Clinical trial results:
EFFICACY AND SAFETY OF LANREOTIDE AUTOGEL® 120 MG ADMINISTERED EVERY 14 DAYS IN WELL DIFFERENTIATED, METASTATIC OR LOCALLY ADVANCED, UNRESECTABLE PANCREATIC OR MIDGUT NEUROENDOCRINE TUMOURS HAVING PROGRESSED RADIOLOGICALLY WHILE PREVIOUSLY TREATED WITH LANREOTIDE AUTOGEL® 120 MG ADMINISTERED EVERY 28 DAYS

Summary

EudraCT number	2014-005607-24
Trial protocol	DE BE NL DK ES PL IT
Global end of trial date	24 October 2019

Results information

Result version number	v1 (current)
This version publication date	01 November 2020
First version publication date	01 November 2020

Trial information

Trial identification

Sponsor protocol code	8-79-52030-326

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02651987
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Innovation
Sponsor organisation address	5 Avenue du Canada, Les Ulis, France, 91940
Public contact	Medical Director, Ipsen Innovation, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen Innovation, 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	24 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess progression free survival (PFS) in subjects with well differentiated, metastatic or locally advanced, unresectable, pancreatic or midgut neuroendocrine tumours (NETs) when treated with lanreotide Autogel® 120 milligrams (mg) administered subcutaneously (SC) every 14 days based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.0, and according to central review.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki of World Medical Association, Independent Ethics Committee/Institutional Review Boards, informed consent regulations, and in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice [ICH E6], and also adhered to all applicable local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 8
Worldwide total number of subjects	99
EEA total number of subjects	99

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)	43
From 65 to 84 years	56
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with well differentiated, metastatic or locally advanced, unresectable, pancreatic or midgut NETs and who had radiologically documented disease progression (as per RECIST v1.0) whilst receiving treatment with lanreotide Autogel® 120mg, every 28 days for at least 24 weeks were enrolled into this study in 25 centres across 10 countries.

Pre-assignment

Screening details:

Subjects who had radiologically documented disease progression within 24 months prior to enrolment and whilst receiving treatment with lanreotide Autogel® 120 mg, administered every 28 days for at least 24 weeks, were recruited into one of two cohorts based on the primary location of NET (i.e. pancreatic NET [panNET] or midgut NET cohort).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PanNET Cohort

Arm description:

Subjects were treated with lanreotide Autogel® 120 mg, administered as deep SC injections, every 14 days starting from Day 1 (at a reduced dosing interval) for up to 48 weeks or until disease progression, death or unacceptable toxicity or tolerability. Subjects who had not progressed at Week 48 could continue study treatment with lanreotide Autogel® 120 mg every 14 days until 25 events (Progressive disease [PD] or death) in the panNET cohort had been observed. Additional visits were performed every 12 weeks until disease progression or death, or unacceptable toxicity or tolerability.

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

Dosage and administration details:

Subjects received lanreotide Autogel® 120 mg, administered as deep SC injections in the superior, external quadrant of the buttock, every 14 days.

Arm title	Midgut NET Cohort

Arm description:

Subjects were treated with lanreotide Autogel® 120 mg, administered as deep SC injections, every 14 days starting from Day 1 (at a reduced dosing interval) for up to 96 weeks or until disease progression, death or unacceptable toxicity or tolerability. Subjects who had not progressed at Week 96 could continue study treatment with lanreotide Autogel® 120 mg every 14 days until 25 events (PD or death) in the midgut NET cohort had been observed. Additional visits were performed every 12 weeks until disease progression or death, or unacceptable toxicity or tolerability.

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

Dosage and administration details:

Subjects received lanreotide Autogel® 120 mg, administered as deep SC injections in the superior, external quadrant of the buttock, every 14 days.

Number of subjects in period 1	PanNET Cohort	Midgut NET Cohort
Started	48	51
Completed	43	46
Not completed	5	5
Consent withdrawn by subject	2	-
Adverse event, non-fatal	2	2
Investigator Decision	1	1
Local PD	-	2

Baseline characteristics

Reporting groups	
Reporting group title	PanNET Cohort
Reporting group description:	
Subjects were treated with lanreotide Autogel® 120 mg, administered as deep SC injections, every 14 days starting from Day 1 (at a reduced dosing interval) for up to 48 weeks or until disease progression, death or unacceptable toxicity or tolerability. Subjects who had not progressed at Week 48 could continue study treatment with lanreotide Autogel® 120 mg every 14 days until 25 events (Progressive disease [PD] or death) in the panNET cohort had been observed. Additional visits were performed every 12 weeks until disease progression or death, or unacceptable toxicity or tolerability.	
Reporting group title	Midgut NET Cohort
Reporting group description:	
Subjects were treated with lanreotide Autogel® 120 mg, administered as deep SC injections, every 14 days starting from Day 1 (at a reduced dosing interval) for up to 96 weeks or until disease progression, death or unacceptable toxicity or tolerability. Subjects who had not progressed at Week 96 could continue study treatment with lanreotide Autogel® 120 mg every 14 days until 25 events (PD or death) in the midgut NET cohort had been observed. Additional visits were performed every 12 weeks until disease progression or death, or unacceptable toxicity or tolerability.	

Reporting group values	PanNET Cohort	Midgut NET Cohort	Total
Number of subjects	48	51	99
Age categorical Units: Subjects			
Adults (18-64 years)	25	18	43
From 65-84 years	23	33	56
Age continuous Units: years			
arithmetic mean	63.3	67.1	
standard deviation	± 10.6	± 8.2	-
Gender categorical Units: Subjects			
Female	28	22	50
Male	20	29	49
Race Units: Subjects			
Asian	0	1	1
White	35	37	72
Other	1	0	1
Not collected due to local regulations (France)	12	13	25
Categories of Proliferation index Ki67 Units: Subjects			
≥10%	7	4	11
<10%	41	46	87
Missing	0	1	1
Tumour grading (according to WHO 2010 classification) Units: Subjects			
Grade 1	12	29	41
Grade 2	36	22	58
Hepatic tumour load			

Units: Subjects			
>25%	7	9	16
≤25%	41	42	83

End points

End points reporting groups

Reporting group title	PanNET Cohort

Reporting group description:

Subjects were treated with lanreotide Autogel® 120 mg, administered as deep SC injections, every 14 days starting from Day 1 (at a reduced dosing interval) for up to 48 weeks or until disease progression, death or unacceptable toxicity or tolerability. Subjects who had not progressed at Week 48 could continue study treatment with lanreotide Autogel® 120 mg every 14 days until 25 events (Progressive disease [PD] or death) in the panNET cohort had been observed. Additional visits were performed every 12 weeks until disease progression or death, or unacceptable toxicity or tolerability.

Reporting group title	Midgut NET Cohort

Reporting group description:

Subjects were treated with lanreotide Autogel® 120 mg, administered as deep SC injections, every 14 days starting from Day 1 (at a reduced dosing interval) for up to 96 weeks or until disease progression, death or unacceptable toxicity or tolerability. Subjects who had not progressed at Week 96 could continue study treatment with lanreotide Autogel® 120 mg every 14 days until 25 events (PD or death) in the midgut NET cohort had been observed. Additional visits were performed every 12 weeks until disease progression or death, or unacceptable toxicity or tolerability.

Subject analysis set title	Overall
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

Primary: Median PFS

End point title	Median PFS[1]

End point description:

PFS was defined as the time from first injection of lanreotide Autogel® 120 mg every 14 days to progression or death. Disease progression was assessed by tumour response evaluation according to RECIST v1.0, every 12 weeks, measured by independent central review using the same imaging technique (computed tomography [CT] scan or magnetic resonance imaging [MRI]) for each subject throughout the study. The median PFS time was estimated using the Kaplan Meier method for each cohort.

Analysis was performed on the Full Analysis Set (FAS) which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

End point type	Primary

End point timeframe:

From Day 1 up to Week 60 for the panNET cohort and Week 103 for the midgut NET cohort

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analyses were planned for the primary endpoint.

End point values	PanNET Cohort	Midgut NET Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: months				
median (confidence interval 95%)	5.6 (5.5 to 8.3)	8.3 (5.6 to 11.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Progression

End point title	Median Time to Progression

End point description:

Time to Progression was defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression. Disease progression was assessed by tumour response evaluation according to RECIST v1.0, every 12 weeks, measured by independent central review using the same imaging technique (CT scan or MRI) for each subject throughout the study. Median time to progression was estimated using the Kaplan Meier method for each cohort.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

End point type	Secondary

End point timeframe:

From Day 1 up to Week 60 for the panNET cohort and Week 103 for the midgut NET cohort

End point values	PanNET Cohort	Midgut NET Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: months				
median (confidence interval 95%)	5.6 (5.5 to 8.3)	8.7 (8.3 to 13.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Alive and Progression Free

End point title	Percentage of Subjects Alive and Progression Free

End point description:

The percentage of subjects alive and progression-free was assessed throughout the study up to Week 72 for the panNET cohort and Week 108 for the midgut cohort. Disease progression was assessed by tumour response evaluation according to RECIST v1.0, every 12 weeks measured by independent central review using the same imaging technique (CT scan or MRI) for each subject throughout the study. The percentage of subjects alive and progression free was estimated using the Kaplan Meier method for each cohort.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 36, 48, 60 (for both cohorts) and Weeks 72, 84 and 96 (for midgut NET cohort)

End point values	PanNET Cohort	Midgut NET Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[2]	51		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 12	93.3 (80.7 to 97.8)	91.8 (79.7 to 96.9)		
Week 24	64.4 (48.7 to 76.5)	65.3 (50.3 to 76.8)		
Week 36	37.8 (23.9 to 51.6)	59.2 (44.2 to 71.4)		
Week 48	28.5 (16.2 to 42.1)	38.3 (24.8 to 51.6)		
Week 60	20.7 (9.0 to 35.7)	36.1 (22.9 to 49.5)		
Week 72	99999 (99999 to 99999)	29.8 (17.6 to 42.9)		
Week 84	99999 (99999 to 99999)	27.5 (15.7 to 40.5)		
Week 96	99999 (99999 to 99999)	25.2 (13.9 to 38.1)		

Notes:

[2] - 99999 = This cohort was not included after Week 72.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time in months from the first injection of lanreotide Autogel® 120 mg every 14 days to death due to any cause. Median overall survival was estimated using the Kaplan Meier method for each cohort.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

End point type	Secondary

End point timeframe:

From Day 1 up to Week 60 for the panNET cohort and Week 103 for the midgut NET cohort

End point values	PanNET Cohort	Midgut NET Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[3]	51[4]		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[3] - 99999 = The median overall survival from the Kaplan Meier model was not reached for this cohort.

[4] - 99999 = The median overall survival from the Kaplan Meier model was not reached for this cohort.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

The ORR was defined as the percentage of subjects who achieve either complete response (CR) or partial response (PR) according to RECIST v1.0 criteria. ORR was evaluated every 12 weeks and results are presented for each cohort.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 36, 48, 60 (for both cohorts) and Weeks 72, 84, and 96 (for midgut cohort)

End point values	PanNET Cohort	Midgut NET Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[5]	51		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 12	0.0 (0.0 to 7.4)	0.0 (0.0 to 7.0)		
Week 24	0.0 (0.0 to 7.4)	0.0 (0.0 to 7.0)		
Week 36	0.0 (0.0 to 7.4)	0.0 (0.0 to 7.0)		
Week 48	0.0 (0.0 to 7.4)	0.0 (0.0 to 7.0)		
Week 60	0.0 (0.0 to 7.4)	2.0 (0.0 to 10.4)		
Week 72	99999 (99999 to 99999)	3.9 (0.5 to 13.5)		
Week 84	99999 (99999 to 99999)	2.0 (0.0 to 10.4)		
Week 96	99999 (99999 to 99999)	2.0 (0.0 to 10.4)		

Notes:

[5] - 99999 = This cohort was not included after Week 72.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

The DCR was defined as the percentage of subjects who achieved CR plus PR plus Stable Disease (SD), evaluated according to RECIST v1.0 criteria. The DCR at Weeks 24 and 48 is presented for each cohort.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

End point type	Secondary

End point timeframe:

Weeks 24 and 48

End point values	PanNET Cohort	Midgut NET Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 24	43.8 (29.5 to 58.8)	58.8 (44.2 to 72.4)		
Week 48	22.9 (12.0 to 37.3)	33.3 (20.8 to 47.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate

End point title	Best Overall Response Rate

End point description:

Best overall response was defined as the best response recorded from the initiation of treatment until disease progression, according to RECIST v1.0 evaluation. The percentage of subjects in each response category and those who were non-evaluable (i.e. with no tumour assessment after the start of study treatment) throughout the study are presented for each cohort.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

End point type	Secondary

End point timeframe:

From Day 1 up to Week 60 for the panNET cohort and Week 103 for the midgut NET cohort

End point values	PanNET Cohort	Midgut NET Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: percentage of subjects				
number (confidence interval 95%)				
CR	0.0 (0.0 to 7.4)	0.0 (0.0 to 7.0)		
PR	0.0 (0.0 to 7.4)	3.9 (0.5 to 13.5)		
SD	66.7 (51.6 to 79.6)	68.6 (54.1 to 80.9)		
PD	31.3 (18.7 to 46.3)	23.5 (12.8 to 37.5)		
Not evaluable	0.0 (0.0 to 7.4)	2.0 (0.0 to 10.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Duration of Stable Disease

End point title	Median Duration of Stable Disease

End point description:

Median duration of SD was the time from first injection of lanreotide Autogel® 120 mg every 14 days until the first occurrence of PD by central assessment. Disease progression was assessed by tumour response evaluation according to RECIST v1.0, every 12 weeks, measured using the same imaging technique (CT scan or MRI) for each subject throughout the study. Median duration of SD was estimated using the Kaplan Meier method for each cohort.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

End point type	Secondary

End point timeframe:

From Day 1 up to Week 60 for the panNET cohort and Week 103 for the midgut NET cohort

End point values	PanNET Cohort	Midgut NET Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51[6]		
Units: months				
median (confidence interval 95%)	8.3 (8.0 to 13.8)	13.8 (8.6 to 99999)		

Notes:

[6] - 99999 = could not be calculated as an insufficient number of events were observed.

Statistical analyses

No statistical analyses for this end point

Secondary: Factors Associated With PFS

End point title	Factors Associated With PFS

End point description:

A univariate cox proportional hazards model was used to assess whether the following factors were associated with PFS:

- Hepatic tumour load: >25% versus reference ≤25%
- Tumour Grade: Grade 2 versus reference Grade 1,
- Previous surgery of the primary tumour: No versus reference Yes,
- Proliferation index Ki67: ≥10% versus reference <10%
- Duration of treatment with lanreotide Autogel® 120 mg every 28 days by category: ≥median value versus reference <median value,
- Age by category: ≥65 years versus reference <65 years,
- Time from diagnosis to study entry by category: ≥3 years versus reference <3 years,

• Time interval between the two CT scans (pre-screening/screening): ≥12 months versus reference <12 months and
• Symptoms (diarrhoea or flushing at baseline): No versus reference Yes.

Each factor was assessed for its importance in the Cox model for PFS in a univariate fashion.

End point type	Secondary

End point timeframe:

Screening/Baseline (Day 1)

End point values	PanNET Cohort	Midgut NET Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[7]	51[8]		
Units: Hazard ratio				
number (confidence interval 95%)				
Hepatic tumour load: >25% Vs ≤25%	0.96 (0.40 to 2.32)	1.54 (0.70 to 3.40)		
Tumour grade: Grade 2 Vs Grade 1	0.68 (0.32 to 1.45)	0.90 (0.46 to 1.77)		
Previous surgery: No Vs Yes	1.04 (0.53 to 2.04)	2.14 (0.83 to 5.52)		
Ki67: ≥10% Vs <10%	3.60 (1.39 to 9.32)	2.26 (0.67 to 7.60)		
Duration of treatment*: ≥median Vs <median	0.68 (0.34 to 1.34)	0.76 (0.40 to 1.47)		
Age: ≥65 years Vs <65 years	1.55 (0.79 to 3.06)	1.15 (0.58 to 2.31)		
Time from diagnosis: ≥3 years Vs <3 years	0.49 (0.25 to 0.96)	0.94 (0.49 to 1.82)		
Time between CT scans: ≥12 months Vs <12 months	0.47 (0.24 to 0.94)	0.72 (0.37 to 1.39)		
Symptoms: No Vs Yes	2.55 (0.89 to 7.28)	1.32 (0.68 to 2.56)		

Notes:

[7] - *Duration of treatment with lanreotide Autogel® 120 mg every 28 days

[8] - Except: Ki67 + symptoms, n=50
*Duration of treatment with lanreotide Autogel® 120 mg every 28 days

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Symptom control was measured by the total number of stools (diarrhoea) and flushing episodes during the 7 days prior to the visit, reported orally by the subject to the investigator. The mean change from baseline in the number of stools and flushing episodes reported at each visit is presented for each cohort.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study. Numbers analysed at each time point correspond to the number of subjects reporting episodes in the 7 days prior to the visit.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 8, 12, 48 and EoS

End point values	PanNET Cohort	Midgut NET Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[9]	13[10]		
Units: episodes				
arithmetic mean (standard deviation)				
Stools - Week 8	1.0 (± 5.5)	-1.0 (± 8.2)		
Stools - Week 12	-1.2 (± 7.9)	0.7 (± 2.5)		
Stools - Week 48	-1.0 (± 0.0)	3.4 (± 4.8)		
Stools - EoS	0.5 (± 5.4)	-1.2 (± 12.2)		
Flushing - Week 8	0.7 (± 2.1)	-3.3 (± 8.3)		
Flushing - Week 12	-1.0 (± 0.0)	1.5 (± 10.0)		
Flushing - Week 48	-1.0 (± 0.0)	-1.5 (± 2.1)		
Flushing - EoS	0.0 (± 1.4)	-0.5 (± 6.2)		

Notes:

[9] - Except Stools - Week 48=2, EoS=4
Flushing- Week 8=3, Weeks 12, 48 and EOS=2
[10] - Except Stools -Week 48 & EoS=5,
Flushing-Week 8=9, Week 12=6, Week 24=5, Week 48=2, Eos=4

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in QoL Measured Using European Organisation Into the Research and Treatment of Cancer (EORTC), Quality of Life (QoL) Questionnaire Core 30 (QLQ-C30 v3.0) (Global Health Status Sub-score)

End point title	Mean Change From Baseline in QoL Measured Using European Organisation Into the Research and Treatment of Cancer (EORTC), Quality of Life (QoL) Questionnaire Core 30 (QLQ-C30 v3.0) (Global Health Status Sub-score)

End point description:

Subjects were instructed to complete the 30 questions in the EORTC-QLQ-C30 v3.0 questionnaire at baseline and every 12 weeks throughout the study.
The global health status sub-score was assessed using the last 2 questions which represented subject's assessment of overall health & QoL. Each question was coded on a 7-point scale (1=very poor to 7=excellent). The sub-score was transformed to range from 0-100, with a high score for global health status representing a high QoL. The mean change from baseline in the transformed global health status are presented for the EoS visit, with a positive change indicating an improvement in QoL.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study. Only subjects with data available for analysis are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1), EoS

End point values	PanNET Cohort	Midgut NET Cohort	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	22	25	47	
Units: score on a scale				
arithmetic mean (standard deviation)	-0.38 (± 15.32)	-1.33 (± 17.13)	-0.89 (± 16.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline EuroQoL 5 Dimensions, 5 Levels (EQ-5D-5L) v 1.0 Questionnaire (Descriptive System)

End point title	Mean Change From Baseline EuroQoL 5 Dimensions, 5 Levels (EQ-5D-5L) v 1.0 Questionnaire (Descriptive System)

End point description:

Subjects were instructed to complete the EQ-5D-5L descriptive system at baseline and every 12 weeks throughout the study.

The EQ-5D-5L descriptive system comprised the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension had 5 levels: no problems, slight problems, moderate problems, severe problems, extreme problems. The EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, was converted into a single index value with scores ranging from 0 (no problems) to 1 (extreme problems). The mean change from baseline at the EoS visit is presented with a positive change from baseline in the index values indicating a worsening of symptoms.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study. Only subjects with data available for analysis are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1), EoS

End point values	PanNET Cohort	Midgut NET Cohort	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	22	21	43	
Units: Index value				
arithmetic mean (standard deviation)	-0.04 (± 0.12)	0.00 (± 0.11)	-0.02 (± 0.12)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in EQ-5D-5L v1.0 Questionnaire (Visual Analogue Scale [VAS])

End point title	Mean Change From Baseline in EQ-5D-5L v1.0 Questionnaire

	(Visual Analogue Scale [VAS])

End point description:

Subjects were instructed to complete the EQ-5D-5L VAS at baseline and every 12 weeks throughout the study. The EQ-5D-5L VAS recorded the subject's self-rated health on a vertical VAS which is numbered from 0 (worst health state) to 100 (best health state). The mean change from baseline at the EoS visit is presented with a positive change in the VAS indicating an improvement in symptoms.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study. Only subjects with data available for analysis are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1), EoS

End point values	PanNET Cohort	Midgut NET Cohort	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21	21	42	
Units: score on a scale				
arithmetic mean (standard deviation)	-1.90 (± 14.80)	-1.76 (± 9.34)	-1.83 (± 12.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in QoL Questionnaire Gastrointestinal Neuroendocrine Tumour 21 (QLQ-GI.NET21; 2006)

End point title	Mean Change From Baseline in QoL Questionnaire Gastrointestinal Neuroendocrine Tumour 21 (QLQ-GI.NET21; 2006)

End point description:

Subjects were asked to complete the EORTC QLQ-GI.NET21 module which comprised 21 questions that used a 4-point scale (1 = Not at all, 2 = A little, 3 = Quite a bit, 4 = Very much) to evaluate 3 defined multi-item symptom scales (endocrine, gastrointestinal and treatment related side effects), 2 single item symptoms (bone/muscle pain and concern about weight loss), 2 psychosocial scales (social function and disease-related worries) and 2 other single items (sexuality and communication). Answers were converted into grading scale, with values between 0 and 100. Each individual sub-score was transformed to range from 0 to 100. The mean change from baseline at the EoS visit is presented with a higher score representing more or worse problems.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study. Only subjects with data available for analysis are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1), EoS

End point values	PanNET Cohort	Midgut NET Cohort	Overall	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	21[11]	24[12]	45[13]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Endocrine Symptoms	-0.53 (± 11.37)	-5.09 (± 17.33)	-2.96 (± 14.87)	
Gastrointestinal Symptoms	-3.49 (± 14.24)	-2.78 (± 15.96)	-3.11 (± 15.02)	
Treatment Related Symptoms (TRS)	5.93 (± 15.64)	-3.47 (± 14.47)	1.08 (± 15.54)	
Social Function	-0.79 (± 13.41)	-9.49 (± 18.20)	-5.43 (± 16.56)	
Disease Related Worries	3.17 (± 15.47)	-0.93 (± 27.40)	0.99 (± 22.48)	
Muscle/Bone Pain (MBP)	-1.67 (± 33.29)	0.00 (± 36.78)	-0.76 (± 34.84)	
Sexual Function (SF)	2.38 (± 15.82)	-2.78 (± 26.43)	0.00 (± 21.08)	
Information/Communication Function (ICF)	7.94 (± 29.64)	-2.90 (± 9.60)	2.27 (± 22.04)	
Body Image (BI)	0.00 (± 15.29)	-7.58 (± 28.97)	-3.97 (± 23.52)	

Notes:

[11] - Except TRS=15, MBP=20, SF=14, BI=20

[12] - Except TRS=16, SF=12, ICF=23, BI=22

[13] - Except TRS=31, MBP=44, SF=26, ICF=44, BI=42

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Nonspecific Tumour Biomarkers

End point title	Mean Change From Baseline in Nonspecific Tumour Biomarkers

End point description:

Nonspecific tumour peptide biomarkers (chromogranin A [CgA], neuron specific enolase [NSE] and plasma/urinary 5-hydroxyindoleacetic acid [5-HIAA]) were evaluated in both pancreas and midgut subjects at baseline and Week 12 and every 12 weeks thereafter. At all scheduled visits, except baseline, plasma/urinary 5-HIAA was only performed in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above upper limit of normal [ULN]) at baseline. Mean change from baseline values were normalised by the ULN (xULN) and are presented for each cohort.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study. Only subjects with data available for analysis are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and EoS

End point values	PanNET Cohort	Midgut NET Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[14]	24[15]		
Units: xULN				
arithmetic mean (standard deviation)				
CgA	0.205 (± 1.258)	0.370 (± 1.843)		
NSE	0.03 (± 1.00)	-0.49 (± 1.86)		
Plasma 5-HIAA	-0.42 (± 1.44)	3.90 (± 7.39)		

Notes:

[14] - Except NSE=15, Plasma5-HIAA=20

[15] - Except NSE=10, Plasma5-HIAA=17

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in PanNet Specific Tumour Biomarkers: Pancreatic Polypeptide, Gastrin

End point title	Mean Change From Baseline in PanNet Specific Tumour Biomarkers: Pancreatic Polypeptide, Gastrin[16]

End point description:

PanNET specific tumour peptide biomarkers were evaluated in pancreas subjects at baseline. Only the tumour biomarkers that were above normal range at baseline were evaluated every 12 weeks thereafter and at the EoS visit. The mean change from baseline values in picomole/liter (pmol/L) are presented for the EoS visit.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study. Only subjects with data available for analysis are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and EoS

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Specific tumour biomarkers were only evaluated in pancreas NET subjects in the panNET cohort. Subjects in the midgut NET cohort were not evaluated.

End point values	PanNET Cohort			
Subject group type	Reporting group			
Number of subjects analysed	4[17]			
Units: pmol/L				
arithmetic mean (standard deviation)				
Pancreatic Polypeptide	82.7 (± 146.7)			
Gastrin	-9.8 (± 70.7)			

Notes:

[17] - Except pancreatic polypeptide=3

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in PanNet Specific Tumour Biomarkers: Glucagon

End point title	Mean Change From Baseline in PanNet Specific Tumour Biomarkers: Glucagon[18]

End point description:

PanNET specific tumour peptide biomarkers were evaluated in pancreas subjects at baseline. Only the tumour biomarkers that were above normal range at baseline were evaluated every 12 weeks thereafter and at the EoS visit. The mean change from baseline values in nanograms (ng)/L are presented for the EoS visit.

Analysis was performed on the FAS which included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study. Only subjects with data available for analysis are presented.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and EoS

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Specific tumour biomarkers were only evaluated in pancreas NET subjects in the panNET cohort. Subjects in the midgut NET cohort were not evaluated.

End point values	PanNET Cohort			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: ng/L				
arithmetic mean (standard deviation)	5.5 (± 36.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were recorded from the first dose of lanreotide Autogel® 120 mg on Day 1 until 28 days after the last treatment. Up to Week 64 for panNet cohort and Week 108 for midgut NET (and overall) cohort.

Adverse event reporting additional description:

The FAS included all subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	PanNET Cohort

Reporting group description:

Subjects were treated with lanreotide Autogel® 120 mg, administered as deep SC injections, every 14 days starting from Day 1 (at a reduced dosing interval) for up to 48 weeks or until disease progression, death or unacceptable toxicity or tolerability. Subjects who had not progressed at Week 48 could continue study treatment with lanreotide Autogel® 120 mg every 14 days until 25 events (PD or death) in the panNET cohort had been observed. Additional visits were performed every 12 weeks until disease progression or death, or unacceptable toxicity or tolerability.

Reporting group title	Midgut NET Cohort

Reporting group description:

Subjects were treated with lanreotide Autogel® 120 mg, administered as deep SC injections, every 14... more days starting from Day 1 (at a reduced dosing interval) for up to 96 weeks or until disease progression, death or unacceptable toxicity or tolerability. Subjects who had not progressed at Week 96 could continue study treatment with lanreotide Autogel® 120 mg every 14 days until 25 events (PD or death) in the midgut NET cohort had been observed. Additional visits were performed every 12 weeks until disease progression or death, or unacceptable toxicity or tolerability.

Reporting group title	Overall Subjects

Reporting group description:

All subjects who received at least one dose of lanreotide Autogel® 120 mg every 14 days during the study.

Serious adverse events	PanNET Cohort	Midgut NET Cohort	Overall Subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 48 (10.42%)	13 / 51 (25.49%)	18 / 99 (18.18%)
number of deaths (all causes)	1	3	4
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone neoplasm			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulseless electrical activity			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Nervous system disorders			
Spinal cord compression			

subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intestinal obstruction			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Peritonitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	PanNET Cohort	Midgut NET Cohort	Overall Subjects
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 48 (85.42%)	47 / 51 (92.16%)	88 / 99 (88.89%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to liver			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Flushing			
subjects affected / exposed	2 / 48 (4.17%)	9 / 51 (17.65%)	11 / 99 (11.11%)
occurrences (all)	2	14	16

Haematoma			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Hot flush			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	14	14
Hypertension			
subjects affected / exposed	2 / 48 (4.17%)	9 / 51 (17.65%)	11 / 99 (11.11%)
occurrences (all)	2	9	11
Venous thrombosis limb			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Peripheral venous disease			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Surgical and medical procedures			
Injection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 48 (8.33%)	4 / 51 (7.84%)	8 / 99 (8.08%)
occurrences (all)	24	5	29
Chest pain			
subjects affected / exposed	0 / 48 (0.00%)	3 / 51 (5.88%)	3 / 99 (3.03%)
occurrences (all)	0	3	3
Fatigue			
subjects affected / exposed	7 / 48 (14.58%)	8 / 51 (15.69%)	15 / 99 (15.15%)
occurrences (all)	8	11	19
Gait disturbance			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Hunger			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Influenza like illness			

subjects affected / exposed	1 / 48 (2.08%)	3 / 51 (5.88%)	4 / 99 (4.04%)
occurrences (all)	1	3	4
Injection site bruising			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Injection site pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Malaise			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	2	3
Medical device site pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Oedema peripheral			
subjects affected / exposed	2 / 48 (4.17%)	2 / 51 (3.92%)	4 / 99 (4.04%)
occurrences (all)	2	2	4
Pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Peripheral swelling			
subjects affected / exposed	0 / 48 (0.00%)	3 / 51 (5.88%)	3 / 99 (3.03%)
occurrences (all)	0	3	3
Polyp			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	2 / 48 (4.17%)	2 / 51 (3.92%)	4 / 99 (4.04%)
occurrences (all)	2	5	7
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Reproductive system and breast disorders			

Gynaecomastia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Cough			
subjects affected / exposed	3 / 48 (6.25%)	3 / 51 (5.88%)	6 / 99 (6.06%)
occurrences (all)	3	3	6
Dysphonia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Dyspnoea			
subjects affected / exposed	0 / 48 (0.00%)	4 / 51 (7.84%)	4 / 99 (4.04%)
occurrences (all)	0	5	5
Dyspnoea exertional			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	2	3
Increased upper airway secretion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Orthopnoea			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Productive cough			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Sputum discoloured			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Psychiatric disorders			

Acrophobia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Confusional state			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 51 (0.00%)	2 / 99 (2.02%)
occurrences (all)	2	0	2
Mood altered			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Panic attack			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Sleep disorder			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	2	3
Aspartate aminotransferase abnormal			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Bacterial test positive			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 48 (6.25%)	1 / 51 (1.96%)	4 / 99 (4.04%)
occurrences (all)	3	1	4
Blood bilirubin increased			

subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Blood chromogranin A increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Blood glucose decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Blood glucose increased			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Blood potassium increased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Blood triglycerides increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Blood urea increased			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Blood urine present			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
C-reactive protein increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Gamma-glutamyltransferase abnormal			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Gamma-glutamyltransferase decreased			

subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	2	3
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Lymphocyte count decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Neutrophil count decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Platelet count decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Specific gravity urine increased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Urine ketone body present			
subjects affected / exposed	2 / 48 (4.17%)	0 / 51 (0.00%)	2 / 99 (2.02%)
occurrences (all)	2	0	2
Weight decreased			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	2	3
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Incision site pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Incisional hernia			

subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Ligament sprain			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Muscle strain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Post procedural complication			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Radiation skin injury			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Skin abrasion			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Cardiac failure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	2	2
Heart valve incompetence			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Palpitations			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Right ventricular failure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Tachycardia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1

Tricuspid valve disease			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Aphasia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	2	2
Balance disorder			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	3 / 48 (6.25%)	5 / 51 (9.80%)	8 / 99 (8.08%)
occurrences (all)	3	7	10
Dizziness postural			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Head discomfort			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Headache			
subjects affected / exposed	3 / 48 (6.25%)	4 / 51 (7.84%)	7 / 99 (7.07%)
occurrences (all)	3	5	8
Lethargy			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Poor quality sleep			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Presyncope			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Sciatica			

subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Syncope			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Taste disorder			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Tremor			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	2	3
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Monocytopenia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Deafness unilateral			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Ear pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Hypoacusis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Vertigo			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	2	2
Vertigo positional			

subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Dry eye			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Eye pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Eye pruritus			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Glaucoma			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Ocular hyperaemia			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Abdominal distension			
subjects affected / exposed	0 / 48 (0.00%)	6 / 51 (11.76%)	6 / 99 (6.06%)
occurrences (all)	0	7	7
Abdominal pain			
subjects affected / exposed	7 / 48 (14.58%)	12 / 51 (23.53%)	19 / 99 (19.19%)
occurrences (all)	13	16	29
Abdominal pain lower			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Abdominal pain upper			

subjects affected / exposed	2 / 48 (4.17%)	6 / 51 (11.76%)	8 / 99 (8.08%)
occurrences (all)	2	7	9
Anal incontinence			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Anorectal discomfort			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Ascites			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Constipation			
subjects affected / exposed	2 / 48 (4.17%)	2 / 51 (3.92%)	4 / 99 (4.04%)
occurrences (all)	3	3	6
Diarrhoea			
subjects affected / exposed	14 / 48 (29.17%)	27 / 51 (52.94%)	41 / 99 (41.41%)
occurrences (all)	20	35	55
Dry mouth			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	3	3
Faeces discoloured			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Flatulence			
subjects affected / exposed	1 / 48 (2.08%)	6 / 51 (11.76%)	7 / 99 (7.07%)
occurrences (all)	1	8	9
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	2	3
Gingival bleeding			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Glossodynia			

subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Haematochezia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Haemorrhoids			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Hernial eventration			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Inguinal hernia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	5 / 48 (10.42%)	6 / 51 (11.76%)	11 / 99 (11.11%)
occurrences (all)	5	9	14
Oral pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Pancreatic failure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Proctalgia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Steatorrhoea			
subjects affected / exposed	2 / 48 (4.17%)	3 / 51 (5.88%)	5 / 99 (5.05%)
occurrences (all)	2	3	5
Stomatitis			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Toothache			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Vomiting			

subjects affected / exposed	6 / 48 (12.50%)	4 / 51 (7.84%)	10 / 99 (10.10%)
occurrences (all)	9	4	13
Gingival pain			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Cholelithiasis			
subjects affected / exposed	0 / 48 (0.00%)	3 / 51 (5.88%)	3 / 99 (3.03%)
occurrences (all)	0	3	3
Hepatic failure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Liver injury			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Hyperhidrosis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Photosensitivity reaction			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Pruritus			
subjects affected / exposed	1 / 48 (2.08%)	3 / 51 (5.88%)	4 / 99 (4.04%)
occurrences (all)	1	4	5
Pruritus generalised			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Rash			

subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Skin fissures			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Skin irritation			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Urticaria			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Night sweats			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Dysuria			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Haematuria			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	2	3
Urethral stenosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 48 (0.00%)	5 / 51 (9.80%)	5 / 99 (5.05%)
occurrences (all)	0	7	7
Back pain			
subjects affected / exposed	2 / 48 (4.17%)	2 / 51 (3.92%)	4 / 99 (4.04%)
occurrences (all)	2	2	4
Exostosis			

subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Flank pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Intervertebral disc degeneration			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Intervertebral disc protrusion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Joint swelling			
subjects affected / exposed	0 / 48 (0.00%)	3 / 51 (5.88%)	3 / 99 (3.03%)
occurrences (all)	0	5	5
Mobility decreased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Muscle spasms			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	3	4
Musculoskeletal chest pain			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Musculoskeletal discomfort			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Musculoskeletal pain			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	2	3
Myalgia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	2	2
Neck pain			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Osteoarthritis			

subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Osteoporosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Pain in extremity			
subjects affected / exposed	2 / 48 (4.17%)	1 / 51 (1.96%)	3 / 99 (3.03%)
occurrences (all)	2	2	4
Periarthritis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Rheumatoid arthritis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	2	2
Spinal pain			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	2	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Carbuncle			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Cystitis			
subjects affected / exposed	2 / 48 (4.17%)	1 / 51 (1.96%)	3 / 99 (3.03%)
occurrences (all)	2	1	3
Cystitis bacterial			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Diverticulitis			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Folliculitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1

Herpes zoster			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Influenza			
subjects affected / exposed	2 / 48 (4.17%)	3 / 51 (5.88%)	5 / 99 (5.05%)
occurrences (all)	2	6	8
Lower respiratory tract infection			
subjects affected / exposed	1 / 48 (2.08%)	3 / 51 (5.88%)	4 / 99 (4.04%)
occurrences (all)	2	3	5
Nasopharyngitis			
subjects affected / exposed	7 / 48 (14.58%)	5 / 51 (9.80%)	12 / 99 (12.12%)
occurrences (all)	7	6	13
Respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Tonsillitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	4 / 48 (8.33%)	1 / 51 (1.96%)	5 / 99 (5.05%)
occurrences (all)	6	1	7
Metabolism and nutrition disorders			
Carbohydrate intolerance			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Decreased appetite			
subjects affected / exposed	5 / 48 (10.42%)	2 / 51 (3.92%)	7 / 99 (7.07%)
occurrences (all)	5	2	7
Hypercholesterolaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Hyperglycaemia			

subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2
Hyperkalaemia			
subjects affected / exposed	0 / 48 (0.00%)	2 / 51 (3.92%)	2 / 99 (2.02%)
occurrences (all)	0	2	2
Hypernatraemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Hyperuricaemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Hypoalbuminaemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Hypocalcaemia			
subjects affected / exposed	1 / 48 (2.08%)	2 / 51 (3.92%)	3 / 99 (3.03%)
occurrences (all)	1	2	3
Hypoglycaemia			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	3	1	4
Hypokalaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Hyponatraemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 51 (0.00%)	1 / 99 (1.01%)
occurrences (all)	1	0	1
Malnutrition			
subjects affected / exposed	0 / 48 (0.00%)	1 / 51 (1.96%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Vitamin D deficiency			
subjects affected / exposed	1 / 48 (2.08%)	1 / 51 (1.96%)	2 / 99 (2.02%)
occurrences (all)	1	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2015	• The criteria of treatment terminations was added to the protocol on request of German Regulatory authorities.
16 December 2015	• Clarification that specific tumour biomarkers were only applicable to the panNET cohort and not the midgut NET cohort • Clarification of which subjects in the panNET cohort were to have 5-HIAA repeated during the study treatment period • Removal of the following assessments at Visit 3 (Week 2): electrocardiogram (ECG), clinical laboratory tests, nonspecific biomarkers, specific tumour biomarkers and biobanking; and addition of ECG at Week 4 (Visit 4) • Clarification of radiology imaging assessments • Addition of tertiary objective and endpoint to include the use of MRI as a method of texture analysis • Addition and clarification of exclusion criteria • Recalculation of blood volumes
09 January 2017	• Redefined some exclusion criteria to allow more subjects to enter the study without impacting their safety, physical, or mental integrity, or the scientific value of the trial • Exclusion criterion modified to authorise inclusion of subjects treated by long acting formulation of octreotide and who stopped this treatment for other reason than disease progression • Exclusion criterion modified to exclude subjects with symptomatic gallbladder lithiasis/sludge at screening or history of symptomatic cholelithiasis • Exclusion criterion modified to allow re-screening of subjects who screen failed following central reviewers eligibility assessment (ie non PD). • Clarifications for exclusion criterion where subject has had previous cancer (except basocellular carcinoma of the skin and/or in situ carcinoma of the cervix/uterus if subjects were treated with curative intent and free from disease for more than 5 years) • Clarifications for the technique of imaging of the tertiary endpoints • The removal of United States as a country for study conduct.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Please note that 99999 (or any variants thereof) is used when data is not available.

Notes: