patients received or adhered to the allocated treatment group). Patients from the ITT population were analysed under the randomised treatment group.

End point type	Secondary
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End point timeframe:

Day 1 (Week 0) to end of Week 16.

End point values	Lanreotide Autogel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	56		
Units: Percentage of patients				
number (not applicable)	18.6	21.4		

Statistical analyses

Statistical analysis title	Proportion of ERO patients
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Statistical analysis description:

Odds Ratio (reference: Placebo) adjusted for stratification factors was based on a Logistic Regression model.

Comparison groups	Lanreotide Autogel v Placebo
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Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	2.1

Secondary: Change from baseline in Global Health Status/Quality of Life Score at Week 12 of the double-blind phase using the European Organisation for the Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ)-C30 Module

End point title	Change from baseline in Global Health Status/Quality of Life Score at Week 12 of the double-blind phase using the European Organisation for the Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ)-C30 Module
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End point description:

The EORTC QLQ-C30 Module was used to measure the Global Health Status/Quality of Life score at baseline and every 12 weeks during the double-blind phase and initial open-label phase, and then every 24 weeks during the long-term open-label extension.

The Global Health Status/Quality of Life dimension of the EORTC QLQ-C30 score (based on Items 29 and 30) ranged from 1 (very poor) to 7 (excellent), and the responses were transformed to range from 0 (worst) to 100 (best) according to the EORTC scoring instructions. The mean change from baseline at Week 12 of the double-blind phase in the Global Health Status/Quality of Life dimension score is presented.

The ITT population consisted of all randomised patients (regardless of whether the patients received or adhered to the allocated treatment group). Patients from the ITT population were analysed under the randomised treatment group. Only patients with no missing data are included.

End point type	Secondary
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End point timeframe:

Visits 1 (Baseline) and 4 (Week 12).

End point values	Lanreotide Autogel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	34		
Units: Units on a scale				
arithmetic mean (standard deviation)	4.17 (± 14.18)	-1.72 (± 18.21)		

Statistical analyses

Statistical analysis title	Treatment difference (Lanreotide - Placebo)
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Statistical analysis description:

An ANCOVA model adjusted for stratification factors and baseline Global Health Status/Quality of Life score was used.

Comparison groups	Lanreotide Autogel v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1931
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	4.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.09
upper limit	10.2

Secondary: Change from baseline in the Gastrointestinal (GI) Symptoms Subscore at Week 12 of the double-blind phase using the EORTC QLQ Carcinoid/Neuroendocrine tumours (GI.NET21) Module

End point title	Change from baseline in the Gastrointestinal (GI) Symptoms Subscore at Week 12 of the double-blind phase using the EORTC QLQ Carcinoid/Neuroendocrine tumours (GI.NET21) Module
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End point description:

The EORTC QLQ-GI.NET21 Module was used to measure the GI symptoms subscore at baseline and every 12 weeks during the double-blind phase and initial open-label phase, and then every 24 weeks during the long-term open-label extension.

The EORTC QLQ-GI.NET21 questionnaire contains 21 items (Items 31 to 51), each with a response ranging from 1 (worst) to 4 (best) for the extent to which the patient has experienced the detailed problem/symptom in the past week. Responses were transformed to range from 0 (worst) to 100 (best) according to the EORTC scoring instructions. The mean change from baseline at Week 12 of the double-blind phase in the GI symptoms subscore (based on items Q34 - Q38 only) is presented.

The ITT population consisted of all randomised patients (regardless of whether the patients received or adhered to the allocated treatment group). Patients from the ITT population were analysed under the randomised treatment group. Only patients with no missing data are included.

End point type	Secondary
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End point timeframe:

Visits 1 (Baseline) and 4 (Week 12).

End point values	Lanreotide Autogel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	33		
Units: Units on a scale				
arithmetic mean (standard deviation)	-4.06 (± 12.80)	0.10 (± 13.83)		

Statistical analyses

Statistical analysis title	Treatment difference (Lanreotide - Placebo)
Statistical analysis description: An ANCOVA model adjusted for stratification factors and baseline EORTC QLQ-GI.NET21 GI subscore was used.	
Comparison groups	Lanreotide Autogel v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0632
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-4.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.63
upper limit	0.26

Secondary: Change from baseline in the Endocrine Symptoms Subscore at Week 12 of the double-blind phase using the EORTC QLQ-GI.NET21 Module

End point title	Change from baseline in the Endocrine Symptoms Subscore at Week 12 of the double-blind phase using the EORTC QLQ-GI.NET21 Module
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End point description:

The EORTC QLQ-GI.NET21 Module was used to measure the endocrine symptoms subscore at baseline and every 12 weeks during the double-blind phase and initial open-label phase, and then every 24 weeks during the long-term open-label extension.

The EORTC QLQ-GI.NET21 questionnaire contains 21 items, each with a response ranging from 1 (worst) to 4 (best) for the extent to which the patient has experienced the detailed problem/symptom in the past week. Responses were transformed to range from 0 (worst) to 100 (best) according to the EORTC scoring instructions. The mean change from baseline at Week 12 of the double-blind phase in the endocrine symptoms subscore (based on items Q31 - Q33 only) is presented.

The ITT population consisted of all randomised patients (regardless of whether the patients received or adhered to the allocated treatment group). Patients from the ITT population were analysed under the randomised treatment group. Only patients with no missing data are included.

End point type	Secondary
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End point timeframe:

Visits 1 (Baseline) and 4 (Week 12).

End point values	Lanreotide Autogel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	33		
Units: Units on a scale				
arithmetic mean (standard deviation)	-6.83 (± 18.98)	-2.69 (± 22.23)		

Statistical analyses

Statistical analysis title	Treatment difference (Lanreotide - Placebo)
Statistical analysis description: An ANCOVA model adjusted for stratification factors and baseline EORTC QLQ-GI.NET21 endocrine symptoms subscore was used.	
Comparison groups	Lanreotide Autogel v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.075
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-7.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.8
upper limit	0.73

Secondary: Absolute change from baseline in plasma Chromogranin A (CgA) at Week 12 during the double-blind phase

End point title	Absolute change from baseline in plasma Chromogranin A (CgA) at Week 12 during the double-blind phase
End point description: Plasma CgA levels were evaluated as a biochemical marker of NETs. The mean change in plasma CgA level from baseline at Week 12 of the double-blind phase is presented. The ITT population consisted of all randomised patients (regardless of whether the patients received or adhered to the allocated treatment group). Patients from the ITT population were analysed under the randomised treatment group. Only patients with no missing data are included.	
End point type	Secondary
End point timeframe: Visits 1 (Baseline) and 4 (Week 12).	

End point values	Lanreotide Autogel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	28		
Units: micrograms per litre				
arithmetic mean (standard deviation)	1125.8 (± 12579.4)	801.5 (± 2294.0)		

Statistical analyses

Statistical analysis title	Treatment difference (Lanreotide - Placebo)
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Statistical analysis description:

An ANCOVA model adjusted for stratification factors and baseline CgA levels was used.

Comparison groups	Lanreotide Autogel v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2695
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2147.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6574.03
upper limit	2278.14

Secondary: Absolute change from baseline in urinary 5-hydroxyindoleacetic acid (5-HIAA) at Week 12 during the double-blind phase

End point title	Absolute change from baseline in urinary 5-hydroxyindoleacetic acid (5-HIAA) at Week 12 during the double-blind phase
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End point description:

Urinary 5-HIAA levels were evaluated as a biochemical marker of NETs. The mean change in urinary 5-HIAA level from baseline at Week 12 of the double-blind phase is presented.

The ITT population consisted of all randomised patients (regardless of whether the patients received or adhered to the allocated treatment group). Patients from the ITT population were analysed under the randomised treatment group. Only patients with no missing data are included.

End point type	Secondary
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End point timeframe:

Visits 1 (Baseline) and 4 (Week 12).

End point values	Lanreotide Autogel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	27		
Units: micromol per decilitre (micromol/dL)				
arithmetic mean (standard deviation)	-201.4 (\pm 1009.9)	36.3 (\pm 142.3)		

Statistical analyses

Statistical analysis title	Treatment difference (Lanreotide - Placebo)
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Statistical analysis description:

An ANCOVA model adjusted for stratification factors and baseline 5-HIAA levels was used.

Comparison groups	Lanreotide Autogel v Placebo
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Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5787
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-39.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-202.28
upper limit	123.22

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the time of informed consent until the exit visit (up to 16 weeks for the double-blind phase, 32 weeks for the initial open-label phase and at least 2 years in the long-term open-label phase).

Adverse event reporting additional description:

The safety population consisted of all randomised patients who received at least 1 injection of study treatment. Subjects were analysed under the actual treatment received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Placebo (Double-blind phase)
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Reporting group description:

Patients were randomised to receive placebo deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks).

Reporting group title	Lanreotide (Double-blind phase)
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Reporting group description:

Patients were randomised to receive lanreotide Autogel 120 mg deep s.c. injections administered every 4 weeks (± 3 days) for a total of 4 injections during the double-blind phase (16 weeks).

Reporting group title	Lanreotide (Initial Open-label phase)
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Reporting group description:

All patients in the initial open-label phase received lanreotide Autogel 120 mg deep s.c. injections every 4 weeks for 32 weeks. The analysis set includes patients who were randomised to either lanreotide or placebo in the double-blind phase and entered into the initial open-label phase. As such the analysis set includes 101 patients, consisting of 56 patients who were randomised to lanreotide and 45 patients randomised to placebo in the double-blind phase.

Reporting group title	Lanreotide (Long-term Open-label extension)
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Reporting group description:

In the long-term open-label extension, patients continued to receive lanreotide Autogel 120 mg deep s.c. injections every 4 weeks having completed the initial open-label phase. The analysis set includes patients who were initially randomised to either lanreotide or placebo in the double-blind phase. As such the analysis set includes 57 patients, consisting of 32 patients who were randomised to lanreotide and 25 patients randomised to placebo in the double-blind phase.

Serious adverse events	Placebo (Double-blind phase)	Lanreotide (Double-blind phase)	Lanreotide (Initial Open-label phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 57 (8.77%)	2 / 58 (3.45%)	8 / 101 (7.92%)
number of deaths (all causes)	2	0	2
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 101 (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
Metastases to liver			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to pleura			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to spine			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour necrosis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Malignant neoplasm progression			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Disease progression			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Pyrexia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Pneumothorax			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Patella fracture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 101 (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
Dizziness			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Sciatica			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Syncope			

subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Ear and labyrinth disorders			
Deafness permanent			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	3 / 101 (2.97%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 101 (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	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 101 (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
Intestinal obstruction			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 101 (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
Subileus			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Renal and urinary disorders			

Ureteric stenosis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 101 (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
Pain in extremity			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 57 (1.75%)	1 / 58 (1.72%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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

Pyelonephritis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Infection			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (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
Glucose tolerance impaired			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Lanreotide (Long-term Open-label extension)		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 57 (26.32%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			

subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to pleura			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to spine			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour necrosis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pancreatic carcinoma			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General physical health deterioration			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Patella fracture			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hydrocephalus			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			

Deafness permanent subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 57 (0.00%) 0 / 0 0 / 0		
Gastrointestinal disorders Small intestinal obstruction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 57 (0.00%) 0 / 0 0 / 0		
Vomiting subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 57 (1.75%) 0 / 1 0 / 0		
Abdominal pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 57 (1.75%) 0 / 1 0 / 0		
Diarrhoea subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 57 (0.00%) 0 / 0 0 / 0		
Intestinal obstruction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 57 (0.00%) 0 / 0 0 / 0		
Subileus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 57 (1.75%) 0 / 1 0 / 0		
Renal and urinary disorders Ureteric stenosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 57 (1.75%) 0 / 1 0 / 0		

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Kidney infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pyelonephritis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pyelonephritis acute			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Glucose tolerance impaired			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo (Double-blind phase)	Lanreotide (Double-blind phase)	Lanreotide (Initial Open-label phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 57 (54.39%)	20 / 58 (34.48%)	59 / 101 (58.42%)
Investigations			
Weight decreased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	9 / 101 (8.91%)
occurrences (all)	0	1	9
Blood triglycerides increased			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	2 / 101 (1.98%)
occurrences (all)	0	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	2 / 101 (1.98%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			

subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 58 (0.00%) 0	1 / 101 (0.99%) 1
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 58 (0.00%) 0	2 / 101 (1.98%) 2
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 58 (0.00%) 0	9 / 101 (8.91%) 10
Flushing subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 58 (0.00%) 0	1 / 101 (0.99%) 1
Hot flush subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 58 (0.00%) 0	1 / 101 (0.99%) 1
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3	7 / 58 (12.07%) 7	10 / 101 (9.90%) 15
Dizziness subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	4 / 58 (6.90%) 4	5 / 101 (4.95%) 5
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 4	2 / 58 (3.45%) 2	10 / 101 (9.90%) 10
Oedema peripheral subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3	0 / 58 (0.00%) 0	3 / 101 (2.97%) 3
Asthenia subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	2 / 58 (3.45%) 2	2 / 101 (1.98%) 2
Influenza like illness subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 58 (0.00%) 0	0 / 101 (0.00%) 0
Disease progression			

subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 58 (0.00%) 0	0 / 101 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	1 / 58 (1.72%) 1	1 / 101 (0.99%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 58 (0.00%) 0	4 / 101 (3.96%) 4
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	7 / 57 (12.28%) 7	5 / 58 (8.62%) 5	11 / 101 (10.89%) 14
Nausea subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 5	5 / 58 (8.62%) 5	8 / 101 (7.92%) 9
Vomiting subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2	4 / 58 (6.90%) 6	6 / 101 (5.94%) 6
Flatulence subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 2	3 / 58 (5.17%) 3	3 / 101 (2.97%) 3
Diarrhoea subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 58 (0.00%) 0	0 / 101 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2	2 / 58 (3.45%) 2	4 / 101 (3.96%) 5
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	1 / 58 (1.72%) 1	4 / 101 (3.96%) 4
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 4	0 / 58 (0.00%) 0	6 / 101 (5.94%) 6
Cough			

subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	2 / 58 (3.45%) 2	3 / 101 (2.97%) 3
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 58 (0.00%) 0	5 / 101 (4.95%) 5
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 58 (0.00%) 0	3 / 101 (2.97%) 3
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	3 / 58 (5.17%) 3	6 / 101 (5.94%) 6
Back pain subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 4	1 / 58 (1.72%) 1	5 / 101 (4.95%) 5
Arthralgia subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 58 (0.00%) 0	7 / 101 (6.93%) 8
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 58 (0.00%) 0	1 / 101 (0.99%) 1
Pain in extremity subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 58 (0.00%) 0	3 / 101 (2.97%) 3
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	0 / 58 (0.00%) 0	1 / 101 (0.99%) 1
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2	2 / 58 (3.45%) 2	1 / 101 (0.99%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2	0 / 58 (0.00%) 0	3 / 101 (2.97%) 3

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 57 (1.75%)	1 / 58 (1.72%)	7 / 101 (6.93%)
occurrences (all)	1	1	8
Hyperglycaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	4 / 101 (3.96%)
occurrences (all)	1	0	9
Hypoglycaemia			
subjects affected / exposed	1 / 57 (1.75%)	2 / 58 (3.45%)	0 / 101 (0.00%)
occurrences (all)	1	2	0
Gout			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 101 (0.00%)
occurrences (all)	1	0	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 57 (1.75%)	1 / 58 (1.72%)	2 / 101 (1.98%)
occurrences (all)	1	1	2

Non-serious adverse events	Lanreotide (Long-term Open-label extension)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 57 (75.44%)		
Investigations			
Weight decreased			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Blood triglycerides increased			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	5		
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	12		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Blood creatine phosphokinase increased			

subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Flushing			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Hot flush			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	7		
Dizziness			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	14		
Oedema peripheral			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Asthenia			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	9		
Influenza like illness			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Disease progression			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Pyrexia			

subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 6		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 57 (10.53%) 7		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	13 / 57 (22.81%) 25 4 / 57 (7.02%) 5 5 / 57 (8.77%) 8 0 / 57 (0.00%) 0 8 / 57 (14.04%) 10 5 / 57 (8.77%) 5 7 / 57 (12.28%) 9		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2 3 / 57 (5.26%) 3		
Hepatobiliary disorders			

Cholelithiasis subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 5		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Intervertebral disc protrusion subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1 8 / 57 (14.04%) 10 6 / 57 (10.53%) 9 4 / 57 (7.02%) 4 4 / 57 (7.02%) 4 3 / 57 (5.26%) 3		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	7 / 57 (12.28%) 7 3 / 57 (5.26%) 3		
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Hyperglycaemia			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	12		
Hypoglycaemia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	7		
Gout			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Hypertriglyceridaemia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2008	-Clarification of the timing of somatostatin receptor scintigraphy. -Modification of inclusion criterion relating to prior somatostatin analogue treatment to include a more clinically relevant patient population. -Clarification of the monitoring of patient compliance for the IVRS diary.
01 March 2010	-Tercica became part of the Ipsen Group resulting in several administrative changes to the protocol. -Further clarifications of some of the protocol requirements and inclusion and exclusion criteria were made.
08 July 2010	-Technical change to extend the screening period to 4 months for any country where a computerised tomography scan was not performed as part of the routine examination for patients with neuroendocrine tumours.
18 March 2011	-Addition of the long-term open-label extension phase in order to allow patients in countries where lanreotide Autogel had not yet been approved for the treatment of carcinoid syndrome, who were well controlled at the end of the 32-week initial open-label phase and who chose to continue receiving lanreotide Autogel to continue receiving the treatment.
21 July 2011	-Additional clarification to the exclusion criterion related to liver impairment, so that patients with a bilirubin level more than 1.5 mg/dL but no other evidence of liver impairment to be included in the study. -Additional text relating to Sponsor responsibilities regarding AE follow up added. -The composition of the Data and Safety Monitoring Committee was amended to reflect its charter.
29 October 2012	-To include additional statistical information relating to the addition of 2 baseline covariates in the ANCOVA model used for the primary efficacy analysis, and clarification of the planned imputation for the primary efficacy endpoint calculation. -Clarification of the analysis planned for the secondary efficacy endpoints. -Addition of information regarding the definition of the per protocol population to ensure consistency with the reporting and analysis plan.
16 July 2014	-To cancel the second clinical study report which was to have been written with the results of a second analysis performed when the last patient in the double-blind treatment phase completed the 32-week initial open-label phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported