



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/m² per day. Depending on the safety laboratory values, the temozolomide dose was increased to 200 mg/m² 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/m² per day and from cycle 2 to 6 it could be increased to 200 mg/m² per day. The BSA was monitored every 4 weeks and the temozolomide dose was calculated with a maximum of BSA of 2.0 m².

| | |
|--|--|
| 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 Binomial 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: | |
| <p>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.</p> | |
| 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: | |
| <p>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]).</p> | |

Biochemical response based on CgA levels was categorised as:

PR = decrease of CgA \geq 50%, compared to the baseline CgA

SD = decrease < 50 % or an increase \leq 25%, compared to the baseline CgA

PD = defined as an increase \geq 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 (\geq 100 mcg/L).

Biochemical response based on CgA levels was categorised as:

PR = decrease of CgA \geq 50%, compared to the baseline CgA

SD = decrease < 50% or an increase \leq 25%, compared to the baseline CgA

PD = defined as an increase \geq 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 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 evaluable | 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-GI.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

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-GI.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) |
|-----------------|---|

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/m² per day. Depending on the safety laboratory values, the temozolomide dose was increased to 200 mg/m² 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 occurrences (all) | 1 / 57 (1.75%) 1 | 1 / 11 (9.09%) 1 | 0 / 14 (0.00%) 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 occurrences (all) | 0 / 57 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Lymphopenia subjects affected / exposed occurrences (all) | 8 / 57 (14.04%) 10 | 0 / 11 (0.00%) 0 | 2 / 14 (14.29%) 2 |
| Neutropenia subjects affected / exposed occurrences (all) | 6 / 57 (10.53%) 7 | 1 / 11 (9.09%) 1 | 0 / 14 (0.00%) 0 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 16 / 57 (28.07%) 28 | 1 / 11 (9.09%) 1 | 3 / 14 (21.43%) 3 |
| Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) | 0 / 57 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Vertigo subjects affected / exposed occurrences (all) | 3 / 57 (5.26%) 6 | 0 / 11 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Eye disorders Ocular vascular disorder subjects affected / exposed occurrences (all) | 0 / 57 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 14 (0.00%) 0 |
| Photopsia subjects affected / exposed occurrences (all) | 0 / 57 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 14 (0.00%) 0 |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 3 / 57 (5.26%) 3 | 0 / 11 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 57 (1.75%) 1 | 0 / 11 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Abdominal distension subjects affected / exposed occurrences (all) | 4 / 57 (7.02%) 7 | 0 / 11 (0.00%) 0 | 1 / 14 (7.14%) 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 |
| Eruclation | | | |
| 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 occurrences (all) | 5 / 57 (8.77%) 6 | 2 / 11 (18.18%) 2 | 2 / 14 (14.29%) 2 |
| Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 57 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 14 (0.00%) 0 |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 57 (1.75%) 1 | 1 / 11 (9.09%) 1 | 1 / 14 (7.14%) 1 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 5 / 57 (8.77%) 9 | 1 / 11 (9.09%) 1 | 2 / 14 (14.29%) 2 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 57 (3.51%) 2 | 0 / 11 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Joint swelling subjects affected / exposed occurrences (all) | 1 / 57 (1.75%) 1 | 0 / 11 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Muscle tightness subjects affected / exposed occurrences (all) | 1 / 57 (1.75%) 1 | 0 / 11 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 0 / 57 (0.00%) 0 | 1 / 11 (9.09%) 4 | 0 / 14 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 3 / 57 (5.26%) 3 | 1 / 11 (9.09%) 1 | 0 / 14 (0.00%) 0 |
| Synovial cyst subjects affected / exposed occurrences (all) | 0 / 57 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 14 (7.14%) 1 |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 1 / 57 (1.75%) 1 | 1 / 11 (9.09%) 1 | 0 / 14 (0.00%) 0 |

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

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

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Investigations | | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Blood uric acid increased subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Liver function test abnormal subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Red blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 3 / 12 (25.00%) 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 | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | | |
| occurrences (all) | 3 | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | | |
| occurrences (all) | 8 | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Ocular vascular disorder | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Photopsia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |

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

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

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