Clinical trial results:
A Phase IV, Multicentre, Open Label, Single Group Exploratory Study to Assess the Clinical Value of Enumeration of Circulating Tumour Cells (CTCs) to Predict Clinical Symptomatic Response and Progression Free Survival in Patients Receiving Deep Subcutaneous Administrations of Somatuline® (Lanreotide) Autogel® to Treat the Symptoms of Functioning Midgut Neuroendocrine Tumours (NET).

Summary

EudraCT number	2013-002194-22
Trial protocol	GB
Global end of trial date	22 June 2017

Results information

Result version number	v1 (current)
This version publication date	29 September 2018
First version publication date	29 September 2018

Trial information

Trial identification

Sponsor protocol code	A-97-52030-270

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02075606
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Ltd
Sponsor organisation address	190 Bath Road, Slough, United Kingdom, SL1 3XE
Public contact	Medical Director, Ipsen, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen, 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	22 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2017
Global end of trial reached?	Yes
Global end of trial date	22 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to assess the clinical value of enumeration of CTCs to predict the clinical symptomatic response in subjects receiving deep subcutaneous injections of lanreotide Autogel to treat the symptoms of functioning midgut NET over a period of one year.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, in accordance with the International Council for Harmonisation Consolidated Guideline on Good Clinical Practice and in compliance with Independent Ethics Committees and informed consent regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	29
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment to this prospective, pilot, phase IV, multicentre, open-label, single-group study began on 16 May 2014. Subjects with a documented diagnosis of functioning midgut NET and who suffered from symptoms of diarrhoea and/or flushing at the time of enrolment were recruited to 11 study centres in the United Kingdom.

Pre-assignment

Screening details:

Overall, 54 subjects were screened, 50 of whom were enrolled and treated in the study.

Period 1

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

Arms

Arm title	Lanreotide Autogel

Arm description:

Subjects received deep subcutaneous injections of lanreotide Autogel for 1 year to treat the symptoms of functioning midgut NETs.

A washout period was required for subjects receiving either subcutaneous octreotide (at least 2 weeks) or 1 injection of long-acting somatostatin analogue (at least 6 weeks) prior to treatment in the study.

Initially subjects began treatment with a dose of lanreotide Autogel 120 milligrams (mg) every 28 days for 3 months. Thereafter, the dose administered was determined on an individual subject basis by the treating clinician. Subjects could remain on the 120 mg dose, or be titrated to either 60 mg or 90 mg lanreotide Autogel, administered every 28 days according to their symptomatic response.

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

Dosage and administration details:

Lanreotide Autogel was injected by a healthcare professional via the deep subcutaneous route into the superior external quadrant of the buttock.

All subjects received 120 mg lanreotide Autogel every 28 days for 3 months, after which doses of 60, 90 or 120 mg lanreotide Autogel were administered every 28 days according to symptomatic response.

Number of subjects in period 1	Lanreotide Autogel
Started	50
Completed	40
Not completed	10
Increasing Symptoms	1
Consent withdrawn by subject	1

Investigator's decision	1
Adverse event, non-fatal	5
Death	1
Symptom management	1

Baseline characteristics

Reporting groups

Reporting group title	Lanreotide Autogel

Reporting group description:

Subjects received deep subcutaneous injections of lanreotide Autogel for 1 year to treat the symptoms of functioning midgut NETs.

A washout period was required for subjects receiving either subcutaneous octreotide (at least 2 weeks) or 1 injection of long-acting somatostatin analogue (at least 6 weeks) prior to treatment in the study.

Initially subjects began treatment with a dose of lanreotide Autogel 120 milligrams (mg) every 28 days for 3 months. Thereafter, the dose administered was determined on an individual subject basis by the treating clinician. Subjects could remain on the 120 mg dose, or be titrated to either 60 mg or 90 mg lanreotide Autogel, administered every 28 days according to their symptomatic response.

Reporting group values	Lanreotide Autogel	Total	
Number of subjects	50	50	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.4		
standard deviation	± 8.6	-	
Gender categorical Units: Subjects			
Female	23	23	
Male	27	27	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	2	2	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	3	3	
White	45	45	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Lanreotide Autogel

Reporting group description:

Subjects received deep subcutaneous injections of lanreotide Autogel for 1 year to treat the symptoms of functioning midgut NETs.

A washout period was required for subjects receiving either subcutaneous octreotide (at least 2 weeks) or 1 injection of long-acting somatostatin analogue (at least 6 weeks) prior to treatment in the study.

Initially subjects began treatment with a dose of lanreotide Autogel 120 milligrams (mg) every 28 days for 3 months. Thereafter, the dose administered was determined on an individual subject basis by the treating clinician. Subjects could remain on the 120 mg dose, or be titrated to either 60 mg or 90 mg lanreotide Autogel, administered every 28 days according to their symptomatic response.

Subject analysis set title	CTC Presence at Baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with a baseline presence of CTCs, determined by either or both baseline CTC blood samples having a CTC enumeration >0.
Baseline is defined as the 7 days preceding the first study treatment injection, or for subjects who required a washout period, these 7 days were during the washout period.

Subject analysis set title	No CTC Presence at Baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with no baseline presence of CTCs, determined by both baseline CTC blood samples having a CTC enumeration = 0.
Baseline is defined as the 7 days preceding the first study treatment injection, or for subjects who required a washout period, these 7 days were during the washout period.

Subject analysis set title	Missing CTC Status at Baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects whose CTC status at baseline could not be evaluated as both CTC blood samples were missing.
Baseline is defined as the 7 days preceding the first study treatment injection, or for subjects who required a washout period, these 7 days were during the washout period.

Primary: Assessment of Clinical Symptomatic Response

End point title	Assessment of Clinical Symptomatic Response

End point description:

This endpoint was assessed using 2 efficacy variables:
• CTCs, enumerated at baseline and Weeks 5, 17, 25, 53
• Clinical symptomatic response, assessed by the use of symptom reporting
Subjects recorded 24-hour symptom frequency and severity for 7 days prior to first treatment (baseline), throughout the study, and up to 28 days following final drug administration. Symptoms were recorded by answering predetermined questions on the interactive voice response system (IVRS).
Subjects were considered to have a clinical symptomatic response between baseline and last study visit if any 1 of the following criteria were fulfilled: the average number of episodes of diarrhoea decreased by at least 50%, the average number of episodes of flushing decreased by at least 50%, the mode severity of flushing decreased by at least 1 level.
Clinical symptomatic response was assessed as a qualitative variable (Yes/No) and reported according to CTC presence at baseline and overall.

End point type	Primary

End point timeframe:

From baseline up to Week 53.

End point values	Lanreotide Autogel	CTC Presence at Baseline	No CTC Presence at Baseline	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	40[1]	18[2]	22[3]	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Clinical Symptomatic Response = Yes	87.5 (73.9 to 94.5)	77.8 (54.8 to 91.0)	95.5 (78.2 to 99.2)	
Clinical Symptomatic Response = No	12.5 (5.5 to 26.1)	22.2 (9.0 to 45.2)	4.5 (0.8 to 21.8)	

Notes:

[1] - Subjects in the intention-to-treat (ITT) population, with data available for analysis are presented.

[2] - Subjects in the ITT population, with data available for analysis are presented.

[3] - Subjects in the ITT population, with data available for analysis are presented.

Statistical analyses

Statistical analysis title	Analysis of Clinical Symptomatic Response

Statistical analysis description:

Clinical symptomatic response as dependent variable and CTC presence at baseline as explanatory variable was used to perform the logistic regression analysis.

Comparison groups	CTC Presence at Baseline v No CTC Presence at Baseline
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.126
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	1.65

Primary: Assessment of Progression-Free Survival (PFS)

End point title	Assessment of Progression-Free Survival (PFS)

End point description:

Subjects underwent Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans at baseline, Week 25 and Week 53. Progression was assessed by investigators using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. The best overall response to study treatment is the highest time point response achieved by the subject and was assessed as a complete response, partial response, stable disease, progressive disease or non evaluable. For analysis of PFS, event dates were assigned to the first time that progressive disease was noted or the date of death. In case of progressive disease followed by death, the first event was considered in the analysis. Censoring dates were defined in subjects with no progressive disease or death before end of study.

Median, minimum and maximum PFS time was analysed by CTC presence at baseline and overall and estimated using the Kaplan-Meier method. Subjects in the ITT population with data available for analysis

are presented.

End point type	Primary

End point timeframe:

From baseline up to Week 53.

End point values	Lanreotide Autogel	CTC Presence at Baseline	No CTC Presence at Baseline	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	48[4]	22[5]	26[6]	
Units: months				
median (full range (min-max))	9.999999 (0.00 to 12.48)	9.999999 (0.03 to 12.19)	9.999999 (0.00 to 12.48)	

Notes:

[4] - 9.999999 = non calculable (Median PFS was not reached).

[5] - 9.999999 = non calculable (Median PFS was not reached).

[6] - 9.999999 = non calculable (Median PFS was not reached).

Statistical analyses

Statistical analysis title	Assessment of PFS According to CTC Presence
Comparison groups	CTC Presence at Baseline v No CTC Presence at Baseline
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.806
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	2.73

Secondary: Mean Change from Baseline in Number of Episodes of Diarrhoea and Flushing

End point title	Mean Change from Baseline in Number of Episodes of Diarrhoea and Flushing

End point description:

The effect of lanreotide Autogel on the symptoms of diarrhoea and flushing in subjects was assessed through patient reporting of NET symptoms.

Subjects recorded 24-hour symptom severity for the 7 days prior to treatment (baseline), for the first 16 weeks and on days 11 to 17 of each subsequent injection interval until Week 49. After the final study drug injection at Week 49, subjects provided 24-hour symptom frequency on days 11 to 28. Symptom frequency was recorded by answering predetermined questions on the IVRS.

Mean change from baseline in frequency (number of episodes) of diarrhoea and flushing are described at Week 1 (Visit 2) and at Week 49 (Visit 14) by CTC presence at baseline and overall. A negative change indicates an improvement in symptoms from baseline.

Subjects in the ITT population with data available for analysis, according to CTC presence and overall, are presented for each time point.

End point type	Secondary

End point timeframe:

From baseline up to Week 53.

End point values	Lanreotide Autogel	CTC Presence at Baseline	No CTC Presence at Baseline	Missing CTC Status at Baseline
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50[7]	22[8]	26[9]	2[10]
Units: number of episodes				
arithmetic mean (confidence interval 95%)				
Diarrhoea: Visit 2 (daily)	-0.42 (-0.92 to 0.08)	-0.66 (-1.68 to 0.36)	-0.27 (-0.73 to 0.2)	0.38 (-11.18 to 11.93)
Diarrhoea: Visit 14 (days 11-17)	-1.18 (-1.83 to -0.54)	-1.91 (-3.24 to -0.57)	-0.64 (-1.16 to -0.11)	9.999999 (9.999999 to 9.999999)
Diarrhoea: Visit 14 (days 11-28)	-1.30 (-1.98 to -0.63)	-2.15 (-3.49 to -0.82)	-0.63 (-1.19 to -0.08)	9.999999 (9.999999 to 9.999999)
Flushing: Visit 2 (daily)	-1.43 (-2.24 to -0.62)	-1.76 (-3.41 to -0.11)	-1.25 (-2.02 to -0.48)	0.00 (0.00 to 0.00)
Flushing: Visit 14 (days 11-17)	-2.88 (-4.05 to -1.71)	-3.37 (-5.76 to -0.98)	-2.51 (-3.68 to -1.33)	9.999999 (9.999999 to 9.999999)
Flushing: Visit 14 (days 11-28)	-2.79 (-3.99 to -1.58)	-3.49 (-6.00 to -0.99)	-2.23 (-3.34 to -1.13)	9.999999 (9.999999 to 9.999999)

Notes:

[7] - Subjects analysed:
Visit 2 (daily), n=49
Visit 14 (days 11-17), n=37
Visit 14 (days 11-28), n=34

[8] - Subjects analysed:
Visit 2 (daily), n=22
Visit 14 (days 11-17), n=16
Visit 14 (days 11-28), n=15

[9] - Subjects analysed:
Visit 2 (daily), n=25
Visit 14 (days 11-17), n=21
Visit 14 (days 11-28), n=19

[10] - Visit 2 (daily), n=2
9.99999 = Non calculable due to no subjects analysed at Visit 14.

Statistical analyses

No statistical analyses for this end point

Secondary: Mode Symptom Severity of Episodes of Flushing

End point title	Mode Symptom Severity of Episodes of Flushing

End point description:

The effect of lanreotide Autogel on the mode severity of flushing was assessed through patient reporting of NET symptoms.
Subjects recorded 24-hour symptom severity for the 7 days prior to treatment (baseline), for the first 16 weeks and on days 11 to 17 of each subsequent injection interval until Week 49. After the final study

drug injection at Week 49, subjects provided 24-hour symptom severity on days 11 to 28. Symptom severity was recorded by answering predetermined questions on the IVRS. Severity of flushing was recorded using a three-point system (mild, moderate or severe).
The mode (most frequent) intensity of flushing are reported at baseline and at Week 49 (Visit 14).
Percentages of subjects in each severity category are based on the number of subjects in the analysis set with available responses.
Subjects in the ITT population with data available for analysis, according to CTC presence and overall, are presented at each time point.

End point type	Secondary

End point timeframe:

From Baseline up to Week 53.

End point values	Lanreotide Autogel	CTC Presence at Baseline	No CTC Presence at Baseline	Missing CTC Status at Baseline
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50[11]	22[12]	26[13]	2[14]
Units: percentage of subjects				
number (confidence interval 95%)				
No flushing: Baseline	14.0 (7.0 to 26.2)	22.7 (10.1 to 43.4)	0.0 (0.0 to 12.9)	100 (34.2 to 100)
Mild: Baseline	38.0 (25.9 to 51.8)	27.3 (13.2 to 48.2)	50.0 (32.1 to 67.9)	0.0 (0.0 to 65.8)
Moderate: Baseline	46.0 (33.0 to 59.6)	45.5 (26.9 to 65.3)	50.0 (32.1 to 67.9)	0.0 (0.0 to 65.8)
Severe: Baseline	2.0 (0.4 to 10.5)	4.5 (0.8 to 21.8)	0.0 (0.0 to 12.9)	0.0 (0.0 to 65.8)
No flushing: Visit 14 (days 11-17)	32.4 (19.6 to 48.5)	37.5 (18.5 to 61.4)	28.6 (13.8 to 50.0)	9.999999 (9.999999 to 9.999999)
Mild: Visit 14 (days 11-17)	45.9 (31.0 to 61.6)	43.8 (23.1 to 66.8)	47.6 (28.3 to 67.6)	9.999999 (9.999999 to 9.999999)
Moderate: Visit 14 (days 11-17)	21.6 (11.4 to 37.2)	18.8 (6.6 to 43.0)	23.8 (10.6 to 45.1)	9.999999 (9.999999 to 9.999999)
Severe: Visit 14 (days 11-17)	0.0 (0.0 to 9.4)	0.0 (0.0 to 19.4)	0.0 (0.0 to 15.5)	9.999999 (9.999999 to 9.999999)
No flushing: Visit 14 (days 11-28)	23.5 (12.4 to 40.0)	13.3 (3.7 to 37.9)	31.6 (15.4 to 54.0)	9.999999 (9.999999 to 9.999999)
Mild: Visit 14 (days 11-28)	55.9 (39.5 to 71.1)	60.0 (35.7 to 80.2)	52.6 (31.7 to 72.7)	9.999999 (9.999999 to 9.999999)
Moderate: Visit 14 (days 11-28)	17.6 (8.3 to 33.5)	26.7 (10.9 to 52.0)	10.5 (2.9 to 31.4)	9.999999 (9.999999 to 9.999999)
Severe: Visit 14 (days 11-28)	2.9 (0.5 to 14.9)	0.0 (0.0 to 20.4)	5.3 (0.9 to 24.6)	9.999999 (9.999999 to 9.999999)

Notes:

[11] - Subjects analysed:
Baseline, n=50
Visit 14 (days 11-17), n=37
Visit 14 (days 11-28), n=34

[12] - Subjects analysed:
Baseline, n=22

Visit 14 (days 11-17), n=16
Visit 14 (days 11-28), n=15
[13] - Subjects analysed:
Baseline, n=26
Visit 14 (days 11-17), n=21
Visit 14 (days 11-28), n=19
[14] - Visit 2 (daily), n=2
9.99999 = Non calculable due to no subjects analysed at Visit 14.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life (QoL) Questionnaire: European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ)-C30

End point title	Quality of Life (QoL) Questionnaire: European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ)-C30

End point description:

The effect of lanreotide Autogel treatment on QoL was assessed using the EORTC QLQ-C30 at baseline, Weeks 13 (Visit 5), 25 (Visit 8) and 53 (Visit 15/end of study). The 30 item scale is divided into 9 multi-item scales (including 5 functional scales, 1 global health status/QoL scale and 3 general symptom scales) and 6 single items. Possible answers to the first 28 items (all items except the 2 concerning global quality of life) go from 1 (Not at all) to 4 (Very much). The answers for the 2 last questions (Q29-30) go from 1 (Very poor) to 7 (Excellent). All of the scales and single-item measures range in score from 0 to 100. For multi-item scales, the raw score will be calculated by the addition of item responses divided by the number of items. Higher scores for global health and functional domains indicate a better QoL, while higher symptom scores indicate worse symptoms.

The mean change from baseline at each time point is reported for each of the category subscores.

End point type	Secondary

End point timeframe:

From baseline up to Week 53.

End point values	Lanreotide Autogel			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Physical functioning: Visit 5 (n=39)	1.2 (± 17.9)			
Physical functioning: Visit 8 (n=36)	2.0 (± 17.6)			
Physical functioning: End of study (n=36)	1.9 (± 21.7)			
Role functioning: Visit 5 (n=39)	1.3 (± 30.9)			
Role functioning: Visit 8 (n=36)	3.2 (± 32.1)			
Role functioning: End of study (n=36)	-1.4 (± 33.7)			
Emotional functioning: Visit 5 (n=36)	6.1 (± 24.8)			
Emotional functioning: Visit 8 (n=34)	4.3 (± 18.3)			
Emotional functioning: End of study (n=35)	1.1 (± 23.0)			
Cognitive functioning: Visit 5 (n=36)	-0.9 (± 19.9)			
Cognitive functioning: Visit 8 (n=34)	1.5 (± 15.6)			
Cognitive functioning: End of study (n=35)	-2.4 (± 19.9)			
Social functioning: Visit 5 (n=35)	10.0 (± 26.9)			

Social functioning: Visit 8 (n=33)	4.5 (± 30.1)			
Social functioning: End of study (n=34)	3.9 (± 27.8)			
Global QoL: Visit 5 (n=36)	12.5 (± 26.4)			
Global QoL: Visit 8 (n=34)	7.4 (± 24.3)			
Global QoL: End of study (n=35)	4.3 (± 22.8)			
Fatigue: Visit 5 (n=39)	-4.4 (± 26.7)			
Fatigue: Visit 8 (n=36)	-6.3 (± 21.2)			
Fatigue: End of study (n=36)	-4.2 (± 25.6)			
Nausea and vomiting: Visit 5 (n=40)	-4.2 (± 20.9)			
Nausea and vomiting: Visit 8 (n=37)	-1.4 (± 20.9)			
Nausea and vomiting: End of study (n=37)	-0.9 (± 29.1)			
Pain: Visit 5 (n=40)	-7.9 (± 32.5)			
Pain: Visit 8 (n=37)	-2.3 (± 30.2)			
Pain: End of study (n=37)	1.8 (± 30.6)			
Dyspnoea: Visit 5 (n=38)	-3.5 (± 25.5)			
Dyspnoea: Visit 8 (n=35)	1.0 (± 20.6)			
Dyspnoea: End of study (n=35)	-4.8 (± 30.4)			
Insomnia: Visit 5 (n=37)	-6.3 (± 27.0)			
Insomnia: Visit 8 (n=35)	-5.7 (± 22.1)			
Insomnia: End of study (n=34)	-2.9 (± 37.0)			
Appetite loss: Visit 5 (n=39)	-0.9 (± 37.1)			
Appetite loss: Visit 8 (n=36)	-6.5 (± 36.4)			
Appetite loss: End of study (n=36)	-0.0 (± 34.7)			
Constipation: Visit 5 (n=36)	1.9 (± 19.4)			
Constipation: Visit 8 (n=33)	-1.0 (± 13.1)			
Constipation: End of study (n=35)	1.9 (± 13.9)			
Diarrhoea: Visit 5 (n=36)	-18.5 (± 33.3)			
Diarrhoea: Visit 8 (n=34)	-12.7 (± 30.7)			
Diarrhoea: End of study (n=34)	-10.8 (± 32.5)			
Financial difficulties: Visit 5 (n=35)	-6.7 (± 25.3)			
Financial difficulties: Visit 8 (n=33)	-4.0 (± 30.9)			
Financial difficulties: End of study (n=34)	-1.0 (± 38.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: QoL Questionnaire: EORTC QLQ-G.I.NET21

End point title	QoL Questionnaire: EORTC QLQ-G.I.NET21

End point description:

The effect of lanreotide Autogel treatment on QoL was assessed using the EORTC QLQ-G.I.NET21 at baseline, Weeks 13 (Visit 5), 25 (Visit 8) and 53 (Visit 15/end of study).The QLQ-G.I.NET21 questionnaire contains 21 single items (Q31 – Q51) which are supplemental items to the EORTC QLQ-C30 questionnaire. Q31 – Q51 scores range from 1 to 4 with 1 being the most favourable answer and 4 the worst case (1 = Not at all, 2 = A little, 3 = Quite a bit, 4 = Very much). Based on these items the subscores were generated. Higher scores indicate worse symptoms or more problems.

The mean change from baseline at each time point is reported for each of the category subscores. Subjects in the ITT population with data available for analysis is presented.

End point type	Secondary

End point timeframe:

From baseline up to Week 53.

End point values	Lanreotide Autogel			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Endocrine symptoms: Visit 5 (n=39)	-15.4 (± 21.6)			
Endocrine symptoms: Visit 8 (n=37)	-17.0 (± 22.9)			
Endocrine symptoms: End of study (n=36)	-16.0 (± 22.8)			
Gastrointestinal symptoms: Visit 5 (n=39)	2.1 (± 16.9)			
Gastrointestinal symptoms: Visit 8 (n=37)	1.2 (± 15.6)			
Gastrointestinal symptoms: End of study (n=36)	1.0 (± 16.7)			
Treatment symptoms: Visit 5 (n=9)	1.2 (± 15.2)			
Treatment symptoms: Visit 8 (n=8)	7.6 (± 8.9)			
Treatment symptoms: End of study (n=6)	12.0 (± 12.4)			
Social function: Visit 5 (n=39)	-11.3 (± 26.6)			
Social function: Visit 8 (n=37)	-6.5 (± 29.3)			
Social function: End of study (n=36)	-4.5 (± 24.1)			
Disease related worries: Visit 5 (n=39)	-14.1 (± 25.2)			
Disease related worries: Visit 8 (n=37)	-15.9 (± 33.8)			
Disease related worries: End of study (n=36)	-12.2 (± 36.3)			
Muscle/Bone pain: Visit 5 (n=38)	-7.9 (± 36.7)			
Muscle/Bone pain: Visit 8 (n=36)	-6.5 (± 31.7)			
Muscle/Bone pain: End of study (n=34)	-11.8 (± 39.3)			
Sexual function: Visit 5 (n=18)	-5.6 (± 34.8)			
Sexual function: Visit 8 (n=15)	-8.9 (± 34.4)			
Sexual function: End of study (n=15)	-13.3 (± 27.6)			
Info/communication function: Visit 5 (n=39)	-8.5 (± 26.2)			
Info/communication function: Visit 8 (n=36)	-3.7 (± 31.7)			
Info/communication function: End of study (n=36)	-5.6 (± 25.8)			
Body image: Visit 5 (n=36)	0.9 (± 41.0)			
Body image: Visit 8 (n=35)	1.9 (± 41.2)			
Body image: End of study (n=35)	-1.0 (± 35.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of PFS at One Year

End point title	Assessment of PFS at One Year

End point description:

Subjects underwent CT or MRI scans at baseline and Week 53. Progression was assessed by investigators using RECIST v1.1. The best overall response to study treatment is the highest time point response achieved by the subject and was assessed as a complete response, partial response, stable disease, progressive disease or non evaluable. For analysis of PFS, event dates were assigned to the first time that progressive disease was noted or the date of death. In case of progressive disease followed by death, the first event was considered in the analysis. Censoring dates were defined in subjects with no progressive disease or death before end of study.

Median, minimum and maximum PFS time at one year was analysed by CTC presence at baseline and overall and estimated using the Kaplan-Meier method. Subjects in the ITT population with data available for analysis are presented.

End point type	Secondary

End point timeframe:

From baseline up to Week 53.

End point values	Lanreotide Autogel	CTC Presence at Baseline	No CTC Presence at Baseline	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	50	22	26	
Units: percentage of subjects				
arithmetic mean (confidence interval 95%)	66.43 (48.77 to 79.22)	69.00 (40.3 to 85.94)	67.75 (43.42 to 83.39)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to Week 53 (approximately 1 year).

Adverse event reporting additional description:

Treatment emergent adverse events are reported and defined as any adverse event that occurred from the first study drug injection until 28 days after the last study drug injection.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Lanreotide Autogel

Reporting group description:

Subjects received deep subcutaneous injections of lanreotide Autogel for 1 year to treat the symptoms of functioning midgut NETs.

A washout period was required for subjects receiving either subcutaneous octreotide (at least 2 weeks) or 1 injection of long-acting somatostatin analogue (at least 6 weeks) prior to treatment in the study.

Initially subjects began treatment with a dose of lanreotide Autogel mg every 28 days for 3 months. Thereafter, the dose administered was determined on an individual subject basis by the treating clinician. Subjects could remain on the 120 mg dose, or be titrated to either 60 mg or 90 mg lanreotide Autogel, administered every 28 days according to their symptomatic response.

Serious adverse events	Lanreotide Autogel		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 50 (24.00%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Investigations			
Biopsy lymph gland			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Campylobacter test positive			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal resection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multi-organ failure			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Hepatic failure			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lanreotide Autogel		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 50 (94.00%)		
Investigations			
Weight decreased			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Vascular disorders			
Flushing			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	9		
Hypertension			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Hypotension			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Cardiac disorders			
Palpitations			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	6		
Nervous system disorders			

Dizziness			
subjects affected / exposed	12 / 50 (24.00%)		
occurrences (all)	16		
Headache			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	25		
Sciatica			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	4		
Tremor			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	5		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	16 / 50 (32.00%)		
occurrences (all)	19		
Injection site mass			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	16 / 50 (32.00%)		
occurrences (all)	20		
Abdominal pain upper			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	14		
Constipation			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	9		
Diarrhoea			

subjects affected / exposed	24 / 50 (48.00%)		
occurrences (all)	29		
Flatulence			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Gastrointestinal pain			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	13 / 50 (26.00%)		
occurrences (all)	16		
Vomiting			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	13		
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	7		
Muscle spasms			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	8		

Musculoskeletal chest pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5 7 / 50 (14.00%) 12 5 / 50 (10.00%) 5 7 / 50 (14.00%) 8		
Infections and infestations Ear infection subjects affected / exposed occurrences (all) Lower respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5 7 / 50 (14.00%) 8 6 / 50 (12.00%) 7		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	7 / 50 (14.00%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2014	Amendment included the following: • Addition to the inclusion criteria to clarify that subjects must be symptomatic at the time of enrolment. • Modification to include subjects who have had more than one injection of long-acting somatostatin analogue prior to surgery with curative intent. • To clarify the use of concomitant medication for acute symptomatic episodes during the study. • To extend the recruitment period from 12 to 18 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported