Clinical trial results:
PHASE II, MULTICENTRE, OPEN LABEL STUDY TO EVALUATE THE EFFICACY OF THE COMBINATION OF LANREOTIDE AUTOGEL 120 MG AND TEMOZOLOMIDE IN PATIENTS WITH PROGRESSIVE GASTRO-ENTERO-PANCREATIC NEUROENDOCRINE TUMOURS (GEP-NET) G1/G2 - A PILOT-STUDY

Summary

EudraCT number	2013-001697-17
Trial protocol	AT DE
Global end of trial date	01 June 2017

Results information

Result version number	v1 (current)
This version publication date	03 August 2018
First version publication date	03 August 2018

Trial information

Trial identification

Sponsor protocol code	A-94-52030-268

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02231762
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IPSEN Pharma GmbH
Sponsor organisation address	Willy-Brandt-Str. 3, Ettlingen, Germany, 76275
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	01 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2016
Global end of trial reached?	Yes
Global end of trial date	01 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective was to evaluate the efficacy of lanreotide Autogel (ATG) 120 milligrams (mg) in combination with temozolomide in subjects with functioning as well as non-functioning, progressive, GEP-NET G1 or G2.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 2014
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	Austria: 15
Country: Number of subjects enrolled	Germany: 42
Worldwide total number of subjects	57
EEA total number of subjects	57

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	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

57 subjects entered the combination phase and received lanreotide ATG 120 mg plus temozolomide for 6 months. A 6 month maintenance phase then followed where subjects received either lanreotide ATG 120 mg or no treatment, dependent upon whether they had functioning or non-functioning NET, clinical benefit and allocation following randomisation.

Pre-assignment

Screening details:

Overall, 64 subjects were screened, 7 were screening failures of which 5 subjects did not meet the entry criteria. 57 subjects were assigned to receive treatment in the baseline population.

Period 1

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

Arms

Arm title	Combination Phase

Arm description:

All subjects received lanreotide ATG 120 mg plus temozolomide in combination for 6 months.

Subjects received 1 injection of lanreotide ATG 120 mg and temozolomide capsules for 5 consecutive days, in a 28 day treatment cycle. The temozolomide dose was adapted to the subject body surface area (BSA) and the dose in the 1st treatment cycle was 150 mg/metres squared (m^2) per day. Depending on the safety laboratory values, the temozolomide dose was increased to 200 mg/m^2 per day from cycle 2 to cycle 6.

Arm type	Experimental
Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Temozolomide capsules were orally administered for 5 consecutive days every 28 days for 6 months. The capsules were presented as dose strength of 5 mg, 20 mg, 100 mg, or 250 mg. The dose for each treatment cycle was calculated according to the BSA of the subject. One treatment cycle was a period of 28 days. The dose in cycle 1 was 150 mg/m^2 per day and from cycle 2 to 6 it could be increased to 200 mg/m^2 per day. The BSA was monitored every 4 weeks and the temozolomide dose was calculated with a maximum of BSA of 2.0 m^2.

Investigational medicinal product name	Lanreotide ATG
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Lanreotide ATG 120 mg, provided in a ready-to-use pre-filled syringe, was administered deep subcutaneously every 28 days for 6 months in the superior external quadrant of the buttock by a qualified person (no self or partner injection).

Number of subjects in period 1	Combination Phase
Started	57
Completed	37
Not completed	20
Consent withdrawn by subject	2
Disease progression	6
Did not meet inclusion criteria	1
Adverse event, non-fatal	10
Protocol deviation	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Maintenance Phase - Functioning NET, Lanreotide

Arm description:

In case of clinical benefit, defined as either complete response (CR), partial response (PR) or stable disease (SD) after the first 6 months combination phase, all subjects with functioning (serotonin producing) NET continued to receive lanreotide ATG 120 mg for another 6 months. This maintenance phase started with visit 8, week 24.

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

Dosage and administration details:

Lanreotide ATG 120 mg, provided in a ready-to-use pre-filled syringe, was administered deep subcutaneously every 28 days for 6 months in the superior external quadrant of the buttock by a qualified person (no self or partner injection).

Arm title	Maintenance Phase - Non-functioning NET, Lanreotide

Arm description:

Following completion of the 6-month combination phase, all subjects with non-functioning NET and clinical benefit were randomised to continue to receive lanreotide ATG 120 mg for another 6 months. This maintenance phase started with visit 8, week 24.

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

Dosage and administration details:

Lanreotide ATG 120 mg, provided in a ready-to-use pre-filled syringe, was administered deep subcutaneously every 28 days for 6 months in the superior external quadrant of the buttock by a qualified person (no self or partner injection).

Arm title	Maintenance Phase - Non-functioning NET, No Treatment

Arm description:

Following completion of the 6-month combination phase, all subjects with non-functioning NET and clinical benefit were randomised to receive no treatment for 6 months. This maintenance phase started with visit 8, week 24.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Maintenance Phase - Functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, No Treatment
Started	11	14	12
Completed	8	9	7
Not completed	3	5	5
Disease progression	3	4	3
Adverse event, non-fatal	-	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Combination Phase

Reporting group description:

All subjects received lanreotide ATG 120 mg plus temozolomide in combination for 6 months.

Subjects received 1 injection of lanreotide ATG 120 mg and temozolomide capsules for 5 consecutive days, in a 28 day treatment cycle. The temozolomide dose was adapted to the subject body surface area (BSA) and the dose in the 1st treatment cycle was 150 mg/metres squared (m^2) per day. Depending on the safety laboratory values, the temozolomide dose was increased to 200 mg/m^2 per day from cycle 2 to cycle 6.

Reporting group values	Combination Phase	Total	
Number of subjects	57	57	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.1		
standard deviation	± 11.0	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	33	33	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native.	0	0	
Asian.	0	0	
Black or African American	0	0	
Hispanic or Latino	0	0	
Native Hawaiian or Other Pacific Islander.	0	0	
White	57	57	

End points

End points reporting groups

Reporting group title	Combination Phase

Reporting group description:

All subjects received lanreotide ATG 120 mg plus temozolomide in combination for 6 months.

Subjects received 1 injection of lanreotide ATG 120 mg and temozolomide capsules for 5 consecutive days, in a 28 day treatment cycle. The temozolomide dose was adapted to the subject body surface area (BSA) and the dose in the 1st treatment cycle was 150 mg/metres squared (m^2) per day. Depending on the safety laboratory values, the temozolomide dose was increased to 200 mg/m^2 per day from cycle 2 to cycle 6.

Reporting group title	Maintenance Phase - Functioning NET, Lanreotide

Reporting group description:

In case of clinical benefit, defined as either complete response (CR), partial response (PR) or stable disease (SD) after the first 6 months combination phase, all subjects with functioning (serotonin producing) NET continued to receive lanreotide ATG 120 mg for another 6 months. This maintenance phase started with visit 8, week 24.

Reporting group title	Maintenance Phase - Non-functioning NET, Lanreotide

Reporting group description:

Following completion of the 6-month combination phase, all subjects with non-functioning NET and clinical benefit were randomised to continue to receive lanreotide ATG 120 mg for another 6 months. This maintenance phase started with visit 8, week 24.

Reporting group title	Maintenance Phase - Non-functioning NET, No Treatment

Reporting group description:

Following completion of the 6-month combination phase, all subjects with non-functioning NET and clinical benefit were randomised to receive no treatment for 6 months. This maintenance phase started with visit 8, week 24.

Subject analysis set title	Intention-to-treat (ITT) Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All treated subjects having at least one baseline and at least one post baseline assessment of the primary efficacy parameter.

Subject analysis set title	Combination Phase - Functioning NET
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects in the combination phase who were categorised at baseline as having functioning NET.

Subject analysis set title	Pharmacokinetic (PK) Subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects for whom PK assessments were performed and with evaluable PK data.

Primary: Disease Control Rate (DCR) After 6 Months

End point title	Disease Control Rate (DCR) After 6 Months[1]

End point description:

All tumour assessments were performed using the Response Evaluation Criteria In Solid Tumours (RECIST) criteria (1.1). Computer Tomography (CT-scan) or Magnetic Resonance Imaging (MRI) could be used for as method of tumour measurement and the same method of tumour measurement was used throughout the study for each subject. CT scans/MRI were performed at screening or baseline visit then at weeks 12, 24 and at early withdrawal or at anytime during the study in the case of any clinical or biological signs of tumour progression.

The DCR was defined as the proportion of subjects with a response of CR, PR or SD after 6 months of combination treatment and was described in the ITT population along with its 95% Confidence Interval (CI) and was compared to 45% with an exact binomial proportion test. The Last Observation Carried Forward (LOCF) method was used to replace missing assessments at the end of the combination phase.

End point type	Primary

End point timeframe:

6 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the end point only reports on a single arm, no comparative analysis can be presented. A p value of <0.0001 was derived from an Exact Bionomial Proportion Test comparing the DCR to 45%.

End point values	Combination Phase			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: percentage of subjects				
number (confidence interval 95%)	73.5 (58.9 to 85.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: DCR After 12 Months

End point title	DCR After 12 Months

End point description:

All tumour assessments were performed using the RECIST criteria (1.1). CT-scan or MRI could be used for as method of tumour measurement and the same method of tumour measurement was used throughout the study for each subject. CT scans/MRI were performed at screening or baseline visit then at weeks 12, 24, 36, 48 (end of study) and at study withdrawal or at anytime during the study in the case of any clinical or biological signs of tumour progression.

The DCR was defined as the proportion of subjects with a response of CR, PR or SD after 6 months combination treatment followed by either 6 months of lanreotide ATG 120 mg maintenance treatment or no treatment. The DCR was described in the ITT population along with its 95% CI and was compared to 45% with an exact binomial proportion test. The LOCF method was used to replace missing assessments at the end of the maintenance phase.

End point type	Secondary

End point timeframe:

12 months

End point values	Maintenance Phase - Functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, No Treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	14	12	
Units: percentage of subjects				
number (confidence interval 95%)	54.5 (23.4 to 83.3)	71.4 (41.9 to 91.6)	41.7 (15.2 to 72.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression–Free Survival (PFS) Within 12 Months

End point title	Progression–Free Survival (PFS) Within 12 Months

End point description:

PFS was defined as the time from the date of treatment start to the date of the first documented disease progression or death due to any cause within the first 12 months of treatment. If a subject had not progressed or died after 12 months of treatment or when any further anti-neoplastic therapy was received, PFS was censored at the time of the last tumour assessment before the analysis cut-off date or the anti-neoplastic therapy date.
A Kaplan-Meier estimate of the PFS was calculated to determine the number of subjects at risk. Median PFS time (50% of subjects who would not progress or die) of the ITT population is presented along with 95 % CI.

End point type	Secondary

End point timeframe:

12 months

End point values	Intention-to-treat (ITT) Population			
Subject group type	Subject analysis set			
Number of subjects analysed	49[2]			
Units: months				
number (confidence interval 95%)	11.1 (8.3 to 999999.9)			

Notes:

[2] - 999999.9 = non calculable

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Response (TtR) Within 12 Months

End point title	Time To Response (TtR) Within 12 Months

End point description:

TtR was defined as the time from the date of treatment start to the date of the first documented objective response (CR or PR) within the first 12 months of treatment (combination and maintenance phases).
The Kaplan-Meier method was used to estimate the median TtR and its 95% CI for subjects in the ITT population (50% of subjects were expected to have a CR or PR at this time).

End point type	Secondary

End point timeframe:

12 months

End point values	Intention-to-treat (ITT) Population			
Subject group type	Subject analysis set			
Number of subjects analysed	49[3]			
Units: months				
number (confidence interval 95%)	999999.9 (999999.9 to 999999.9)			

Notes:

[3] - 999999.9 = non calculable

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) Within 12 Months

End point title	Duration of Response (DoR) Within 12 Months

End point description:

The DoR is an estimation of the time from first documented objective response (CR or PR) to the first date of progressive disease (PD) or death due to disease progression for subjects who experienced an objective response within the first 12 months of treatment (combination and maintenance phases). The Kaplan-Meier method was used to estimate the median DoR and its 95% CI for subjects in the ITT population who had an objective response.

End point type	Secondary

End point timeframe:

12 months

End point values	Intention-to-treat (ITT) Population			
Subject group type	Subject analysis set			
Number of subjects analysed	6[4]			
Units: months				
number (confidence interval 95%)	999999.9 (999999.9 to 999999.9)			

Notes:

[4] - 999999.9 = non calculable

Statistical analyses

No statistical analyses for this end point

Secondary: Biochemical Response Using Chromogranin-A (CgA) Levels After 6 Months

End point title	Biochemical Response Using Chromogranin-A (CgA) Levels After 6 Months

End point description:

Blood samples for CgA blood tumour marker analysis were taken at baseline, weeks 12, 24 and at early withdrawal. The biochemical response after 6 months combination treatment was estimated for subjects with abnormal CgA levels at baseline. Abnormal CgA levels were defined as above the upper limit of normal range (≥100 micrograms/litre [mcg/L]).

Biochemical response based on CgA levels was categorised as:
PR = decrease of CgA ≥ 50%, compared to the baseline CgA
SD = decrease < 50 % or an increase ≤25%, compared to the baseline CgA
PD = defined as an increase ≥25 %, compared to the baseline CgA

The number of subjects in each response category at each time point in the combination phase is presented. Analysis was only carried out on subjects in the ITT population who had abnormal CgA at baseline.

End point type	Secondary

End point timeframe:

6 months

End point values	Combination Phase			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: subjects				
Week 12 - PD	8			
Week 12 - SD	15			
Week 12 - PR	10			
Week 12 - Missing	1			
Week 24 - PD	5			
Week 24 - SD	9			
Week 24 - PR	7			
Week 24 - Missing	0			
Early Withdrawal - PD	1			
Early Withdrawal - SD	2			
Early Withdrawal - PR	1			
Early Withdrawal - Missing	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Biochemical Response using CgA Levels After 12 Months

End point title	Biochemical Response using CgA Levels After 12 Months

End point description:

Blood samples for CgA blood tumour marker analysis were taken at baseline, weeks 24, 36, 48 (end of study) and at early withdrawal. The biochemical response after 12 months combination and maintenance treatment was estimated for subjects with abnormal CgA levels at baseline. Abnormal CgA levels were defined as above the upper limit of normal range (≥100 mcg/L).

Biochemical response based on CgA levels was categorised as:
PR = decrease of CgA ≥ 50%, compared to the baseline CgA
SD = decrease < 50% or an increase ≤ 25%, compared to the baseline CgA
PD = defined as an increase ≥ 25%, compared to the baseline CgA

The number of subjects in each response category at each time point in the maintenance phase is presented. Analysis was only carried out on subjects in the ITT population who had abnormal CgA at baseline.

End point type	Secondary

End point timeframe:

12 months

End point values	Maintenance Phase - Functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, No Treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	9	9	
Units: subjects				
Week 24 - PD	2	1	2	
Week 24 - SD	3	4	2	
Week 24 - PR	0	3	3	
Week 24 - Missing	0	1	2	
Week 36 - PD	1	1	3	
Week 36 - SD	2	4	2	
Week 36 - PR	0	1	4	
Week 36 - Missing	0	1	0	
Week 48 - PD	1	1	2	
Week 48 - SD	0	2	3	
Week 48 - PR	1	2	1	
Week 48 - Missing	0	0	0	
Early Withdrawal - PD	1	2	1	
Early Withdrawal - SD	0	0	0	
Early Withdrawal - PR	0	1	1	
Early Withdrawal - Missing	2	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Biochemical Response using 5-Hydroxy-Indol-Amino-Acid (5-HIAA) Levels After 6 Months

End point title	Biochemical Response using 5-Hydroxy-Indol-Amino-Acid (5-HIAA) Levels After 6 Months

End point description:

Urine samples for 5-HIAA urinary tumour marker analysis were taken at at baseline, weeks 12, 24 and early withdrawal.

Biochemical response based on 5-HIAA levels was categorised as:
Response = 5-HIAA reduction compared to baseline
Progression = 5-HIAA increase compared to baseline

The number of subjects in each response category at each time point in the combination phase is presented. Analysis was only carried out on subjects in the ITT population with functioning NET.

End point type	Secondary

End point timeframe:

6 months

End point values	Combination Phase - Functioning NET			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: subjects				
Week 12 - Progression	4			
Week 12 - Response	6			
Week 12 - Not evaulable	1			
Week 12 - Missing	6			
Week 24 - Progression	6			
Week 24 - Response	3			
Week 24 - Not evaluable	1			
Week 24 - Missing	3			
Early Withdrawal - Progression	0			
Early Withdrawal - Response	1			
Early Withdrawal - Not Evaluable	0			
Early Withdrawal - Missing	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Biochemical Response using 5-HIAA Levels After 12 Months

End point title	Biochemical Response using 5-HIAA Levels After 12 Months

End point description:

Urine samples for 5-HIAA a urinary tumour marker analysis were taken at baseline, weeks 12, 24, 36, 48 (end of study) and early withdrawal.

Biochemical response based on 5-HIAA levels was categorised as:
Response = 5-HIAA reduction compared to baseline
Progression = 5-HIAA increase compared to baseline

The number of subjects in each response category at each time point in the maintenance phase is presented. Analysis was only carried out on subjects in the ITT population with functioning NET.

End point type	Secondary

End point timeframe:

12 months

End point values	Maintenance Phase - Functioning NET, Lanreotide			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: subjects				
Week 24 - Progression	6			
Week 24 - Response	3			
Week 24 - Not evaluable	1			
Week 24 - Missing	1			
Week 36 - Progression	3			
Week 36 - Response	3			
Week 36 - Not evaluable	0			
Week 36 - Missing	3			
Week 48 - Progression	4			
Week 48 - Response	2			
Week 48 - Not evaluable	0			
Week 48 - Missing	2			
Early Withdrawal - Progression	0			
Early Withdrawal - Response	0			
Early Withdrawal - Not evaluable	0			
Early Withdrawal - Missing	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Symptomatic Response After 6 Months

End point title	Symptomatic Response After 6 Months

End point description:

Symptomatic response was evaluated as absolute change from baseline in the number of episodes of the lead symptoms (i.e. diarrhoea and flushing) using the mean of the last 3 days before the visit, at each visit, as compared to baseline.

Symptomatic responses were categorised as:
Reduction, Increase or Stability of occurrences of diarrhoea
Reduction, Increase or Stability of occurrences of flushing

The number of subjects in each response category at week 24 (end of the combination phase) is presented. Analysis was only carried out on subjects in the ITT population with functioning NET.

End point type	Secondary

End point timeframe:

6 months

End point values	Combination Phase - Functioning NET			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: subjects				
Diarrhoea - Reduction	4			
Diarrhoea - Increase	2			
Diarrhoea - Stability	5			
Diarrhoea - Missing	6			
Flushing - Reduction	4			
Flushing - Increase	4			
Flushing - Stability	3			
Flushing - Missing	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Symptomatic Response After 12 Months

End point title	Symptomatic Response After 12 Months

End point description:

Symptomatic response was evaluated as absolute change from baseline in the number of episodes of the lead symptoms (i.e. diarrhoea and flushing) using the mean of the last 3 days before the visit, at each visit, as compared to baseline.

Symptomatic responses were categorised as:
Reduction, Increase or Stability of occurrences of diarrhoea
Reduction, Increase or Stability of occurrences of flushing

The number of subjects in each response category at week 48 (end of study) is presented. Analysis was only carried out on subjects in the ITT population with functioning NET.

End point type	Secondary

End point timeframe:

12 months

End point values	Maintenance Phase - Functioning NET, Lanreotide			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: subjects				
Diarrhoea - Reduction	4			
Diarrhoea - Increase	1			
Diarrhoea - Stability	3			
Diarrhoea - Missing	3			
Flushing - Reduction	2			
Flushing - Increase	3			

Flushing - Stability	3			
Flushing - Missing	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life (QoL) Core 30 Questionnaire (QLQ-C30): Mean Change from Baseline at 6 Months

End point title	Quality of Life (QoL) Core 30 Questionnaire (QLQ-C30): Mean Change from Baseline at 6 Months

End point description:

Subjects were instructed to complete the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire at baseline, weeks 12, 24 or at early withdrawal.

The QLQ-C30 questionnaire contains 30 single items (Q1 – Q30). Q1 –Q28 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). Q29 and Q30 scores range from 1 (= Very poor) to 7 (= Excellent) with 1 being the worst case and 7 the most favourable answer. Subscores from the 5 functional scales, 3 symptom scales, a global health status/QoL scale, and 6 single items were derived according to the rules contained within the EORTC Scoring Manual.

The mean change from baseline at week 24 (end of the combination phase) is presented for each of the category subscores. Only subjects with data available for analysis are presented.

End point type	Secondary

End point timeframe:

6 months

End point values	Combination Phase			
Subject group type	Reporting group			
Number of subjects analysed	34[5]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Global health status	-4.9 (± 18.2)			
Physical functioning	-9.6 (± 19.4)			
Role functioning	-8.3 (± 27.6)			
Emotional functioning	-4.7 (± 17.7)			
Cognitive functioning	-5.9 (± 15.8)			
Social functioning	-11.8 (± 23.8)			
Fatigue	6.9 (± 20.1)			
Nausea and vomiting	6.9 (± 14.9)			
Pain	-1.0 (± 31.0)			
Dyspnoea	12.7 (± 30.7)			
Insomnia	0.0 (± 34.9)			
Appetite loss	2.0 (± 24.5)			
Constipation	6.9 (± 33.6)			
Diarrhoea	-3.9 (± 34.6)			
Financial difficulties	2.9 (± 17.1)			

Notes:
[5] - Insomnia (n=32)

Statistical analyses

No statistical analyses for this end point

Secondary: QoL Questionnaire QLQ-C30: Mean Change from Baseline at 12 Months

End point title	QoL Questionnaire QLQ-C30: Mean Change from Baseline at 12 Months

End point description:

Subjects were instructed to complete the EORTC QLQ-C30 questionnaire at baseline, weeks 12, 24, 36, 48 (end of study) or at early withdrawal.

The QLQ-C30 questionnaire contains 30 single items (Q1 – Q30). Q1 –Q28 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). Q29 and Q30 scores range from 1 (= Very poor) to 7 (= Excellent) with 1 being the worst case and 7 the most favourable answer. Subscores from the 5 functional scales, 3 symptom scales, a global health status/QoL scale, and 6 single items were derived according to the rules contained within the EORTC Scoring Manual.

The mean change from baseline at week 48 (end of study) is presented for each of the category subscores. Only subjects with data available for analysis are presented for each arm.

End point type	Secondary

End point timeframe:

12 months

End point values	Maintenance Phase - Functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, No Treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[6]	8	7[7]	
Units: units on a scale				
arithmetic mean (standard deviation)				
Global health status	-11.7 (± 40.7)	-3.1 (± 10.9)	-7.1 (± 15.5)	
Physical functioning	8.0 (± 22.8)	-12.5 (± 17.6)	-11.4 (± 13.7)	
Role functioning	3.3 (± 29.8)	-2.1 (± 20.8)	-7.1 (± 13.1)	
Emotional functioning	15.0 (± 19.0)	-6.2 (± 20.3)	-6.0 (± 12.5)	
Cognitive functioning	3.3 (± 24.7)	-2.1 (± 20.8)	2.4 (± 6.3)	
Social functioning	13.3 (± 34.2)	-22.9 (± 34.4)	-4.8 (± 15.9)	
Fatigue	-22.2 (± 30.4)	9.7 (± 24.1)	4.8 (± 16.8)	
Nausea and vomiting	-10.0 (± 14.9)	4.2 (± 23.1)	2.4 (± 6.3)	
Pain	-13.3 (± 32.1)	4.2 (± 24.8)	9.5 (± 23.3)	
Dyspnoea	-8.3 (± 41.9)	4.2 (± 33.0)	9.5 (± 16.3)	
Insomnia	-13.3 (± 50.6)	-8.3 (± 34.5)	16.7 (± 27.9)	
Appetite loss	0.0 (± 23.6)	0.0 (± 39.8)	14.3 (± 17.8)	
Constipation	20.0 (± 38.0)	-4.2 (± 11.8)	-4.8 (± 35.6)	
Diarrhoea	-40.0 (± 36.5)	8.3 (± 15.4)	0.0 (± 27.2)	

Financial difficulties	6.7 (± 14.9)	4.2 (± 27.8)	9.5 (± 25.2)	

Notes:

[6] - Dyspnoea (n=4)

[7] - Insomnia (n=6)

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life Gastrointestinal Neuroendocrine Tumour 21 Questionnaire (QLQ-GI.NET21): Mean Change from Baseline at 6 Months

End point title	Quality of Life Gastrointestinal Neuroendocrine Tumour 21 Questionnaire (QLQ-GI.NET21): Mean Change from Baseline at 6 Months

End point description:

Subjects were instructed to complete the QLQ-GI.NET21 questionnaire at baseline, weeks 12, 24 or at early withdrawal.
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. The mean change from baseline at 6 months (week 24) is presented for each of the category subscores. Only subjects with data available for analysis are presented.

End point type	Secondary

End point timeframe:

6 months

End point values	Combination Phase			
Subject group type	Reporting group			
Number of subjects analysed	34[8]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Endocrine symptoms	-1.0 (± 13.5)			
Gastrointestinal (G.I.) symptoms	5.7 (± 14.0)			
Treatment related symptoms	3.6 (± 30.1)			
Social function	2.3 (± 25.3)			
Disease related worries	1.6 (± 27.1)			
Muscle/bone pain symptoms	1.0 (± 37.1)			
Body image	0.0 (± 23.2)			
Weight gain	-11.8 (± 30.5)			
Information/communication (Info/com) function	-9.4 (± 22.8)			
Sexual function	-4.8 (± 17.8)			

Notes:

[8] - Treatment related symptoms (n=14) Weight gain (n=31) Info/com function (n=32) Sexual function (n=14)

Statistical analyses

No statistical analyses for this end point

Secondary: QoL questionnaire QLQ-GI.NET21: Mean Change from Baseline at 12 Months

End point title	QoL questionnaire QLQ-GI.NET21: Mean Change from Baseline at 12 Months

End point description:

Subjects were instructed to complete the QLQ-GI.NET21 questionnaire at baseline, weeks 12, 24, 36, 48 (end of study) or at early withdrawal.
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. The mean change from baseline at 12 months (week 48) is presented for each of the category subscores.

End point type	Secondary

End point timeframe:

12 months

End point values	Maintenance Phase - Functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, No Treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[9]	8[10]	7[11]	
Units: units on a scale				
arithmetic mean (standard deviation)				
Endocrine symptoms	-13.3 (± 21.4)	-5.6 (± 19.7)	1.6 (± 4.2)	
G.I. symptoms	-4.0 (± 21.9)	0.0 (± 19.2)	6.7 (± 7.7)	
Treatment related symptoms	0.0 (± 0.0)	-11.1 (± 34.7)	999999.9 (± 999999.9)	
Social function	-6.7 (± 23.0)	9.7 (± 20.9)	-6.3 (± 16.8)	
Disease related worries	-6.7 (± 36.5)	1.4 (± 15.1)	-3.2 (± 30.6)	
Muscle/bone pain symptoms	-6.7 (± 14.9)	4.2 (± 33.0)	4.8 (± 30.0)	
Body image	0.0 (± 23.6)	4.2 (± 27.8)	4.8 (± 12.6)	
Weight gain	-20.0 (± 29.8)	9.5 (± 25.2)	-9.5 (± 56.8)	
Information/communication function	0.0 (± 70.7)	0.0 (± 17.8)	-4.8 (± 12.6)	
Sexual function	0.0 (± 0.0)	0.0 (± 0.0)	0.0 (± 0.0)	

Notes:

[9] - Treatment related symptoms (n=2) Sexual function (n=2)

[10] - Treatment related symptoms (n=3) Weight gain (n=7) Sexual function (n=4)

[11] - Treatment related symptoms (n=0) Sexual function (n=3)

999999.9 = non calculable

Statistical analyses

No statistical analyses for this end point

Secondary: DCR by O6-methylguanine-DNA methyl-transferase (MGMT) Expression and Methylation and Somatostatin Receptor (SSTR) Expression After 6 Months

End point title	DCR by O6-methylguanine-DNA methyl-transferase (MGMT) Expression and Methylation and Somatostatin Receptor (SSTR)

	Expression After 6 Months

End point description:

In all subjects whose tumour tissue was available, MGMT expression/methylation and SSTR expression was analysed. After 6 months, the DCR (SD+PR+CR) by MGMT methylation and expression and by SSTR 2a and SSTR 5 expression was evaluated.

DCR in response to MGMT methylation and expression results are presented.
SSTR 2a and SSTR 5 expression is categorised as: No Receptors, Cytoplasmatic Expression (CE), Focal Expression (FE), Complete Circumferent Membrane Expression (CCME).

The DCR was defined as the proportion of subjects with a response of CR, PR or SD after 6 months of combination treatment within each methylation/expression category. The DCR was described in the ITT population along with its 95% CI and was compared to 45% with an exact binomial proportion test.

Only subjects with data available for analysis are presented.

End point type	Secondary

End point timeframe:

6 months

End point values	Combination Phase			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: percentage of subjects				
number (confidence interval 95%)				
MGMT Methylation (n=9)	100 (66.4 to 100)			
MGMT No methylation (n=13)	84.6 (54.6 to 98.1)			
MGMT Expression (n=11)	90.9 (58.7 to 99.8)			
MGMT No expression (n=20)	70.0 (45.7 to 88.1)			
SSTR 2a No Receptors (n=0)	9999999.9 (9999999.9 to 9999999.9)			
SSTR 2a CE (n=0)	9999999.9 (9999999.9 to 9999999.9)			
SSTR 2a FE (n=15)	86.7 (59.5 to 98.3)			
SSTR 2a CCME (n=22)	72.7 (49.8 to 89.3)			
SSTR 5 - No Receptors (n=24)	75.0 (53.3 to 90.2)			
SSTR 5 CE (n=2)	100.0 (15.8 to 100.0)			
SSTR 5 FE (n=11)	81.8 (48.2 to 97.7)			
SSTR 5 CCME (n=0)	9999999.9 (9999999.9 to 9999999.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Results: Lanreotide ATG 120 mg Serum After 12 Months

End point title	Pharmacokinetic (PK) Results: Lanreotide ATG 120 mg Serum After 12 Months

End point description:

Lanreotide ATG levels were measured in a subset of subjects to evaluate if temozolomide co-treatment had an impact on lanreotide serum concentration over a 12 month period.
Blood samples were collected for the determination of lanreotide ATG in serum at baseline, weeks 12, 24 and 48 (end of study).
The concentrations of lanreotide ATG in serum were determined by a validated radioimmunoassay analysis method with a lower limit of quantitation of 0.08 nanograms [ng]/mL).
Serum concentrations of lanreotide ATG at each of the time points in the combination and maintenance phase are presented. Only subjects with data available for analysis are presented.

End point type	Secondary

End point timeframe:

12 months

End point values	Pharmacokinetic (PK) Subset			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: Nanograms (ng)/mL				
arithmetic mean (standard deviation)				
Baseline	0.44 (± 1.22)			
Week 4 (n=14)	2.45 (± 1.16)			
Week 12 (n=11)	5.06 (± 3.01)			
Week 24 (n=9)	1.93 (± 6.13)			
Week 48 (n=7)	3.68 (± 3.36)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

13 months (12 month study treatment plus 28 days)

Adverse event reporting additional description:

Treatment Emergent Adverse Events (TEAEs) are reported for both the combination and maintenance phases and include events with an onset after the start of study drug treatment to the last intake of study drug plus 28 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Combination Phase

Reporting group description:

All subjects received lanreotide ATG 120 mg plus temozolomide in combination for 6 months. Subjects received one injection of lanreotide ATG 120 mg and temozolomide capsules for 5 consecutive days, in a 28 days treatment cycle . The temozolomide dose was adapted to the subject BSA, and the dose in the 1st treatment cycle was 150 mg/m^2 per day. Depending on the safety laboratory values, the temozolomide dose was increased to 200 mg/m^2 per day from cycle 2 to cycle 6.

Reporting group title	Maintenance Phase - Functioning NET, Lanreotide

Reporting group description:

In case of clinical benefit, defined as either CR, PR or SD after the first 6 months combination phase, all subjects with functioning (serotonin producing) NET continued to receive lanreotide ATG 120 mg for another 6 months. This maintenance phase started with visit 8, week 24.

Reporting group title	Maintenance Phase - Non-functioning NET, Lanreotide

Reporting group description:

Following completion of the 6-month combination phase, all subjects with non-functioning NET and clinical benefit were randomised to continue to receive lanreotide ATG 120 mg for another 6 months. This maintenance phase started with visit 8, week 24.

Reporting group title	Maintenance Phase - Non-functioning NET, No Treatment

Reporting group description:

Following completion of the 6-month combination phase, all subjects with non-functioning NET and clinical benefit were randomised to receive no treatment for 6 months. This maintenance phase started with visit 8, week 24.

Serious adverse events	Combination Phase	Maintenance Phase - Functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, Lanreotide
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 57 (29.82%)	3 / 11 (27.27%)	4 / 14 (28.57%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to gastrointestinal tract			

subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Penile squamous cell carcinoma			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			

subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tricuspid valve incompetence			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 57 (5.26%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ocular vascular disorder			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intestinal perforation			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			

subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seronegative arthritis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Maintenance Phase - Non-functioning NET, No Treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to gastrointestinal tract			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to peritoneum			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Penile squamous cell carcinoma			

subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral swelling				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pulmonary embolism			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congestive cardiomyopathy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tricuspid valve incompetence			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leukocytosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ocular vascular disorder			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Vomiting				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bile duct stenosis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Petechiae				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seronegative arthritis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cachexia			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Combination Phase	Maintenance Phase - Functioning NET, Lanreotide	Maintenance Phase - Non-functioning NET, Lanreotide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 57 (91.23%)	9 / 11 (81.82%)	13 / 14 (92.86%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Neoplasm progression			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tumour pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Haematoma			
subjects affected / exposed	3 / 57 (5.26%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	5	3	0
Hypertension			
subjects affected / exposed	5 / 57 (8.77%)	1 / 11 (9.09%)	2 / 14 (14.29%)
occurrences (all)	5	1	2
Lymphoedema			

subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	3 / 57 (5.26%)	1 / 11 (9.09%)	2 / 14 (14.29%)
occurrences (all)	3	1	2
Chest discomfort			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	2
Fatigue			
subjects affected / exposed	19 / 57 (33.33%)	2 / 11 (18.18%)	4 / 14 (28.57%)
occurrences (all)	32	2	4
Feeling cold			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
General physical health deterioration			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	4 / 57 (7.02%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	4	0	1
Pain			
subjects affected / exposed	2 / 57 (3.51%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Pyrexia			
subjects affected / exposed	4 / 57 (7.02%)	1 / 11 (9.09%)	3 / 14 (21.43%)
occurrences (all)	5	1	4
Thirst			

subjects affected / exposed	1 / 57 (1.75%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Dysphonia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	3 / 57 (5.26%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	6	0	1
Dyspnoea exertional			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Pleural effusion			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Sleep apnoea syndrome			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Disorientation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	3 / 57 (5.26%)	0 / 11 (0.00%)	2 / 14 (14.29%)
occurrences (all)	3	0	2
Investigations			
Blood bilirubin increased			
subjects affected / exposed	3 / 57 (5.26%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	4	0	0
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	3 / 57 (5.26%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	3	0	1
Blood uric acid increased			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	4	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 57 (10.53%)	1 / 11 (9.09%)	1 / 14 (7.14%)
occurrences (all)	6	2	1
Liver function test abnormal			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Red blood cell count decreased			
subjects affected / exposed	1 / 57 (1.75%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Weight decreased			
subjects affected / exposed	8 / 57 (14.04%)	0 / 11 (0.00%)	2 / 14 (14.29%)
occurrences (all)	8	0	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 57 (3.51%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Atrial thrombosis			

subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Atrioventricular block			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Bradycardia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Cardiac failure			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Diastolic dysfunction			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Mitral valve incompetence			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tricuspid valve incompetence			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Ventricular extrasystoles			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Nervous system disorders			
Carotid arteriosclerosis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	1 / 57 (1.75%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Dizziness			
subjects affected / exposed	3 / 57 (5.26%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	6	0	0

Dysgeusia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	3 / 14 (21.43%)
occurrences (all)	1	0	3
Headache			
subjects affected / exposed	7 / 57 (12.28%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	9	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Polyneuropathy			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	1 / 57 (1.75%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 57 (12.28%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	9	0	0
Coagulopathy			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	2
Leukocytosis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Leukopenia			
subjects affected / exposed	6 / 57 (10.53%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	8	0	0
Lymphadenopathy			

subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	8 / 57 (14.04%)	0 / 11 (0.00%)	2 / 14 (14.29%)
occurrences (all)	10	0	2
Neutropenia			
subjects affected / exposed	6 / 57 (10.53%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	7	1	0
Thrombocytopenia			
subjects affected / exposed	16 / 57 (28.07%)	1 / 11 (9.09%)	3 / 14 (21.43%)
occurrences (all)	28	1	3
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	3 / 57 (5.26%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	6	0	0
Eye disorders			
Ocular vascular disorder			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Photopsia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 57 (5.26%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Abdominal discomfort			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Abdominal distension			
subjects affected / exposed	4 / 57 (7.02%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	7	0	1
Abdominal pain			

subjects affected / exposed	12 / 57 (21.05%)	2 / 11 (18.18%)	4 / 14 (28.57%)
occurrences (all)	22	3	6
Anal inflammation			
subjects affected / exposed	1 / 57 (1.75%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Ascites			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	11 / 57 (19.30%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	16	0	1
Diarrhoea			
subjects affected / exposed	21 / 57 (36.84%)	0 / 11 (0.00%)	3 / 14 (21.43%)
occurrences (all)	35	0	4
Dyspepsia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eructation			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Faecal incontinence			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	10 / 57 (17.54%)	1 / 11 (9.09%)	2 / 14 (14.29%)
occurrences (all)	16	1	3
Frequent bowel movements			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Intestinal ischaemia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lip dry			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Melaena			

subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	24 / 57 (42.11%)	1 / 11 (9.09%)	4 / 14 (28.57%)
occurrences (all)	55	1	5
Pancreatic insufficiency			
subjects affected / exposed	1 / 57 (1.75%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Steatorrhoea			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	19 / 57 (33.33%)	1 / 11 (9.09%)	2 / 14 (14.29%)
occurrences (all)	40	1	3
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Hepatic pain			
subjects affected / exposed	3 / 57 (5.26%)	2 / 11 (18.18%)	0 / 14 (0.00%)
occurrences (all)	3	2	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	2 / 57 (3.51%)	1 / 11 (9.09%)	2 / 14 (14.29%)
occurrences (all)	2	1	2
Rash			

subjects affected / exposed	5 / 57 (8.77%)	2 / 11 (18.18%)	2 / 14 (14.29%)
occurrences (all)	6	2	2
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 57 (1.75%)	1 / 11 (9.09%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 57 (8.77%)	1 / 11 (9.09%)	2 / 14 (14.29%)
occurrences (all)	9	1	2
Back pain			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Joint swelling			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Muscle tightness			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	0	4	0
Pain in extremity			
subjects affected / exposed	3 / 57 (5.26%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	3	1	0
Synovial cyst			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 57 (1.75%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	1	1	0

Nasopharyngitis			
subjects affected / exposed	7 / 57 (12.28%)	3 / 11 (27.27%)	2 / 14 (14.29%)
occurrences (all)	8	4	3
Otitis media			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 57 (1.75%)	1 / 11 (9.09%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Decreased appetite			
subjects affected / exposed	3 / 57 (5.26%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	3	0	1
Dehydration			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Diabetes mellitus			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Electrolyte imbalance			
subjects affected / exposed	0 / 57 (0.00%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Glucose tolerance impaired			
subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	2 / 57 (3.51%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Hypercholesterolaemia			

subjects affected / exposed	1 / 57 (1.75%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	2 / 14 (14.29%)
occurrences (all)	2	0	2
Hypertriglyceridaemia			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Hypocalcaemia			
subjects affected / exposed	2 / 57 (3.51%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Hypokalaemia			
subjects affected / exposed	3 / 57 (5.26%)	0 / 11 (0.00%)	1 / 14 (7.14%)
occurrences (all)	3	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 57 (0.00%)	1 / 11 (9.09%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Maintenance Phase - Non-functioning NET, No Treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Neoplasm progression			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tumour pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Haematoma			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Lymphoedema			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	7		
Feeling cold			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General physical health deterioration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Pain			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	8		
Thirst			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dyspnoea exertional			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Disorientation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Insomnia			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood uric acid increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Liver function test abnormal			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Red blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Atrial thrombosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Atrioventricular block			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Bradycardia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cardiac failure			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Diastolic dysfunction			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Mitral valve incompetence			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tricuspid valve incompetence			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Ventricular extrasystoles			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			

Carotid arteriosclerosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Polyneuropathy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Coagulopathy			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Leukocytosis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Leukopenia subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3		
Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Lymphopenia subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 8		
Neutropenia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Vertigo subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Eye disorders			
Ocular vascular disorder subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Photopsia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Gastrointestinal disorders			

Abdominal pain upper				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Abdominal discomfort				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Abdominal distension				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Abdominal pain				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Anal inflammation				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Ascites				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Dyspepsia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Eructation				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Faecal incontinence				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Flatulence				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			

Frequent bowel movements subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Intestinal ischaemia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Lip dry subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Melaena subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Nausea subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Pancreatic insufficiency subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Steatorrhoea subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Hepatobiliary disorders Cholangitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Hepatic pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Erythema			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Night sweats			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Muscle tightness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pain in extremity			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Synovial cyst			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Otitis media			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dehydration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Diabetes mellitus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Electrolyte imbalance			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Glucose tolerance impaired			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypercholesterolaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Hypertriglyceridaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		
Hypocalcaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2014	This amendment included 1 addition to inclusion criteria and 1 addition to exclusion criteria and to reference the results of the previous CLARINET study. Minor changes and clarifications concerning stopping rules and discontinuation criteria, the secondary efficacy criterion (DCR) and the choice of methods for tumour assessment were also added.
06 November 2014	This amendment included an update of the synopsis, the Schedule of Assessment table and the addition of a section "Reporting Exemptions'. Clarifications were also added concerning the baseline visit, the providing of capsules of temozolomide (bottles or blisters), haematology tests, concomitant medications or therapies not permitted during the study, the reference documents for assessment of expected adverse events (AEs) and Data Safety Monitoring Committee.
24 November 2015	This amendment included an increase in number of screened subjects (total number of evaluable subjects unchanged), an update of the Schedule of Assessment and other administrative changes. Clarifications concerning the follow-up visit, CT/MRI scan, laboratory assessment related to temozolodine dosing and dose adjustment, report of Serious AE related to temozolodine and the interim analysis were also included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported