



## Clinical trial results:

An open-label, multi-center, expanded access study of everolimus in participants with advanced neuroendocrine tumors (NETs) (core study) and an extension study to the open-label, multi-center, expanded access study of everolimus in patients with advanced NETs (E1)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-001099-13 |
| Trial protocol           | DE             |
| Global end of trial date | 09 August 2016 |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 06 July 2018 |
| First version publication date | 06 July 2018 |

## Trial information

### Trial identification

|                       |                                 |
|-----------------------|---------------------------------|
| Sponsor protocol code | CRAD001K24133 / CRAD001K24133E1 |
|-----------------------|---------------------------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01595009 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

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                       | 09 August 2016 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 09 August 2016 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

Core and Extension: The primary objective was to evaluate additional safety of everolimus in advanced pancreatic neuroendocrine tumors (pNETs) patients.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 27 April 2011 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Austria: 14            |
| Country: Number of subjects enrolled | Belgium: 34            |
| Country: Number of subjects enrolled | Czech Republic: 11     |
| Country: Number of subjects enrolled | Germany: 90            |
| Country: Number of subjects enrolled | Italy: 60              |
| Country: Number of subjects enrolled | Korea, Republic of: 16 |
| Country: Number of subjects enrolled | Saudi Arabia: 2        |
| Country: Number of subjects enrolled | Taiwan: 18             |
| Country: Number of subjects enrolled | Thailand: 1            |
| Worldwide total number of subjects   | 246                    |
| EEA total number of subjects         | 209                    |

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)                      | 124 |
| From 65 to 84 years                       | 122 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

In this expanded access core study, CRAD001K24133, participants with pNets and non-pNets (GI and Lung Nets) were enrolled. In the extension study, CRAD001K24133E1, participants with GI Nets and Lung Nets from the core study were enrolled.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Core (overall period)       |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | pNET (core) |

Arm description:

Participants received Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Everolimus   |
| Investigational medicinal product code | RAD001       |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Non-pNET (core) |
|------------------|-----------------|

Arm description:

Participants received Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Everolimus   |
| Investigational medicinal product code | RAD001       |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason.

| <b>Number of subjects in period 1</b> | pNET (core) | Non-pNET (core) |
|---------------------------------------|-------------|-----------------|
| Started                               | 126         | 120             |
| Completed                             | 0           | 0               |
| Not completed                         | 126         | 120             |
| Adverse event, serious fatal          | 3           | 6               |
| Consent withdrawn by subject          | 4           | 17              |
| Disease progression                   | 14          | 26              |
| Adverse event, non-fatal              | 19          | 23              |
| Protocol deviation                    | -           | 1               |
| Administrative problems               | -           | 1               |
| Study terminated by sponsor           | 85          | 44              |
| Lost to follow-up                     | 1           | 2               |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | pNET (core) |
|-----------------------|-------------|

Reporting group description:

Participants received Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Non-pNET (core) |
|-----------------------|-----------------|

Reporting group description:

Participants received Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason.

| Reporting group values                             | pNET (core) | Non-pNET (core) | Total |
|--|-------------|-----------------|-------|
| Number of subjects                                 | 126         | 120             | 246   |
| Age categorical                                    |             |                 |       |
| Units: Subjects                                    |             |                 |       |
| In utero   | 0           | 0               | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0           | 0               | 0     |
| Newborns (0-27 days)                               | 0           | 0               | 0     |
| Infants and toddlers (28 days-23 months)           | 0           | 0               | 0     |
| Children (2-11 years)                              | 0           | 0               | 0     |
| Adolescents (12-17 years)                          | 0           | 0               | 0     |
| Adults (18-64 years)                               | 74          | 50              | 124   |
| From 65-84 years                                   | 52          | 70              | 122   |
| 85 years and over                                  | 0           | 0               | 0     |
| Age Continuous                                     |             |                 |       |
| Units: years                                       |             |                 |       |
| arithmetic mean                                    | 59.3        | 64.4            |       |
| standard deviation                                 | ± 13.04     | ± 9.28          | -     |
| Gender, Male/Female                                |             |                 |       |
| Units: Subjects                                    |             |                 |       |
| Female   | 58          | 61              | 119   |
| Male   | 68          | 59              | 127   |

## End points

### End points reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | pNET (core)     |
| Reporting group description:<br>Participants received Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason.      |                 |
| Reporting group title  | Non-pNET (core) |
| Reporting group description:<br>Participants received Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason.      |                 |
| Subject analysis set title   | GI NET          |
| Subject analysis set type  | Full analysis   |
| Subject analysis set description:<br>Participants received Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason. |                 |
| Subject analysis set title   | GI NET          |
| Subject analysis set type  | Full analysis   |
| Subject analysis set description:<br>Participants received Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason. |                 |
| Subject analysis set title   | Lung Net        |
| Subject analysis set type  | Full analysis   |
| Subject analysis set description:<br>Participants received Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason. |                 |
| Subject analysis set title   | Lung Net        |
| Subject analysis set type  | Full analysis   |
| Subject analysis set description:<br>Participants received Everolimus 10 mg orally once daily until documented tumor progression, unacceptable toxicity or any other reason. |                 |

### Primary: Number of participants with adverse events (AEs), serious adverse events (SAEs) and deaths (core)

|   |  |
|---|--|
| End point title   | Number of participants with adverse events (AEs), serious adverse events (SAEs) and deaths (core) <sup>[1]</sup> |
| End point description:<br>The number of participants with AEs, SAEs and deaths were assessed. |  |
| End point type  | Primary  |
| End point timeframe:<br>up to 17 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: Statistical analysis does not apply to this end point.

| End point values            | pNET (core)     | Non-pNET (core) |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 123             | 117             |  |  |
| Units: Participants         |                 |                 |  |  |
| Adverse events              | 90              | 109             |  |  |
| Serious adverse events      | 25              | 59              |  |  |

|        |   |    |  |  |
|--------|---|----|--|--|
| Deaths | 5 | 10 |  |  |
|--------|---|----|--|--|

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with adverse events (AEs), serious adverse events (SAEs) and deaths (E1)

|                 |  |
|-----------------|--|
| End point title | Number of participants with adverse events (AEs), serious adverse events (SAEs) and deaths (E1) <sup>[2]</sup> |
|-----------------|--|

End point description:

The number of participants with AEs, SAEs and deaths were assessed.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

up to 4 years

Notes:

[2] - 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: Statistical analysis does not apply to this end point.

| End point values            | GI NET               | Lung Net             |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 11                   | 4                    |  |  |
| Units: participants         |                      |                      |  |  |
| AEs                         | 11                   | 4                    |  |  |
| SAEs                        | 4                    | 1                    |  |  |
| Deaths                      | 1                    | 0                    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Investigator-assessed Progression Free Survival (PFS) (core)

|                 |  |
|-----------------|--|
| End point title | Investigator-assessed Progression Free Survival (PFS) (core) |
|-----------------|--|

End point description:

PFS was defined as the time from the date of the first dose to the date of the first radiologically documented disease progression or death due to any cause. If a participant had not progressed or died at the study end date or when he/she received any further anti-neoplastic therapy, PFS was censored at the time of the last tumor assessment before the end of study date.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

from the day of first treatment up to 19 months



| End point values                 | pNET (core)         | Non-pNET (core)      |  |  |
|----------------------------------|---------------------|----------------------|--|--|
| Subject group type               | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed      | 126                 | 120                  |  |  |
| Units: Months                    |                     |                      |  |  |
| median (confidence interval 95%) | 7.62 (5.52 to 7.62) | 10.78 (8.77 to 9999) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) score (Core)

|                 |  |
|-----------------|--|
| End point title | Mean European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) score (Core) |
|-----------------|--|

End point description:

The EORTC QLQ-C30 contains 30 questions assessed by the participant. There are 9 multiple-item scales: 5 scales that assess aspects of functioning (physical, role functioning, cognitive, emotional, and social); 3 symptom scales (Fatigue, Pain, and Nausea and Vomiting); and a global health status/Quality of Life (QOL) scale. There are 5 single-item measures assessing additional symptoms (i.e., dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and a single item concerning perceived financial impact of the disease. All but two questions have 4-point scales ranging from "Not at all" to "Very much." The two questions concerning global health status/ QOL have 7 point scales with ratings ranging from "Very poor" to "Excellent." For each of the 14 domains, final scores are transformed such that they range from 0-100, whereas higher scores indicate greater functioning, greater QOL, or greater level of symptom.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, weeks 4, 8, 20, 32, 44, and end of treatment (EOT) up to week 82

| End point values                               | pNET (core)      | Non-pNET (core)  |  |  |
|--|------------------|------------------|--|--|
| Subject group type                             | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed                    | 126              | 120              |  |  |
| Units: units on a scale                        |                  |                  |  |  |
| arithmetic mean (standard deviation)           |                  |                  |  |  |
| Global health status/QOL, Baseline (n=120,110) | 64.93 (± 20.946) | 60.53 (± 21.497) |  |  |
| Global health status/QOL, Week 4 (n=102,102)   | 63.15 (± 19.673) | 58.91 (± 20.622) |  |  |
| Global health status/QOL, Week 8 (n=72,86)     | 59.72 (± 21.303) | 56.59 (± 20.417) |  |  |
| Global health status/QOL, Week 20 (n=28,57)    | 63.1 (± 22.387)  | 59.65 (± 17.663) |  |  |
| Global health status/QOL, Week 32 (n=5,39)     | 50 (± 26.352)    | 56.2 (± 20.297)  |  |  |
| Global health status/QOL, Week 44 (n=3,14)     | 61.11 (± 9.623)  | 57.74 (± 25.205) |  |  |
| Global health/QOL, EOT up to Week 82 (n=87,73) | 61.4 (± 20.847)  | 48.86 (± 27.823) |  |  |

|  |                  |                  |  |  |
|--|------------------|------------------|--|--|
| Physical functioning, Baseline (n=120,111)         | 79.89 (± 20.85)  | 72.97 (± 22.938) |  |  |
| Physical functioning, week 4 (n=103,103)           | 77.02 (± 22.38)  | 68.62 (± 23.648) |  |  |
| Physical functioning, week 8 (n=74,88)             | 76.22 (± 25.81)  | 67.48 (± 24.973) |  |  |
| Physical functioning, week 20 (n=29,57)            | 79.77 (± 18.212) | 73.71 (± 21.351) |  |  |
| Physical functioning, week 32 (n=5,39)             | 68 (± 26.415)    | 71.62 (± 23.729) |  |  |
| Physical functioning, week 44 (n=3,14)             | 68.89 (± 13.878) | 76.19 (± 22.602) |  |  |
| Physical functioning, EOT up to week 82 (n=86,76)  | 75.7 (± 24.509)  | 60.94 (± 28.037) |  |  |
| Role functioning, Baseline (n=120,110)             | 75.28 (± 28.663) | 67.27 (± 32.397) |  |  |
| Role functioning, week 4 (n=103,102)               | 72.49 (± 28.364) | 62.25 (± 30.483) |  |  |
| Role functioning, week 8 (n=71,88)                 | 71.83 (± 30.025) | 58.14 (± 31.46)  |  |  |
| Role functioning, week 20 (n=28,56)                | 79.76 (± 25.803) | 58.33 (± 29.129) |  |  |
| Role functioning, week 32 (n=5,38)                 | 66.67 (± 26.352) | 55.26 (± 35.325) |  |  |
| Role functioning, week 44 (n=3,14)                 | 61.11 (± 9.623)  | 66.67 (± 26.954) |  |  |
| Role functioning, EOT up to week 82 (n=85,77)      | 67.84 (± 31.788) | 49.13 (± 33.212) |  |  |
| Emotional functioning, Baseline (n=120,110)        | 74.79 (± 22.65)  | 67.2 (± 22.988)  |  |  |
| Emotional functioning, week 4 (n=102,103)          | 76.31 (± 20.991) | 66.69 (± 25.38)  |  |  |
| Emotional functioning, week 8 (n=72,88)            | 73.38 (± 24.73)  | 64.02 (± 26.64)  |  |  |
| Emotional functioning, week 20 (n=28,57)           | 76.19 (± 19.072) | 63.16 (± 27.456) |  |  |
| Emotional functioning, week 32 (n=5,39)            | 81.67 (± 14.907) | 61.11 (± 28.184) |  |  |
| Emotional functioning, week 44 (n=3,14)            | 75 (± 8.333)     | 65.67 (± 31.059) |  |  |
| Emotional functioning, EOT up to week 82 (n=86,75) | 74.61 (± 23.602) | 57.63 (± 25.841) |  |  |
| Cognitive functioning, Baseline (n=119,110)        | 84.17 (± 19.63)  | 80.61 (± 23.842) |  |  |
| Cognitive functioning, week 4 (n=102,103)          | 86.11 (± 20.05)  | 78.8 (± 23.708)  |  |  |
| Cognitive functioning, week 8 (n=72,88)            | 81.94 (± 21.803) | 76.33 (± 27.418) |  |  |
| Cognitive functioning, week 20 (n=28,57)           | 83.93 (± 19.501) | 78.65 (± 23.307) |  |  |
| Cognitive functioning, week 32 (n=5,39)            | 86.67 (± 18.257) | 75.21 (± 24.445) |  |  |
| Cognitive functioning, week 44 (n=3,14)            | 94.44 (± 9.623)  | 84.52 (± 20.111) |  |  |
| Cognitive functioning, EOT up to week 82 (n=84,76) | 81.35 (± 21.241) | 73.46 (± 24.522) |  |  |
| Social functioning, Baseline (n=120,111)           | 75.56 (± 28.249) | 67.42 (± 28.989) |  |  |
| Social functioning, week 4 (n=101,103)             | 78.71 (± 23.347) | 67.8 (± 30.093)  |  |  |
| Social functioning, week 8 (n=72,86)               | 75.69 (± 24.695) | 65.31 (± 29.396) |  |  |

|  |                  |                  |  |  |
|--|------------------|------------------|--|--|
| Social functioning, week 20 (n=28,56)            | 73.21 (± 24.148) | 66.07 (± 29.977) |  |  |
| Social functioning, week 32 (n=5,39)             | 60 (± 27.889)    | 66.24 (± 32.329) |  |  |
| Social functioning, week 44 (n=3,14)             | 66.67 (± 0)      | 72.62 (± 31.082) |  |  |
| Social functioning, EOT up to week 82 (n=85,75)  | 75.1 (± 27.533)  | 52.89 (± 33.933) |  |  |
| Fatigue, baseline (n=120,111)                    | 31.3 (± 22.361)  | 42.39 (± 28.534) |  |  |
| Fatigue, week 4 (n=103,103)                      | 35.22 (± 22.887) | 43.58 (± 28.035) |  |  |
| Fatigue, week 8 (n=73,88)                        | 36.91 (± 25.515) | 48.86 (± 29.878) |  |  |
| Fatigue, week 20 (n=29,57)                       | 34.29 (± 18.43)  | 44.44 (± 27.698) |  |  |
| Fatigue, week 32 (n=5,39)                        | 42.22 (± 18.257) | 48.72 (± 29.575) |  |  |
| Fatigue, week 44 (n=3,14)                        | 37.04 (± 6.415)  | 38.89 (± 26.777) |  |  |
| Fatigue, EOT up to week 82 (n=87,77)             | 38.83 (± 24.896) | 56.49 (± 30.474) |  |  |
| Nausea and vomiting, Baseline (n=120,111)        | 11.25 (± 17.442) | 9.46 (± 17.353)  |  |  |
| Nausea and vomiting, week 4 (n=103,101)          | 10.52 (± 15.998) | 7.43 (± 14.995)  |  |  |
| Nausea and vomiting, week 8 (n=73,87)            | 9.59 (± 17.984)  | 10.34 (± 18.015) |  |  |
| Nausea and vomiting, week 20 (n=29,57)           | 8.05 (± 15.185)  | 6.14 (± 12.048)  |  |  |
| Nausea and vomiting, week 32 (5,39)              | 6.67 (± 9.129)   | 5.98 (± 11.139)  |  |  |
| Nausea and vomiting, week 44 (n=3,14)            | 11.11 (± 9.623)  | 4.76 (± 10.187)  |  |  |
| Nausea and vomiting, EOT up to week 82 (n=86,77) | 9.69 (± 17.048)  | 15.8 (± 27.023)  |  |  |
| Pain, Baseline (n=119,110)                       | 21.57 (± 24.582) | 31.21 (± 31.535) |  |  |
| Pain, week 4 (n=101,102)                         | 25.91 (± 26.716) | 30.88 (± 29.796) |  |  |
| Pain, week 8 (n=72,87)                           | 25.23 (± 27.972) | 37.55 (± 32.372) |  |  |
| Pain, week 20 (n=28,57)                          | 27.98 (± 22.247) | 33.33 (± 32.581) |  |  |
| Pain, week 32 (n=5,39)                           | 43.33 (± 27.889) | 34.62 (± 32.977) |  |  |
| Pain, week 44 (n=3,14)                           | 38.89 (± 9.623)  | 26.19 (± 30.462) |  |  |
| Pain, EOT up to week 82 (n=86,71)                | 27.33 (± 28.343) | 43.9 (± 33.362)  |  |  |
| Dyspnea, Baseline (n=120,111)                    | 16.11 (± 22.448) | 24.32 (± 29.11)  |  |  |
| Dyspnea, week 4 (n=103,102)                      | 17.8 (± 24.171)  | 26.14 (± 28.388) |  |  |
| Dyspnea, week 8 (n=73,87)                        | 21 (± 27.502)    | 29.12 (± 31.665) |  |  |
| Dyspnea, week 20 (n=29,57)                       | 11.49 (± 18.422) | 28.07 (± 30.072) |  |  |
| Dyspnea, week 32 (n=5,39)                        | 13.33 (± 18.257) | 35.9 (± 31.885)  |  |  |
| Dyspnea, week 44 (n=3,14)                        | 22.22 (± 19.245) | 21.43 (± 28.063) |  |  |

|  |                  |                  |  |  |
|--|------------------|------------------|--|--|
| Dyspnea, EOT up to week 82 (n=86,77)         | 25.19 (± 30.222) | 33.77 (± 30.824) |  |  |
| Insomnia, Baseline (n=120,110)               | 24.72 (± 30.093) | 28.18 (± 32.929) |  |  |
| Insomnia, week 4 (n=102,103)                 | 27.78 (± 29.324) | 32.36 (± 30.769) |  |  |
| Insomnia, week 8 (n=73,85)                   | 32.88 (± 30.171) | 29.02 (± 28.54)  |  |  |
| Insomnia, week 24 (n=29,57)                  | 24.14 (± 26.572) | 35.09 (± 32.38)  |  |  |
| Insomnia, week 32 (n=5,38)                   | 26.67 (± 27.889) | 33.33 (± 32.88)  |  |  |
| Insomnia, week 48 (n=3,14)                   | 22.22 (± 19.245) | 28.57 (± 36.648) |  |  |
| Insomnia, EOT up to week 82 (n=86,77)        | 32.17 (± 31.289) | 34.63 (± 32.643) |  |  |
| Appetite loss, Baseline (n=120,111)          | 20.56 (± 30.613) | 18.62 (± 29.365) |  |  |
| Appetite loss, week 4 (n=102,102)            | 25.16 (± 31.618) | 21.9 (± 29.849)  |  |  |
| Appetite loss, week 8 (n=73,87)              | 24.66 (± 30.946) | 25.67 (± 31.623) |  |  |
| Appetite loss, week 24 (n=29,57)             | 18.39 (± 27.583) | 20.47 (± 27.998) |  |  |
| Appetite loss, week 36 (n=5,39)              | 20 (± 18.257)    | 23.93 (± 30.54)  |  |  |
| Appetite loss, week 44 (n=3,14)              | 11.11 (± 19.245) | 26.19 (± 29.753) |  |  |
| Appetite loss, EOT up to week 82 (n=87,76)   | 24.14 (± 29.505) | 33.77 (± 37.906) |  |  |
| Constipation, Baseline (n=120,111)           | 13.06 (± 24.175) | 13.21 (± 27.072) |  |  |
| Constipation, week 4 (n=103,103)             | 11 (± 24.427)    | 11.33 (± 24.501) |  |  |
| Constipation, week 8 (n=73,88)               | 10.5 (± 24.137)  | 7.58 (± 22.447)  |  |  |
| Constipation, week 20 (n=29,57)              | 6.9 (± 16.377)   | 8.77 (± 21.387)  |  |  |
| Constipation, week 32 (n=5,39)               | 0 (± 0)          | 4.27 (± 13.636)  |  |  |
| Constipation, week 44 (n=3,14)               | 0 (± 0)          | 2.38 (± 8.909)   |  |  |
| Constipation, EOT up to week 82 (n=86,77)    | 12.79 (± 24.611) | 10.39 (± 23.107) |  |  |
| Diarrhea, Baseline (n=119,110)               | 19.89 (± 29.535) | 36.67 (± 38.828) |  |  |
| Diarrhea, week 4 (n=102,103)                 | 20.92 (± 25.658) | 38.19 (± 36.577) |  |  |
| Diarrhea, week 8 (n=73,88)                   | 27.4 (± 29.576)  | 42.42 (± 39.708) |  |  |
| Diarrhea, week 20 (n=28,57)                  | 16.67 (± 21.276) | 31.58 (± 29.828) |  |  |
| Diarrhea, week 32 (n=5,39)                   | 13.33 (± 18.257) | 40.17 (± 36.015) |  |  |
| Diarrhea, week 44 (n=3,14)                   | 22.22 (± 19.245) | 40.48 (± 37.39)  |  |  |
| Diarrhea, EOT up to week 82 (n=86,76)        | 25.97 (± 32.095) | 39.04 (± 38.639) |  |  |
| Financial difficulties, Baseline (n=119,111) | 18.77 (± 26.975) | 16.52 (± 25.77)  |  |  |
| Financial difficulties, week 4 (n=100,100)   | 16.67 (± 24.845) | 16.67 (± 27.01)  |  |  |

|  |                  |                  |  |  |
|--|------------------|------------------|--|--|
| Financial difficulties, week 8 (n=72,87)           | 19.44 (± 26.091) | 16.86 (± 24.837) |  |  |
| Financial difficulties, week 20 (n=28,57)          | 21.43 (± 22.616) | 19.88 (± 27.357) |  |  |
| Financial difficulties, week 32 (n=5,39)           | 40 (± 27.889)    | 21.37 (± 28.084) |  |  |
| Financial difficulties, week 44 (n=3,14)           | 22.22 (± 19.245) | 19.05 (± 25.198) |  |  |
| Financial difficulties, EOT up to week 82(n=86,76) | 21.71 (± 27.897) | 27.63 (± 30.496) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean EORTC QLQ-G.I. NET21 score (core)

|  |  |
|--|--|
| End point title  | Mean EORTC QLQ-G.I. NET21 score (core) |
| End point description:   |  |
| The EORTC QLQ-G.I. NET21 contains 21 questions and has three defined multi-item symptom scales (endocrine – 3 questions, gastrointestinal – 5 questions, and treatment related side effects – 3 questions), two single item symptoms (bone/muscle pain and concern about weight loss), two psychosocial scales (social function – 3 questions, disease-related worries – 3 questions) and two other single items (sexuality and communication). For each of the 9 domains, final scores are transformed such that they range from 0-100, whereas higher scores indicate greater functioning, greater QOL, or greater level of symptom. |  |
| End point type   | Secondary                              |
| End point timeframe:   |  |
| Baseline, weeks 4, 8, 20, 32, 44, and end of treatment (EOT) up to week 82   |  |

| End point values                       | pNET (core)      | Non-pNET (core)  |  |  |
|--|------------------|------------------|--|--|
| Subject group type                     | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed            | 126              | 120              |  |  |
| Units: units on a scale                |                  |                  |  |  |
| arithmetic mean (standard deviation)   |                  |                  |  |  |
| Endocrine, Baseline (n=65,111)         | 12.99 (± 20.372) | 23.52 (± 23.771) |  |  |
| Endocrine, week 4 (n=53,99)            | 13.21 (± 17.44)  | 17.85 (± 21.403) |  |  |
| Endocrine, week 8 (n=33,88)            | 13.47 (± 17.293) | 16.79 (± 20.216) |  |  |
| Endocrine, week 20 (n=8,56)            | 12.5 (± 12.511)  | 15.87 (± 21.067) |  |  |
| Endocrine, week 32 (n=4,38)            | 16.67 (± 14.344) | 13.74 (± 17.978) |  |  |
| Endocrine, week 44 (n=1,14)            | 0 (± 9999)       | 7.14 (± 11.202)  |  |  |
| Endocrine, EOT up to week 82 (n=41,76) | 9.49 (± 15.627)  | 15.2 (± 18.755)  |  |  |
| G.I., Baseline (n=65,111)              | 23.69 (± 20.183) | 26.19 (± 21.328) |  |  |
| G.I., week 4 (n=53,99)                 | 23.02 (± 20.488) | 23.39 (± 18.958) |  |  |

|  |                  |                  |  |  |
|--|------------------|------------------|--|--|
| G.I., week 8 (n=34,89)                           | 22.34 (± 18.398) | 27.53 (± 21.341) |  |  |
| G.I., week 20 (n=8,56)                           | 25.63 (± 14.056) | 22.31 (± 18.837) |  |  |
| G.I., week 32 (n=4,38)                           | 25 (± 11.386)    | 26.84 (± 19.879) |  |  |
| G.I., week 44 (n=1,14)                           | 0 (± 9999)       | 20.95 (± 16.714) |  |  |
| G.I., EOT up to week 82 (n=41,76)                | 25.85 (± 19.899) | 30.48 (± 24.484) |  |  |
| Treatment, baseline (n=33,69)                    | 9.26 (± 11.675)  | 18.44 (± 19.374) |  |  |
| Treatment, week 4 (n=42,84)                      | 17.72 (± 15.337) | 22.22 (± 20.077) |  |  |
| Treatment, week 8 (n=23,77)                      | 16.18 (± 19.528) | 20.27 (± 17.283) |  |  |
| Treatment, week 20 (n=6,47)                      | 28.7 (± 21.493)  | 19.74 (± 19.755) |  |  |
| Treatment, week 32 (n=2,27)                      | 27.78 (± 7.857)  | 24.49 (± 23.684) |  |  |
| Treatment, week 44 (n=1,11)                      | 16.67 (± 9999)   | 18.18 (± 18.936) |  |  |
| Treatment, EOT up to week 82 (n=35,58)           | 22.06 (± 21.705) | 24.81 (± 21.735) |  |  |
| Social function, Baseline (n=66,110)             | 39.56 (± 23.721) | 47.42 (± 25.726) |  |  |
| Social function, week 4 (n=54,100)               | 36.52 (± 26.294) | 45.28 (± 27.483) |  |  |
| Social function, week 8 (n=31,87)                | 38.35 (± 23.629) | 46.49 (± 26.265) |  |  |
| Social function, week 20 (n=8,56)                | 40.28 (± 14.472) | 42.66 (± 25.648) |  |  |
| Social function, week 32 (n=4,38)                | 38.89 (± 14.344) | 48.54 (± 23.735) |  |  |
| Social function, week 44 (n=1,14)                | 33.33 (± 9999)   | 40.08 (± 26.165) |  |  |
| Social function, EOT up to week 82 (n=43,75)     | 38.89 (± 25.051) | 54.22 (± 28.428) |  |  |
| Disease-related worries, Baseline (n=66,110)     | 43.1 (± 25.599)  | 53.94 (± 27.664) |  |  |
| Disease-related worries, week 4 (n=54,100)       | 39.2 (± 28.562)  | 46.33 (± 28.165) |  |  |
| Disease-related worries, week 8 (n=30,87)        | 40.56 (± 28.183) | 47.32 (± 28.541) |  |  |
| Disease-related worries, week 20 (n=8,56)        | 37.5 (± 8.267)   | 46.83 (± 32.096) |  |  |
| Disease-related worries, week 32 (n=4,38)        | 38.89 (± 11.111) | 53.51 (± 27.137) |  |  |
| Disease-related worries, week 44 (n=1,14)        | 33.33 (± 9999)   | 44.05 (± 32.647) |  |  |
| Disease-rel. worries, EOT up to week 82(n=43,75) | 42.89 (± 28.876) | 55.04 (± 31.667) |  |  |
| Muscle/bone pain, Baseline (n=65,109)            | 26.67 (± 33.347) | 29.66 (± 31.21)  |  |  |
| Muscle/bone pain, week 4 (n=54,100)              | 24.07 (± 29.966) | 33 (± 31.956)    |  |  |
| Muscle/bone pain, week 8 (n=31,88)               | 31.18 (± 34.357) | 33.33 (± 33.524) |  |  |
| Muscle/bone pain, week 20 (n=8,56)               | 41.67 (± 15.43)  | 34.52 (± 33.614) |  |  |
| Muscle/bone pain, week 32 (n=4,38)               | 50 (± 19.245)    | 40.35 (± 34.795) |  |  |

|  |                  |                  |  |  |
|--|------------------|------------------|--|--|
| Muscle/bone pain, week 44 (n=1,14)                 | 33.33 (± 9999)   | 26.19 (± 26.726) |  |  |
| Muscle/bone pain, EOT up to week 82 (n=42,75)      | 34.13 (± 28.973) | 40.89 (± 33.141) |  |  |
| Sexual function, Baseline (n=47,78)                | 35.46 (± 32.899) | 39.32 (± 40.468) |  |  |
| Sexual function, week 4 (n=38,75)                  | 21.05 (± 26.191) | 40.89 (± 40.483) |  |  |
| Sexual function, week 8 (n=22,63)                  | 28.79 (± 33.007) | 43.92 (± 40.083) |  |  |
| Sexual function, week 20 (n=3,35)                  | 33.33 (± 33.333) | 38.1 (± 39.724)  |  |  |
| Sexual function, week 32 (n=3,24)                  | 11.11 (± 19.245) | 29.17 (± 35.864) |  |  |
| Sexual function, week 44 (n=0,7)                   | 9999 (± 9999)    | 47.62 (± 46.576) |  |  |
| Sexual function, EOT up to week 82 (n=31,47)       | 25.81 (± 28.166) | 48.94 (± 43.323) |  |  |
| Communication function, Baseline (n=66,108)        | 7.58 (± 16.325)  | 9.88 (± 22.904)  |  |  |
| Communicatio function, week 4 (n=53,98)            | 8.18 (± 17.179)  | 6.46 (± 15.626)  |  |  |
| Communicatio function, week 8 (n=30,86)            | 12.22 (± 18.535) | 9.69 (± 19.714)  |  |  |
| Communicatio function, week 20 (n=7,55)            | 14.29 (± 17.817) | 10.3 (± 19.108)  |  |  |
| Communicatio function, week 32 (n=4,38)            | 8.33 (± 16.667)  | 7.89 (± 19.658)  |  |  |
| Communicatio function, week 44 (n=1,14)            | 0 (± 9999)       | 4.76 (± 12.105)  |  |  |
| Communicatio function, EOT up to week 82 (n=42,74) | 12.7 (± 22.028)  | 12.61 (± 23.214) |  |  |
| Body image, Baseline (n=65,107)                    | 15.9 (± 28.932)  | 22.43 (± 34.195) |  |  |
| Body image, week 4 (n=53,98)                       | 15.09 (± 27.399) | 22.79 (± 31.239) |  |  |
| Body image, week 8 (n=31,83)                       | 21.51 (± 27.953) | 26.1 (± 31.256)  |  |  |
| Body image, week 20 (n=8,55)                       | 16.67 (± 17.817) | 30.3 (± 34.708)  |  |  |
| Body image, week 32 (n=4,37)                       | 0 (± 0)          | 28.83 (± 33.483) |  |  |
| Body image, week 44 (n=1,14)                       | 0 (± 9999)       | 30.95 (± 27.625) |  |  |
| Body image, EOT up to week 82 (42,73)              | 23.02 (± 32.5)   | 34.7 (± 37.449)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with ratings of 'no problem', 'some problem' and 'extreme problem' in the EuroQol five dimensions questionnaire (EQ-5D) (core)

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with ratings of 'no problem', 'some problem' and 'extreme problem' in the EuroQol five dimensions questionnaire (EQ-5D) (core) |
|-----------------|---|

End point description:

The EQ-5D is divided into two distinct sections. The first section includes one item addressing each of

five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Patients rate each of these items from "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The scores from each section are then transformed into a single health utility score. Overall scores range from 0 to 1 with lower scores representing a higher level of dysfunction.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline, weeks 4, 8, 20, 32, 44, and end of treatment (EOT) up to week 82 |           |

| End point values                              | pNET (core)     | Non-pNET (core) |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                            | Reporting group | Reporting group |  |  |
| Number of subjects analysed                   | 126             | 120             |  |  |
| Units: Participants                           |                 |                 |  |  |
| Baseline, Mobility, No problem                | 84              | 76              |  |  |
| Baseline, Mobility, Some problem              | 31              | 35              |  |  |
| Baseline, Mobility, Extreme problem           | 2               | 1               |  |  |
| Baseline, Self-care, No problem               | 100             | 102             |  |  |
| Baseline, Self-care, Some problem             | 15              | 10              |  |  |
| Baseline, Self-care, Extreme problem          | 2               | 9999            |  |  |
| Baseline, Usual activities, No problem        | 71              | 60              |  |  |
| Baseline, Usual activities, Some problem      | 43              | 46              |  |  |
| Baseline, Usual activities, Extreme problem   | 4               | 6               |  |  |
| Baseline, Pain/Discomfort, No problem         | 59              | 40              |  |  |
| Baseline, Pain/discomfort, Some problem       | 52              | 66              |  |  |
| Baseline, Pain/discomfort, Extreme problem    | 6               | 7               |  |  |
| Baseline, Anxiety/depression, No problem      | 65              | 53              |  |  |
| Baseline, Anxiety/depression, Some problem    | 47              | 54              |  |  |
| Baseline, Anxiety/depression, Extreme problem | 5               | 6               |  |  |
| Week 4, Mobility, No problem                  | 72              | 66              |  |  |
| Week 4, Mobility, Some problem                | 27              | 37              |  |  |
| Week 4, Mobility, Extreme problem             | 2               | 1               |  |  |
| Week 4, Self-care, No problem                 | 89              | 86              |  |  |
| Week 4, Self-care, Some problem               | 10              | 16              |  |  |
| Week 4, Self-care, Extreme problem            | 3               | 2               |  |  |
| Week 4, Usual activities, No problem          | 66              | 55              |  |  |
| Week 4, Usual activities, Some problem        | 31              | 42              |  |  |
| Week 4, Usual activities, Extreme problem     | 4               | 7               |  |  |
| Week 4, Pain/discomfort, No problem           | 39              | 30              |  |  |
| Week 4, Pain/discomfort, Some problem         | 58              | 64              |  |  |
| Week 4, Pain/discomfort, Extreme problem      | 3               | 8               |  |  |
| Week 4, Anxiety/depression, No problem        | 54              | 57              |  |  |



|  |      |      |  |  |
|--|------|------|--|--|
| Week 4, Anxiety depression, Some problem     | 46   | 43   |  |  |
| Week 4, Anxiety/depression, Extreme problem  | 1    | 3    |  |  |
| Week 8, Mobility, No problem                 | 48   | 45   |  |  |
| Week 8, Mobility, Some problem               | 24   | 37   |  |  |
| Week 8, Mobility, Extreme problem            | 2    | 3    |  |  |
| Week 8, Self-care, No problem                | 61   | 70   |  |  |
| Week 8, Self-care, Some problem              | 7    | 15   |  |  |
| Week 8, Self-care, Extreme problem           | 6    | 1    |  |  |
| Week 8, Usual activities, No problem         | 46   | 40   |  |  |
| Week 8, Usual activities, Some problem       | 23   | 41   |  |  |
| Week 8, Usual activities, Extreme problem    | 4    | 5    |  |  |
| Week 8, Pain/discomfort, No problem          | 34   | 25   |  |  |
| Week 8, Pain/discomfort, Some problem        | 32   | 52   |  |  |
| Week 8, Pain/discomfort, Extreme problem     | 7    | 10   |  |  |
| Week 8, Anxiety/depression, No problem       | 43   | 38   |  |  |
| Week 8, Anxiety/depression, Some problem     | 30   | 41   |  |  |
| Week 8, Anxiety/depression, Extreme problem  | 1    | 8    |  |  |
| Week 20, Mobility, No problem                | 26   | 37   |  |  |
| Week 20, Mobility, Some problem              | 3    | 17   |  |  |
| Week 20, Mobility, Extreme problem           | 9999 | 1    |  |  |
| Week 20, Self-care, No problem               | 25   | 49   |  |  |
| Week 20, Self-care, Some problem             | 4    | 6    |  |  |
| Week 20, Self-care, Extreme problem          | 9999 | 9999 |  |  |
| Week 20, Usual activities, No problem        | 18   | 30   |  |  |
| Week 20 Usual activities, Some problem       | 10   | 22   |  |  |
| Week 20, Usual activities, Extreme problem   | 1    | 2    |  |  |
| Week 20, Pain/discomfort, No problem         | 12   | 19   |  |  |
| Week 20, Pain/discomfort, Some problem       | 16   | 34   |  |  |
| Week 20, Pain/discomfort, Extreme problem    | 1    | 2    |  |  |
| Week 20, Anxiety/depression, No problem      | 16   | 27   |  |  |
| Week 20, Anxiety/depression, Some problem    | 12   | 23   |  |  |
| Week 20, Anxiety/depression, Extreme problem | 1    | 5    |  |  |
| Week 32, Mobility, No problem                | 3    | 25   |  |  |
| Week 32, Mobility, Some problem              | 2    | 12   |  |  |
| Week 32, Mobility, Extreme problem           | 9999 | 2    |  |  |
| Week 32, Self-care, No problem               | 5    | 32   |  |  |
| Week 32, Self-care, Some problem             | 9999 | 3    |  |  |
| Week 32, Self-care, Extreme problem          | 9999 | 2    |  |  |
| Week 32, Usual activities, No problem        | 4    | 22   |  |  |
| Week 32, Usual activities, Some problem      | 1    | 14   |  |  |
| Week 32, Usual activities, Extreme problem   | 9999 | 3    |  |  |
| Week 32, Pain/discomfort, No problem         | 1    | 10   |  |  |

|  |      |      |  |  |
|--|------|------|--|--|
| Week 32, Pain/discomfort, Some problem             | 4    | 27   |  |  |
| Week 32, Pain/discomfort, Extreme problem          | 9999 | 2    |  |  |
| Week 32, Anxiety/depression, No problem            | 4    | 20   |  |  |
| Week 32, Anxiety/depression, Some problem          | 1    | 14   |  |  |
| Week 32, Anxiety/depression, Extreme problem       | 9999 | 5    |  |  |
| Week 44, Mobility, No problem                      | 2    | 9    |  |  |
| Week 44, Mobility, Some problem                    | 1    | 4    |  |  |
| Week 44, Mobility, Extreme problem                 | 9999 | 1    |  |  |
| Week 44, Self-care, No problem                     | 3    | 12   |  |  |
| Week 44, Self-care, Some problem                   | 9999 | 2    |  |  |
| Week 44, Self-care, Extreme problem                | 9999 | 9999 |  |  |
| Week 44, Usual activities, No problem              | 9999 | 6    |  |  |
| Week 44, usual activities, Some problem            | 3    | 7    |  |  |
| Week 44, usual activities, Extreme problem         | 9999 | 9999 |  |  |
| Week 44, Pain/discomfort, No problem               | 9999 | 6    |  |  |
| Week 44, Pain/discomfort, Some problem             | 3    | 8    |  |  |
| Week 44, Pain/discomfort, Extreme problem          | 9999 | 9999 |  |  |
| Week 44, Anxiety/depression, No problem            | 1    | 7    |  |  |
| Week 44, Anxiety/depression, Some problem          | 2    | 6    |  |  |
| Week 44, Anxiety/depression, Extreme problem       | 9999 | 1    |  |  |
| EOT up to Week 82, Mobility, No problem            | 59   | 42   |  |  |
| EOT up to Week 82, Mobility, Some problem          | 23   | 31   |  |  |
| EOT up to Week 82, Mobility, Extreme problem       | 4    | 4    |  |  |
| EOT up to Week 82, Self-care, No problem           | 69   | 56   |  |  |
| EOT up to Week 82, Self-care, Some problem         | 12   | 19   |  |  |
| EOT up to Week 82, Self-care, Extreme problem      | 2    | 1    |  |  |
| EOT up to Week 82, Usual activities, No problem    | 54   | 29   |  |  |
| EOT up to Week 82, Usual activities, Some problem  | 24   | 36   |  |  |
| EOT up to Week 82, Usual activities, Extreme prob. | 5    | 11   |  |  |
| EOT up to Week 82, Pain/discomfort, No problem     | 43   | 18   |  |  |
| EOT up to Week 82, Pain/discomfort, Some problem   | 36   | 48   |  |  |
| EOT up to Week 82, Pain/discomfort, Extreme prob.  | 5    | 11   |  |  |
| EOT up to Week 82, Anxiety/depression, No problem  | 48   | 31   |  |  |
| EOT up to Week 82, Anxiety/depression, Some prob.  | 33   | 40   |  |  |

|   |   |   |  |  |
|---|---|---|--|--|
| EOT up to Week 82, Anxiety/depression, Extreme prob | 3 | 6 |  |  |
|---|---|---|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean EQ-5D Visual Analogue Scale (VAS) score (Core)

|                 |   |
|-----------------|---|
| End point title | Mean EQ-5D Visual Analogue Scale (VAS) score (Core) |
|-----------------|---|

End point description:

The EQ-5D is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Patients rate each of these items from "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The scores from each section are then transformed into a single health utility score. Overall scores range from 0 to 1 with lower scores representing a higher level of dysfunction.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, weeks 4, 8, 20, 32, 44, and end of treatment (EOT) up to week 82

| End point values                     | pNET (core)     | Non-pNET (core) |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 126             | 120             |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Baseline (n=118,111)                 | 68.8 (± 19.9)   | 63.9 (± 19.09)  |  |  |
| Week 4 (n=100,104)                   | 69.3 (± 18.06)  | 63.8 (± 18.78)  |  |  |
| Week 8 (n=73,88)                     | 64.6 (± 21.77)  | 61.2 (± 18.65)  |  |  |
| Week 20 (n=28,54)                    | 67.4 (± 19.58)  | 64.6 (± 15.51)  |  |  |
| Week 32 (n=5,37)                     | 42.6 (± 24.67)  | 62 (± 17.65)    |  |  |
| Week 44 (n=3,13)                     | 66.7 (± 15.28)  | 68.6 (± 18.71)  |  |  |
| EOT up to Week 82 (n=86,76)          | 66.5 (± 20.64)  | 55.3 (± 23.02)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Investigator-assessed best overall response (core)

|                 |  |
|-----------------|--|
| End point title | Investigator-assessed best overall response (core) |
|-----------------|--|

End point description:

Best overall response was determined from the sequence of investigator overall lesions responses

according to Response Evaluation Criteria in Solid Tumors (RECIST).

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| from the start of treatment, every 12 weeks for the first year and then every 6 months up to 19 months |           |

| End point values                                  | pNET (core)     | Non-pNET (core) |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                                | Reporting group | Reporting group |  |  |
| Number of subjects analysed                       | 126             | 120             |  |  |
| Units: Participants                               |                 |                 |  |  |
| Partial response (PR)                             | 2               | 1               |  |  |
| Stable disease (SD)                               | 74              | 84              |  |  |
| Progressive disease (PD)                          | 9               | 8               |  |  |
| Unknown   | 41              | 27              |  |  |
| Objective response rate (complete response or PR) | 2               | 1               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Investigator-assessed Progression Free Survival (PFS) (E1)

|  |  |
|--|--|
| End point title  | Investigator-assessed Progression Free Survival (PFS) (E1) |
| End point description:   |  |
| PFS was defined as the time from the date of the start of therapy in the extension study to the date of the first radiologically documented disease progression or death due to any cause. If a participant had not progressed or died at the analysis cut-off date or when he/she received any further anti-neoplastic therapy, PFS was censored at the time of the last adequate tumor evaluation before the cut-off date or the anti-neoplastic therapy start date. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| from first date of treatment in the extension up to 4 years  |  |

| End point values                 | GI NET               | Lung Net             |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 11                   | 4                    |  |  |
| Units: Days                      |                      |                      |  |  |
| median (confidence interval 95%) | 655 (9 to 9999)      | 159 (10 to 1074)     |  |  |

### Statistical analyses

**Secondary: Change in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) score at the end of treatment from baseline (baseline = first day of treatment in the extension) (E1)**

|                 |  |
|-----------------|--|
| End point title | Change in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) score at the end of treatment from baseline (baseline = first day of treatment in the extension) (E1) |
|-----------------|--|

## End point description:

The EORTC QLQ-C30 contains 30 questions assessed by the participant. There are 9 multiple-item scales: 5 scales that assess aspects of functioning (physical, role, cognitive, emotional, and social); 3 symptom scales (Fatigue, Pain, and Nausea and Vomiting); and a global health status and QOL scale. There are 5 single-item measures assessing additional symptoms (i.e., dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and a single item concerning perceived financial impact of the disease. All but two questions have 4-point scales ranging from "Not at all" to "Very much." The two questions concerning global health status and QOL have 7 point scales with ratings ranging from "Very poor" to "Excellent." For each of the 14 domains, final scores are transformed such that they range from 0-100, whereas higher scores indicate greater functioning, greater QOL, or greater level of symptom. A positive change from baseline indicates improvement.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

every 12 weeks and up to 4 years

| End point values                        | GI NET               | Lung Net             |  |  |
|---|----------------------|----------------------|--|--|
| Subject group type                      | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed             | 6                    | 1                    |  |  |
| Units: score on a scale                 |                      |                      |  |  |
| arithmetic mean (standard deviation)    |                      |                      |  |  |
| Global health status/QoL                | 0 (± 11.785)         | 0 (± 9999)           |  |  |
| Functional scale: Physical functioning  | 0 (± 7.303)          | 6.67 (± 9999)        |  |  |
| Functional scale: Role functioning      | 5.56 (± 22.771)      | -16.67 (± 9999)      |  |  |
| Functional scale: Emotional functioning | -1.85 (± 17.003)     | -25 (± 9999)         |  |  |
| Functional scale: Cognitive functioning | -16.67 (± 21.082)    | -66.67 (± 9999)      |  |  |
| Functional scale: Social functioning    | -8.33 (± 9.129)      | 0 (± 9999)           |  |  |
| Symptom scale: Fatigue                  | -3.7 (± 22.951)      | 0 (± 9999)           |  |  |
| Symptom scale: Nausea and vomiting      | 0 (± 18.257)         | 0 (± 9999)           |  |  |
| Symptom scale: Pain                     | 16.67 (± 27.889)     | 0 (± 9999)           |  |  |
| Symptom scale: Dyspnea                  | -5.56 (± 13.608)     | 0 (± 9999)           |  |  |
| Symptom scale: Insomnia                 | 11.11 (± 17.213)     | 33.33 (± 9999)       |  |  |
| Symptom scale: Appetite loss            | 0 (± 21.082)         | 0 (± 9999)           |  |  |
| Symptom scale: Constipation             | 5.56 (± 25.092)      | 0 (± 9999)           |  |  |
| Symptom scale: Diarrhea                 | -16.67 (± 45.947)    | 0 (± 9999)           |  |  |
| Symptom scale: Financial difficulties   | 16.67 (± 18.257)     | -33.33 (± 9999)      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in EORTC QLQ-G.I. NET21 score at the end of treatment from baseline (baseline = first day of treatment in the extension) (E1)

|                 |  |
|-----------------|--|
| End point title | Change in EORTC QLQ-G.I. NET21 score at the end of treatment from baseline (baseline = first day of treatment in the extension) (E1) |
|-----------------|--|

End point description:

The EORTC QLQ-G.I. NET21 contains 21 questions and has three defined multi-item symptom scales (endocrine – 3 questions, gastrointestinal – 5 questions, and treatment related side effects – 3 questions), two single item symptoms (bone/muscle pain and concern about weight loss), two psychosocial scales (social function – 3 questions, disease-related worries – 3 questions) and two other single items (sexuality and communication). For each of the 9 domains, final scores are transformed such that they range from 0-100, whereas higher scores indicate greater functioning, greater QOL, or greater level of symptom. A positive change from baseline indicates improvement.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

every 12 weeks and up to 4 years

| End point values                     | GI NET               | Lung Net             |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 6                    | 1                    |  |  |
| Units: units on a scale              |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Social function (n=6,1)              | 7.41 (± 22.951)      | 11.11 (± 9999)       |  |  |
| Disease-related worries (n=6,1)      | -0.93 (± 7.384)      | 44.44 (± 9999)       |  |  |
| Sexual function (n=1,0)              | 50 (± 43.033)        | 9999 (± 9999)        |  |  |
| Communicative functioning (n=6,1)    | 11.11 (± 17.213)     | 0 (± 9999)           |  |  |
| Endocrine scale (n=6,1)              | 5.56 (± 18.257)      | 11.11 (± 9999)       |  |  |
| G.I scale (n=6,1)                    | 14.44 (± 23.633)     | 0 (± 9999)           |  |  |
| Treatment scale (n=5,1)              | 5.56 (± 12.423)      | -16.67 (± 9999)      |  |  |
| Muscle/bone pain symptom (n=6,0)     | 33.33 (± 29.814)     | 9999 (± 9999)        |  |  |
| Body image (n=6,1)                   | 0 (± 21.082)         | 0 (± 9999)           |  |  |

## Statistical analyses

**Secondary: Change in EuroQol five dimensions questionnaire (EQ-5D) score at the end of treatment from baseline (baseline = first day of treatment in the extension) (E1)**

|                 |   |
|-----------------|---|
| End point title | Change in EuroQol five dimensions questionnaire (EQ-5D) score at the end of treatment from baseline (baseline = first day of treatment in the extension) (E1) |
|-----------------|---|

## End point description:

The EQ-5D is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Patients rate each of these items from "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The scores from each section are then transformed into a single health utility score. Overall scores range from 0 to 1 with lower scores representing a higher level of dysfunction.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

every 12 weeks and up to 4 years

| End point values                     | GI NET               | Lung Net             |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 6                    | 1                    |  |  |
| Units: units on a scale              |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Composite health index               | -8.58 (± 13.302)     | 7.26 (± 9999)        |  |  |
| Self-rated health status             | -4.17 (± 21.479)     | -10 (± 9999)         |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Investigator-assessed best overall response during the extension phase (E1)**

|                 |   |
|-----------------|---|
| End point title | Investigator-assessed best overall response during the extension phase (E1) |
|-----------------|---|

## End point description:

Best overall response was determined from the sequence of investigator overall lesions responses according to Response Evaluation Criteria in Solid Tumors (RECIST).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

from the start of treatment, every 12 weeks for the first year and then every 6 months up to 4 years

| <b>End point values</b>     | GI NET               | Lung Net             |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 11                   | 4                    |  |  |
| Units: Participants         |                      |                      |  |  |
| Complete response           | 0                    | 0                    |  |  |
| Partial response            | 1                    | 0                    |  |  |
| Stable disease              | 7                    | 2                    |  |  |
| Progressive disease         | 3                    | 2                    |  |  |
| Unknown                     | 0                    | 0                    |  |  |

### Statistical analyses

---

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 19.0   |

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | pNET (Core) |
|-----------------------|-------------|

Reporting group description:

pNET (Core)

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Non-pNET (Core) |
|-----------------------|-----------------|

Reporting group description:

Non-pNET (Core)

|                       |               |
|-----------------------|---------------|
| Reporting group title | Lung NET (E1) |
|-----------------------|---------------|

Reporting group description:

Lung NET (E1)

|                       |             |
|-----------------------|-------------|
| Reporting group title | GI NET (E1) |
|-----------------------|-------------|

Reporting group description:

GI NET (E1)

| Serious adverse events  | pNET (Core)       | Non-pNET (Core)   | Lung NET (E1)  |
|---|-------------------|-------------------|----------------|
| Total subjects affected by serious adverse events                   |                   |                   |                |
| subjects affected / exposed   | 25 / 123 (20.33%) | 59 / 117 (50.43%) | 1 / 4 (25.00%) |
| number of deaths (all causes)                                       | 4                 | 9                 | 0              |
| number of deaths resulting from adverse events                      | 0                 | 1                 | 0              |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |                |
| Breast cancer   |                   |                   |                |
| subjects affected / exposed   | 0 / 123 (0.00%)   | 1 / 117 (0.85%)   | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             | 0 / 0          |
| Metastases to liver   |                   |                   |                |

|  |                 |                 |               |
|--|-----------------|-----------------|---------------|
| subjects affected / exposed                          | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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 pancreas                               |                 |                 |               |
| subjects affected / exposed                          | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Neoplasm progression                                 |                 |                 |               |
| subjects affected / exposed                          | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           | 0 / 0         |
| Neuroendocrine tumour                                |                 |                 |               |
| subjects affected / exposed                          | 0 / 123 (0.00%) | 2 / 117 (1.71%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0         |
| Prostate cancer                                      |                 |                 |               |
| subjects affected / exposed                          | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Vipoma   |                 |                 |               |
| subjects affected / exposed                          | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Vascular disorders                                   |                 |                 |               |
| Circulatory collapse                                 |                 |                 |               |
| subjects affected / exposed                          | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0         |
| General disorders and administration site conditions |                 |                 |               |
| Asthenia   |                 |                 |               |
| subjects affected / exposed                          | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| Chills  |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Death   |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Device occlusion                                |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Euthanasia                                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Fatigue   |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 5 / 117 (4.27%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 5           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| General physical health deterioration           |                 |                 |               |
| subjects affected / exposed                     | 2 / 123 (1.63%) | 7 / 117 (5.98%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 2 / 7           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0         |
| Impaired healing                                |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Multi-organ failure                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Oedema  |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Oedema peripheral                               |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pyrexia   |                 |                 |               |
| subjects affected / exposed                     | 2 / 123 (1.63%) | 3 / 117 (2.56%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Reproductive system and breast disorders        |                 |                 |               |
| Metrorrhagia                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Respiratory, thoracic and mediastinal disorders |                 |                 |               |
| Acute respiratory distress syndrome             |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Dyspnoea  |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Epistaxis                                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Lung infiltration                               |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Pleural effusion                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pneumonitis                                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 2 / 117 (1.71%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pulmonary oedema                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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          |
| Respiratory failure                             |                 |                 |                |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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          |
| Psychiatric disorders                           |                 |                 |                |
| Depression                                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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          |
| Major depression                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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          |
| Investigations                                  |                 |                 |                |
| Antineutrophil cytoplasmic antibody increased   |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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          |
| Blood cholesterol increased                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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          |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| Blood uric acid increased<br>subjects affected / exposed        | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0         |
| C-reactive protein increased<br>subjects affected / exposed     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0         |
| Weight decreased<br>subjects affected / exposed                 | 1 / 123 (0.81%) | 2 / 117 (1.71%) | 0 / 4 (0.00%) |
| occurrences causally related to<br>treatment / all              | 1 / 1           | 1 / 2           | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0         |
| White blood cell count increased<br>subjects affected / exposed | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0         |
| Injury, poisoning and procedural<br>complications               |                 |                 |               |
| Femur fracture<br>subjects affected / exposed                   | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0         |
| Limb traumatic amputation<br>subjects affected / exposed        | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0         |
| Ulna fracture<br>subjects affected / exposed                    | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0         |
| Cardiac disorders   |                 |                 |               |
| Atrial fibrillation<br>subjects affected / exposed              | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 1           | 0 / 0         |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0         |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Cardiac failure                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 2 / 117 (1.71%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Coronary artery disease                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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          |
| Mitral valve incompetence                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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          |
| Right ventricular failure                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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          |
| Tricuspid valve incompetence                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nervous system disorders                        |                 |                 |                |
| Hepatic encephalopathy                          |                 |                 |                |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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          |
| Hypoglycaemic seizure                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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          |
| Ischaemic stroke                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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          |
| Loss of consciousness                           |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (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          |
| Peripheral sensory neuropathy                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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            |                 |                 |                |
| Anaemia   |                 |                 |                |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 3 / 117 (2.56%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 3           | 3 / 5          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haemoglobinaemia                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Thrombocytopenia                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Eye disorders                                   |                 |                 |                |
| Retinal vascular thrombosis                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (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          |
| Gastrointestinal disorders                      |                 |                 |                |
| Abdominal hernia                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (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          |
| Abdominal pain                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 5 / 117 (4.27%) | 0 / 4 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 5           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |



|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| Ascites   |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Constipation                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Diarrhoea                                       |                 |                 |               |
| subjects affected / exposed                     | 3 / 123 (2.44%) | 4 / 117 (3.42%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3           | 2 / 4           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Dysphagia                                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Faecal incontinence                             |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Faecaloma                                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Gastric ulcer perforation                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Gastritis haemorrhagic                          |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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 haemorrhage                    |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Ileitis   |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Inguinal hernia                                 |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Intestinal obstruction                          |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Nausea  |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 2 / 117 (1.71%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pancreatitis                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Peptic ulcer                                    |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Proctalgia                                      |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Stomatitis                                      |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Subileus  |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 2 / 117 (1.71%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Tongue oedema                                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 2 / 117 (1.71%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Varices oesophageal                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Vomiting  |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hepatobiliary disorders                         |                 |                 |               |
| Cholangitis                                     |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Cholecystitis                                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Cholecystocholangitis                           |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cholestasis                                     |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Hepatic failure                                 |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Hyperbilirubinaemia                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 2 / 117 (1.71%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Skin and subcutaneous tissue disorders          |                 |                 |               |
| Rash  |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Renal and urinary disorders                     |                 |                 |               |
| Calculus urinary                                |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Cystitis haemorrhagic                           |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Renal failure acute                             |                 |                 |               |
| subjects affected / exposed                     | 3 / 123 (2.44%) | 2 / 117 (1.71%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3           | 1 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Musculoskeletal and connective tissue disorders |                 |                 |               |
| Hypercreatinaemia                               |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| Pain in extremity                               |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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                     |                 |                 |               |
| Abscess limb                                    |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Arthritis infective                             |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Cholecystitis infective                         |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Cystitis  |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Gastrointestinal infection                      |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Herpes zoster                                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Infection                                       |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Peritonitis                                     |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 0 / 123 (0.00%) | 2 / 117 (1.71%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           | 0 / 0         |
| Peritonitis bacterial                           |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pneumonia                                       |                 |                 |               |
| subjects affected / exposed                     | 2 / 123 (1.63%) | 6 / 117 (5.13%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 4 / 6           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Pyelonephritis acute                            |                 |                 |               |
| subjects affected / exposed                     | 2 / 123 (1.63%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Sepsis  |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Septic shock                                    |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Sinusitis                                       |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Upper respiratory tract infection               |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Urinary tract infection                         |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 2 / 123 (1.63%) | 0 / 117 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Urinary tract infection bacterial               |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Metabolism and nutrition disorders              |                 |                 |               |
| Decreased appetite                              |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 1 / 117 (0.85%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Diabetic ketoacidosis                           |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Hyperglycaemia                                  |                 |                 |               |
| subjects affected / exposed                     | 2 / 123 (1.63%) | 0 / 117 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0         |
| Hypertriglyceridaemia                           |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Hypocalcaemia                                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (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         |
| Hypoglycaemia                                   |                 |                 |               |

|   |                 |                 |               |
|---|-----------------|-----------------|---------------|
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Hyponatraemia                                   |                 |                 |               |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (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         |
| Hypophosphataemia                               |                 |                 |               |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (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         |

| <b>Serious adverse events</b>                                       | GI NET (E1)     |  |  |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events                   |                 |  |  |
| subjects affected / exposed   | 4 / 11 (36.36%) |  |  |
| number of deaths (all causes)                                       | 1               |  |  |
| number of deaths resulting from adverse events                      | 0               |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |  |  |
| Breast cancer   |                 |  |  |
| subjects affected / exposed   | 0 / 11 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Metastases to liver   |                 |  |  |
| subjects affected / exposed   | 0 / 11 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Metastases to pancreas  |                 |  |  |
| subjects affected / exposed   | 0 / 11 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Neoplasm progression  |                 |  |  |
| subjects affected / exposed   | 0 / 11 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |



|  |                |  |  |
|--|----------------|--|--|
| Neuroendocrine tumour                                |                |  |  |
| subjects affected / exposed                          | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Prostate cancer                                      |                |  |  |
| subjects affected / exposed                          | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Vipoma   |                |  |  |
| subjects affected / exposed                          | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Vascular disorders                                   |                |  |  |
| Circulatory collapse                                 |                |  |  |
| subjects affected / exposed                          | 0 / 11 (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 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Chills   |                |  |  |
| subjects affected / exposed                          | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Death  |                |  |  |
| subjects affected / exposed                          | 1 / 11 (9.09%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Device occlusion                                     |                |  |  |
| subjects affected / exposed                          | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| Euthanasia                                      |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Fatigue   |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (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                     | 1 / 11 (9.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Impaired healing                                |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Multi-organ failure                             |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Oedema  |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Oedema peripheral                               |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pyrexia   |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Reproductive system and breast disorders        |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Metrorrhagia                                    |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Acute respiratory distress syndrome             |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Epistaxis                                       |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Lung infiltration                               |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonitis                                     |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary oedema                                |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Respiratory failure                             |                |  |  |
| subjects affected / exposed                     | 0 / 11 (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 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Major depression                                |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |
| Antineutrophil cytoplasmic antibody increased   |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood cholesterol increased                     |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood uric acid increased                       |                |  |  |
| subjects affected / exposed                     | 0 / 11 (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 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Weight decreased                                |                |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| White blood cell count increased<br>subjects affected / exposed | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |
| Injury, poisoning and procedural<br>complications               |                |  |  |
| Femur fracture  |                |  |  |
| subjects affected / exposed                                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |
| Limb traumatic amputation                                       |                |  |  |
| subjects affected / exposed                                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |
| Ulna fracture   |                |  |  |
| subjects affected / exposed                                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |
| Cardiac disorders   |                |  |  |
| Atrial fibrillation   |                |  |  |
| subjects affected / exposed                                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |
| Cardiac failure   |                |  |  |
| subjects affected / exposed                                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |
| Coronary artery disease   |                |  |  |
| subjects affected / exposed                                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |
| Mitral valve incompetence                                       |                |  |  |
| subjects affected / exposed                                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |

|  |                |  |  |
|--|----------------|--|--|
| Right ventricular failure<br>subjects affected / exposed     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all           | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                | 0 / 0          |  |  |
| Tricuspid valve incompetence<br>subjects affected / exposed  | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all           | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                | 0 / 0          |  |  |
| Nervous system disorders                                     |                |  |  |
| Hepatic encephalopathy<br>subjects affected / exposed        | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all           | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                | 0 / 0          |  |  |
| Hypoglycaemic seizure<br>subjects affected / exposed         | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all           | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                | 0 / 0          |  |  |
| Ischaemic stroke<br>subjects affected / exposed              | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all           | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                | 0 / 0          |  |  |
| Loss of consciousness<br>subjects affected / exposed         | 1 / 11 (9.09%) |  |  |
| occurrences causally related to<br>treatment / all           | 0 / 1          |  |  |
| deaths causally related to<br>treatment / all                | 0 / 0          |  |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all           | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                | 0 / 0          |  |  |
| Blood and lymphatic system disorders                         |                |  |  |
| Anaemia<br>subjects affected / exposed                       | 0 / 11 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all           | 0 / 0          |  |  |
| deaths causally related to<br>treatment / all                | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Haemoglobinaemia                                |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Thrombocytopenia                                |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Eye disorders                                   |                |  |  |
| Retinal vascular thrombosis                     |                |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Abdominal hernia                                |                |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ascites   |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Constipation                                    |                |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diarrhoea                                       |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| Dysphagia                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Faecal incontinence                             |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Faecaloma                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastric ulcer perforation                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastritis haemorrhagic                          |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastrointestinal haemorrhage                    |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Ileitis   |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Inguinal hernia                                 |                |  |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Intestinal obstruction                          |                |  |  |  |



|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Nausea  |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pancreatitis                                    |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Peptic ulcer                                    |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Proctalgia                                      |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Stomatitis                                      |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Subileus  |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Tongue oedema                                   |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Varices oesophageal                             |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Cholangitis                                     |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cholecystitis                                   |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cholecystocholangitis                           |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cholestasis                                     |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatic failure                                 |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hyperbilirubinaemia                             |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Rash  |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Calculus urinary                                |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cystitis haemorrhagic                           |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal failure acute                             |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Hypercreatinaemia                               |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pain in extremity                               |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Abscess limb                                    |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Arthritis infective                             |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Cholecystitis infective                         |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Cystitis  |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastrointestinal infection                      |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Herpes zoster                                   |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Infection                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Peritonitis                                     |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Peritonitis bacterial                           |                |  |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumonia                                       |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pyelonephritis acute                            |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Sepsis  |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Septic shock                                    |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Sinusitis                                       |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Upper respiratory tract infection               |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary tract infection                         |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary tract infection bacterial               |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Decreased appetite                              |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diabetic ketoacidosis                           |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypercalcaemia                                  |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hyperglycaemia                                  |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypertriglyceridaemia                           |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypocalcaemia                                   |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypoglycaemia                                   |                |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hyponatraemia                                   |                |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypophosphataemia                               |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 11 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | pNET (Core)       | Non-pNET (Core)   | Lung NET (E1)   |
|---|-------------------|-------------------|-----------------|
| Total subjects affected by non-serious adverse events |                   |                   |                 |
| subjects affected / exposed                           | 73 / 123 (59.35%) | 89 / 117 (76.07%) | 4 / 4 (100.00%) |
| Vascular disorders                                    |                   |                   |                 |
| Haematoma   |                   |                   |                 |
| subjects affected / exposed                           | 1 / 123 (0.81%)   | 0 / 117 (0.00%)   | 0 / 4 (0.00%)   |
| occurrences (all)                                     | 1                 | 0                 | 0               |
| Hypertension  |                   |                   |                 |
| subjects affected / exposed                           | 5 / 123 (4.07%)   | 6 / 117 (5.13%)   | 0 / 4 (0.00%)   |
| occurrences (all)                                     | 5                 | 6                 | 0               |
| Hypotension   |                   |                   |                 |
| subjects affected / exposed                           | 1 / 123 (0.81%)   | 1 / 117 (0.85%)   | 0 / 4 (0.00%)   |
| occurrences (all)                                     | 1                 | 1                 | 0               |
| General disorders and administration site conditions  |                   |                   |                 |
| Asthenia  |                   |                   |                 |
| subjects affected / exposed                           | 12 / 123 (9.76%)  | 6 / 117 (5.13%)   | 0 / 4 (0.00%)   |
| occurrences (all)                                     | 12                | 6                 | 0               |
| Chest pain  |                   |                   |                 |
| subjects affected / exposed                           | 0 / 123 (0.00%)   | 0 / 117 (0.00%)   | 0 / 4 (0.00%)   |
| occurrences (all)                                     | 0                 | 0                 | 0               |
| Fatigue   |                   |                   |                 |
| subjects affected / exposed                           | 1 / 123 (0.81%)   | 13 / 117 (11.11%) | 0 / 4 (0.00%)   |
| occurrences (all)                                     | 1                 | 15                | 0               |
| Generalised oedema                                    |                   |                   |                 |
| subjects affected / exposed                           | 1 / 123 (0.81%)   | 0 / 117 (0.00%)   | 0 / 4 (0.00%)   |
| occurrences (all)                                     | 1                 | 0                 | 0               |
| Inflammation  |                   |                   |                 |
| subjects affected / exposed                           | 0 / 123 (0.00%)   | 0 / 117 (0.00%)   | 0 / 4 (0.00%)   |
| occurrences (all)                                     | 0                 | 0                 | 0               |
| Injection site reaction                               |                   |                   |                 |

|   |                  |                   |                |
|---|------------------|-------------------|----------------|
| subjects affected / exposed                     | 0 / 123 (0.00%)  | 0 / 117 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0                | 0                 | 0              |
| Mucosal inflammation                            |                  |                   |                |
| subjects affected / exposed                     | 12 / 123 (9.76%) | 5 / 117 (4.27%)   | 0 / 4 (0.00%)  |
| occurrences (all)                               | 13               | 7                 | 0              |
| Oedema  |                  |                   |                |
| subjects affected / exposed                     | 1 / 123 (0.81%)  | 3 / 117 (2.56%)   | 1 / 4 (25.00%) |
| occurrences (all)                               | 1                | 3                 | 1              |
| Oedema peripheral                               |                  |                   |                |
| subjects affected / exposed                     | 5 / 123 (4.07%)  | 15 / 117 (12.82%) | 0 / 4 (0.00%)  |
| occurrences (all)                               | 5                | 18                | 0              |
| Peripheral swelling                             |                  |                   |                |
| subjects affected / exposed                     | 0 / 123 (0.00%)  | 0 / 117 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0                | 0                 | 0              |
| Pyrexia   |                  |                   |                |
| subjects affected / exposed                     | 8 / 123 (6.50%)  | 5 / 117 (4.27%)   | 0 / 4 (0.00%)  |
| occurrences (all)                               | 11               | 6                 | 0              |
| Immune system disorders                         |                  |                   |                |
| Hypersensitivity                                |                  |                   |                |
| subjects affected / exposed                     | 0 / 123 (0.00%)  | 0 / 117 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0                | 0                 | 0              |
| Respiratory, thoracic and mediastinal disorders |                  |                   |                |
| Chronic obstructive pulmonary disease           |                  |                   |                |
| subjects affected / exposed                     | 0 / 123 (0.00%)  | 0 / 117 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0                | 0                 | 0              |
| Cough   |                  |                   |                |
| subjects affected / exposed                     | 3 / 123 (2.44%)  | 6 / 117 (5.13%)   | 0 / 4 (0.00%)  |
| occurrences (all)                               | 3                | 6                 | 0              |
| Dyspnoea  |                  |                   |                |
| subjects affected / exposed                     | 5 / 123 (4.07%)  | 6 / 117 (5.13%)   | 1 / 4 (25.00%) |
| occurrences (all)                               | 5                | 7                 | 1              |
| Dyspnoea exertional                             |                  |                   |                |
| subjects affected / exposed                     | 0 / 123 (0.00%)  | 0 / 117 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)                               | 0                | 0                 | 0              |
| Epistaxis                                       |                  |                   |                |



|   |                      |                      |                    |
|---|----------------------|----------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)  | 2 / 123 (1.63%)<br>2 | 3 / 117 (2.56%)<br>3 | 0 / 4 (0.00%)<br>0 |
| Pleural effusion<br>subjects affected / exposed<br>occurrences (all)  | 0 / 123 (0.00%)<br>0 | 0 / 117 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Psychiatric disorders<br>Depressed mood<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 123 (0.00%)<br>0 | 0 / 117 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Depression<br>subjects affected / exposed<br>occurrences (all)  | 1 / 123 (0.81%)<br>1 | 3 / 117 (2.56%)<br>3 | 0 / 4 (0.00%)<br>0 |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)  | 0 / 123 (0.00%)<br>0 | 1 / 117 (0.85%)<br>1 | 0 / 4 (0.00%)<br>0 |
| Investigations<br>Blood creatine phosphokinase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 123 (0.00%)<br>0 | 0 / 117 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 123 (0.00%)<br>0 | 0 / 117 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Blood glucose increased<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 123 (0.81%)<br>1 | 0 / 117 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Blood lactate dehydrogenase<br>increased<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 123 (0.00%)<br>0 | 1 / 117 (0.85%)<br>1 | 0 / 4 (0.00%)<br>0 |
| Blood uric acid increased<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 123 (0.00%)<br>0 | 0 / 117 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 123 (0.00%)<br>0 | 3 / 117 (2.56%)<br>3 | 0 / 4 (0.00%)<br>0 |
| Injury, poisoning and procedural<br>complications   |                      |                      |                    |

|  |                        |                        |                     |
|--|------------------------|------------------------|---------------------|
| Incisional hernia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 123 (0.00%)<br>0   | 0 / 117 (0.00%)<br>0   | 1 / 4 (25.00%)<br>1 |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 123 (0.00%)<br>0   | 1 / 117 (0.85%)<br>1   | 0 / 4 (0.00%)<br>0  |
| Cardiac disorders<br>Tachyarrhythmia<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 123 (0.00%)<br>0   | 0 / 117 (0.00%)<br>0   | 0 / 4 (0.00%)<br>0  |
| Nervous system disorders<br>Cervicobrachial syndrome<br>subjects affected / exposed<br>occurrences (all) | 0 / 123 (0.00%)<br>0   | 0 / 117 (0.00%)<br>0   | 0 / 4 (0.00%)<br>0  |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 4 / 123 (3.25%)<br>4   | 9 / 117 (7.69%)<br>11  | 0 / 4 (0.00%)<br>0  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)      | 7 / 123 (5.69%)<br>7   | 10 / 117 (8.55%)<br>11 | 1 / 4 (25.00%)<br>1 |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                                     | 12 / 123 (9.76%)<br>18 | 5 / 117 (4.27%)<br>8   | 1 / 4 (25.00%)<br>1 |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)               | 0 / 123 (0.00%)<br>0   | 0 / 117 (0.00%)<br>0   | 0 / 4 (0.00%)<br>0  |
| Eye disorders<br>Cataract<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 123 (0.00%)<br>0   | 0 / 117 (0.00%)<br>0   | 0 / 4 (0.00%)<br>0  |
| Eyelid oedema<br>subjects affected / exposed<br>occurrences (all)  | 1 / 123 (0.81%)<br>1   | 1 / 117 (0.85%)<br>1   | 0 / 4 (0.00%)<br>0  |
| Gastrointestinal disorders   |                        |                        |                     |

|                             |                  |                   |                |
|-----------------------------|------------------|-------------------|----------------|
| Abdominal hernia            |                  |                   |                |
| subjects affected / exposed | 0 / 123 (0.00%)  | 0 / 117 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 0                | 0                 | 0              |
| Abdominal pain              |                  |                   |                |
| subjects affected / exposed | 4 / 123 (3.25%)  | 10 / 117 (8.55%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 4                | 12                | 0              |
| Abdominal pain upper        |                  |                   |                |
| subjects affected / exposed | 3 / 123 (2.44%)  | 4 / 117 (3.42%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 3                | 4                 | 0              |
| Anal haemorrhage            |                  |                   |                |
| subjects affected / exposed | 1 / 123 (0.81%)  | 1 / 117 (0.85%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 1                | 1                 | 0              |
| Ascites                     |                  |                   |                |
| subjects affected / exposed | 0 / 123 (0.00%)  | 1 / 117 (0.85%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 0                | 1                 | 0              |
| Bowel movement irregularity |                  |                   |                |
| subjects affected / exposed | 0 / 123 (0.00%)  | 0 / 117 (0.00%)   | 1 / 4 (25.00%) |
| occurrences (all)           | 0                | 0                 | 1              |
| Constipation                |                  |                   |                |
| subjects affected / exposed | 0 / 123 (0.00%)  | 4 / 117 (3.42%)   | 2 / 4 (50.00%) |
| occurrences (all)           | 0                | 4                 | 2              |
| Diarrhoea                   |                  |                   |                |
| subjects affected / exposed | 10 / 123 (8.13%) | 34 / 117 (29.06%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 10               | 38                | 0              |
| Dry mouth                   |                  |                   |                |
| subjects affected / exposed | 1 / 123 (0.81%)  | 1 / 117 (0.85%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 1                | 1                 | 0              |
| Flatulence                  |                  |                   |                |
| subjects affected / exposed | 0 / 123 (0.00%)  | 1 / 117 (0.85%)   | 2 / 4 (50.00%) |
| occurrences (all)           | 0                | 1                 | 2              |
| Frequent bowel movements    |                  |                   |                |
| subjects affected / exposed | 0 / 123 (0.00%)  | 0 / 117 (0.00%)   | 1 / 4 (25.00%) |
| occurrences (all)           | 0                | 0                 | 1              |
| Inguinal hernia             |                  |                   |                |
| subjects affected / exposed | 0 / 123 (0.00%)  | 0 / 117 (0.00%)   | 0 / 4 (0.00%)  |
| occurrences (all)           | 0                | 0                 | 0              |

|  |                        |                         |                     |
|--|------------------------|-------------------------|---------------------|
| Mouth ulceration<br>subjects affected / exposed<br>occurrences (all)     | 2 / 123 (1.63%)<br>2   | 2 / 117 (1.71%)<br>2    | 0 / 4 (0.00%)<br>0  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 10 / 123 (8.13%)<br>11 | 10 / 117 (8.55%)<br>10  | 1 / 4 (25.00%)<br>1 |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)           | 11 / 123 (8.94%)<br>11 | 13 / 117 (11.11%)<br>16 | 0 / 4 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 2 / 123 (1.63%)<br>2   | 5 / 117 (4.27%)<br>6    | 1 / 4 (25.00%)<br>1 |
| Skin and subcutaneous tissue disorders                                   |                        |                         |                     |
| Angioedema<br>subjects affected / exposed<br>occurrences (all)           | 0 / 123 (0.00%)<br>0   | 0 / 117 (0.00%)<br>0    | 0 / 4 (0.00%)<br>0  |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)           | 3 / 123 (2.44%)<br>3   | 0 / 117 (0.00%)<br>0    | 1 / 4 (25.00%)<br>2 |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)             | 1 / 123 (0.81%)<br>1   | 1 / 117 (0.85%)<br>1    | 0 / 4 (0.00%)<br>0  |
| Hair growth abnormal<br>subjects affected / exposed<br>occurrences (all) | 0 / 123 (0.00%)<br>0   | 0 / 117 (0.00%)<br>0    | 0 / 4 (0.00%)<br>0  |
| Nail dystrophy<br>subjects affected / exposed<br>occurrences (all)       | 0 / 123 (0.00%)<br>0   | 0 / 117 (0.00%)<br>0    | 0 / 4 (0.00%)<br>0  |
| Onychoclasia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 123 (0.00%)<br>0   | 0 / 117 (0.00%)<br>0    | 0 / 4 (0.00%)<br>0  |
| Panniculitis<br>subjects affected / exposed<br>occurrences (all)         | 0 / 123 (0.00%)<br>0   | 0 / 117 (0.00%)<br>0    | 1 / 4 (25.00%)<br>1 |
| Pityriasis rosea   |                        |                         |                     |

|   |                       |                      |                     |
|---|-----------------------|----------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 123 (0.00%)<br>0  | 0 / 117 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)  | 1 / 123 (0.81%)<br>1  | 4 / 117 (3.42%)<br>6 | 0 / 4 (0.00%)<br>0  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 9 / 123 (7.32%)<br>10 | 7 / 117 (5.98%)<br>8 | 0 / 4 (0.00%)<br>0  |
| Renal and urinary disorders<br>Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)         | 0 / 123 (0.00%)<br>0  | 0 / 117 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)  | 0 / 123 (0.00%)<br>0  | 0 / 117 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 |
| Nephrolithiasis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 123 (0.00%)<br>0  | 0 / 117 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Renal cyst haemorrhage<br>subjects affected / exposed<br>occurrences (all)  | 0 / 123 (0.00%)<br>0  | 0 / 117 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 2 / 123 (1.63%)<br>2  | 2 / 117 (1.71%)<br>2 | 0 / 4 (0.00%)<br>0  |
| Arthritis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 123 (0.00%)<br>0  | 0 / 117 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 123 (0.00%)<br>0  | 6 / 117 (5.13%)<br>7 | 0 / 4 (0.00%)<br>0  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)   | 1 / 123 (0.81%)<br>1  | 0 / 117 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Muscle tightness  |                       |                      |                     |

|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0              |
| Myalgia                     |                 |                 |                |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0              |
| Osteitis                    |                 |                 |                |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0              |
| Pain in extremity           |                 |                 |                |
| subjects affected / exposed | 0 / 123 (0.00%) | 3 / 117 (2.56%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0               | 3               | 0              |
| Infections and infestations |                 |                 |                |
| Bronchitis                  |                 |                 |                |
| subjects affected / exposed | 1 / 123 (0.81%) | 2 / 117 (1.71%) | 2 / 4 (50.00%) |
| occurrences (all)           | 1               | 2               | 5              |
| Conjunctivitis              |                 |                 |                |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0              |
| Cystitis                    |                 |                 |                |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 117 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0              |
| Erysipelas                  |                 |                 |                |
| subjects affected / exposed | 0 / 123 (0.00%) | 2 / 117 (1.71%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0               | 2               | 0              |
| Gastroenteritis             |                 |                 |                |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0              |
| Gastrointestinal infection  |                 |                 |                |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0              |
| Laryngitis                  |                 |                 |                |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 117 (0.85%) | 1 / 4 (25.00%) |
| occurrences (all)           | 0               | 1               | 1              |
| Nasopharyngitis             |                 |                 |                |
| subjects affected / exposed | 2 / 123 (1.63%) | 5 / 117 (4.27%) | 2 / 4 (50.00%) |
| occurrences (all)           | 2               | 6               | 2              |

|                                    |                 |                 |                |
|------------------------------------|-----------------|-----------------|----------------|
| Otitis media acute                 |                 |                 |                |
| subjects affected / exposed        | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0               | 0               | 0              |
| Paronychia                         |                 |                 |                |
| subjects affected / exposed        | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0               | 0               | 0              |
| Pulpitis dental                    |                 |                 |                |
| subjects affected / exposed        | 0 / 123 (0.00%) | 3 / 117 (2.56%) | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0               | 3               | 0              |
| Pyelonephritis                     |                 |                 |                |
| subjects affected / exposed        | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0               | 0               | 0              |
| Pyelonephritis acute               |                 |                 |                |
| subjects affected / exposed        | 0 / 123 (0.00%) | 0 / 117 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all)                  | 0               | 0               | 1              |
| Respiratory tract infection        |                 |                 |                |
| subjects affected / exposed        | 0 / 123 (0.00%) | 4 / 117 (3.42%) | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0               | 4               | 0              |
| Rhinitis                           |                 |                 |                |
| subjects affected / exposed        | 2 / 123 (1.63%) | 0 / 117 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)                  | 2               | 0               | 0              |
| Sinusitis                          |                 |                 |                |
| subjects affected / exposed        | 2 / 123 (1.63%) | 1 / 117 (0.85%) | 0 / 4 (0.00%)  |
| occurrences (all)                  | 2               | 1               | 0              |
| Urinary tract infection            |                 |                 |                |
| subjects affected / exposed        | 1 / 123 (0.81%) | 5 / 117 (4.27%) | 0 / 4 (0.00%)  |
| occurrences (all)                  | 1               | 6               | 0              |
| Metabolism and nutrition disorders |                 |                 |                |
| Decreased appetite                 |                 |                 |                |
| subjects affected / exposed        | 6 / 123 (4.88%) | 9 / 117 (7.69%) | 0 / 4 (0.00%)  |
| occurrences (all)                  | 6               | 9               | 0              |
| Diabetes mellitus                  |                 |                 |                |
| subjects affected / exposed        | 0 / 123 (0.00%) | 2 / 117 (1.71%) | 0 / 4 (0.00%)  |
| occurrences (all)                  | 0               | 2               | 0              |
| Hypercholesterolaemia              |                 |                 |                |

|                             |                   |                 |                |
|-----------------------------|-------------------|-----------------|----------------|
| subjects affected / exposed | 3 / 123 (2.44%)   | 5 / 117 (4.27%) | 1 / 4 (25.00%) |
| occurrences (all)           | 3                 | 6               | 1              |
| Hyperglycaemia              |                   |                 |                |
| subjects affected / exposed | 13 / 123 (10.57%) | 6 / 117 (5.13%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 15                | 7               | 0              |
| Hyperkalaemia               |                   |                 |                |
| subjects affected / exposed | 0 / 123 (0.00%)   | 0 / 117 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all)           | 0                 | 0               | 1              |
| Hypertriglyceridaemia       |                   |                 |                |
| subjects affected / exposed | 3 / 123 (2.44%)   | 1 / 117 (0.85%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 3                 | 1               | 0              |
| Hypoglycaemia               |                   |                 |                |
| subjects affected / exposed | 0 / 123 (0.00%)   | 1 / 117 (0.85%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0                 | 1               | 0              |
| Hypokalaemia                |                   |                 |                |
| subjects affected / exposed | 2 / 123 (1.63%)   | 6 / 117 (5.13%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 3                 | 6               | 0              |

|   |                   |  |  |
|---|-------------------|--|--|
| <b>Non-serious adverse events</b>                     | GI NET (E1)       |  |  |
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 11 / 11 (100.00%) |  |  |
| Vascular disorders                                    |                   |  |  |
| Haematoma   |                   |  |  |
| subjects affected / exposed                           | 1 / 11 (9.09%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Hypertension  |                   |  |  |
| subjects affected / exposed                           | 5 / 11 (45.45%)   |  |  |
| occurrences (all)                                     | 5                 |  |  |
| Hypotension   |                   |  |  |
| subjects affected / exposed                           | 1 / 11 (9.09%)    |  |  |
| occurrences (all)                                     | 2                 |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Asthenia  |                   |  |  |
| subjects affected / exposed                           | 1 / 11 (9.09%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Chest pain  |                   |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                               | 3               |  |  |
| Fatigue   |                 |  |  |
| subjects affected / exposed                     | 3 / 11 (27.27%) |  |  |
| occurrences (all)                               | 4               |  |  |
| Generalised oedema                              |                 |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Inflammation                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Injection site reaction                         |                 |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Mucosal inflammation                            |                 |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Oedema  |                 |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Oedema peripheral                               |                 |  |  |
| subjects affected / exposed                     | 4 / 11 (36.36%) |  |  |
| occurrences (all)                               | 10              |  |  |
| Peripheral swelling                             |                 |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Pyrexia   |                 |  |  |
| subjects affected / exposed                     | 2 / 11 (18.18%) |  |  |
| occurrences (all)                               | 2               |  |  |
| Immune system disorders                         |                 |  |  |
| Hypersensitivity                                |                 |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| Chronic obstructive pulmonary disease  |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Cough                                  |                 |  |  |
| subjects affected / exposed            | 2 / 11 (18.18%) |  |  |
| occurrences (all)                      | 2               |  |  |
| Dyspnoea                               |                 |  |  |
| subjects affected / exposed            | 2 / 11 (18.18%) |  |  |
| occurrences (all)                      | 3               |  |  |
| Dyspnoea exertional                    |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Epistaxis                              |                 |  |  |
| subjects affected / exposed            | 2 / 11 (18.18%) |  |  |
| occurrences (all)                      | 2               |  |  |
| Pleural effusion                       |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Psychiatric disorders                  |                 |  |  |
| Depressed mood                         |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Depression                             |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 2               |  |  |
| Sleep disorder                         |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Investigations                         |                 |  |  |
| Blood creatine phosphokinase increased |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Blood creatinine increased             |                 |  |  |
| subjects affected / exposed            | 2 / 11 (18.18%) |  |  |
| occurrences (all)                      | 2               |  |  |
| Blood glucose increased                |                 |  |  |

|   |  |  |  |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood lactate dehydrogenase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood uric acid increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 11 (9.09%)</p> <p>1</p> <p>1 / 11 (9.09%)</p> <p>1</p> <p>1 / 11 (9.09%)</p> <p>1</p> <p>2 / 11 (18.18%)</p> <p>2</p> |  |  |
| <p>Injury, poisoning and procedural complications</p> <p>Incisional hernia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Ligament sprain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>0 / 11 (0.00%)</p> <p>0</p> <p>2 / 11 (18.18%)</p> <p>2</p>   |  |  |
| <p>Cardiac disorders</p> <p>Tachyarrhythmia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 11 (9.09%)</p> <p>1</p>   |  |  |
| <p>Nervous system disorders</p> <p>Cervicobrachial syndrome</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 11 (9.09%)</p> <p>1</p> <p>0 / 11 (0.00%)</p> <p>0</p>  |  |  |
| <p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombocytopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>3 / 11 (27.27%)</p> <p>3</p> <p>1 / 11 (9.09%)</p> <p>1</p>   |  |  |

|  |  |  |  |
|--|--|--|--|
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)   | 1 / 11 (9.09%)<br>1  |  |  |
| Eye disorders<br>Cataract<br>subjects affected / exposed<br>occurrences (all)<br><br>Eyelid oedema<br>subjects affected / exposed<br>occurrences (all)   | 1 / 11 (9.09%)<br>1<br><br>1 / 11 (9.09%)<br>1   |  |  |
| Gastrointestinal disorders<br>Abdominal hernia<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Anal haemorrhage<br>subjects affected / exposed<br>occurrences (all)<br><br>Ascites<br>subjects affected / exposed<br>occurrences (all)<br><br>Bowel movement irregularity<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry mouth | 1 / 11 (9.09%)<br>1<br><br>5 / 11 (45.45%)<br>7<br><br>1 / 11 (9.09%)<br>1<br><br>1 / 11 (9.09%)<br>1<br><br>1 / 11 (9.09%)<br>1<br><br>0 / 11 (0.00%)<br>0<br><br>1 / 11 (9.09%)<br>1<br><br>3 / 11 (27.27%)<br>3<br><br> |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed            | 2 / 11 (18.18%) |  |  |
| occurrences (all)                      | 2               |  |  |
| Flatulence                             |                 |  |  |
| subjects affected / exposed            | 3 / 11 (27.27%) |  |  |
| occurrences (all)                      | 4               |  |  |
| Frequent bowel movements               |                 |  |  |
| subjects affected / exposed            | 0 / 11 (0.00%)  |  |  |
| occurrences (all)                      | 0               |  |  |
| Inguinal hernia                        |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Mouth ulceration                       |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Nausea                                 |                 |  |  |
| subjects affected / exposed            | 0 / 11 (0.00%)  |  |  |
| occurrences (all)                      | 0               |  |  |
| Stomatitis                             |                 |  |  |
| subjects affected / exposed            | 2 / 11 (18.18%) |  |  |
| occurrences (all)                      | 6               |  |  |
| Vomiting                               |                 |  |  |
| subjects affected / exposed            | 0 / 11 (0.00%)  |  |  |
| occurrences (all)                      | 0               |  |  |
| Skin and subcutaneous tissue disorders |                 |  |  |
| Angioedema                             |                 |  |  |
| subjects affected / exposed            | 2 / 11 (18.18%) |  |  |
| occurrences (all)                      | 3               |  |  |
| Dermatitis                             |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Dry skin                               |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Hair growth abnormal                   |                 |  |  |
| subjects affected / exposed            | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                      | 1               |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Nail dystrophy                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 11 (18.18%) |  |  |
| occurrences (all)                               | 2               |  |  |
| Onychoclasia                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 11 (18.18%) |  |  |
| occurrences (all)                               | 2               |  |  |
| Panniculitis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Pityriasis rosea                                |                 |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Pruritus  |                 |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Rash  |                 |  |  |
| subjects affected / exposed                     | 2 / 11 (18.18%) |  |  |
| occurrences (all)                               | 2               |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Chronic kidney disease                          |                 |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Haematuria                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 11 (0.00%)  |  |  |
| occurrences (all)                               | 0               |  |  |
| Nephrolithiasis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                               | 2               |  |  |
| Renal cyst haemorrhage                          |                 |  |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  |  |  |
| occurrences (all)                               | 1               |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 2 / 11 (18.18%) |  |  |
| occurrences (all)                               | 2               |  |  |
| Arthritis                                       |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Back pain                   |                 |  |  |
| subjects affected / exposed | 4 / 11 (36.36%) |  |  |
| occurrences (all)           | 5               |  |  |
| Muscle spasms               |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Muscle tightness            |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Myalgia                     |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 5               |  |  |
| Osteitis                    |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pain in extremity           |                 |  |  |
| subjects affected / exposed | 2 / 11 (18.18%) |  |  |
| occurrences (all)           | 2               |  |  |
| Infections and infestations |                 |  |  |
| Bronchitis                  |                 |  |  |
| subjects affected / exposed | 0 / 11 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Conjunctivitis              |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Cystitis                    |                 |  |  |
| subjects affected / exposed | 2 / 11 (18.18%) |  |  |
| occurrences (all)           | 2               |  |  |
| Erysipelas                  |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Gastroenteritis             |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 1               |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| Gastrointestinal infection  |                 |  |  |
| subjects affected / exposed | 2 / 11 (18.18%) |  |  |
| occurrences (all)           | 2               |  |  |
| Laryngitis                  |                 |  |  |
| subjects affected / exposed | 0 / 11 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Nasopharyngitis             |                 |  |  |
| subjects affected / exposed | 5 / 11 (45.45%) |  |  |
| occurrences (all)           | 10              |  |  |
| Otitis media acute          |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Paronychia                  |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Pulpitis dental             |                 |  |  |
| subjects affected / exposed | 2 / 11 (18.18%) |  |  |
| occurrences (all)           | 2               |  |  |
| Pyelonephritis              |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pyelonephritis acute        |                 |  |  |
| subjects affected / exposed | 0 / 11 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Respiratory tract infection |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Rhinitis                    |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Sinusitis                   |                 |  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Urinary tract infection     |                 |  |  |
| subjects affected / exposed | 2 / 11 (18.18%) |  |  |
| occurrences (all)           | 2               |  |  |



|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| Metabolism and nutrition disorders |                |  |  |
| Decreased appetite                 |                |  |  |
| subjects affected / exposed        | 0 / 11 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Diabetes mellitus                  |                |  |  |
| subjects affected / exposed        | 1 / 11 (9.09%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Hypercholesterolaemia              |                |  |  |
| subjects affected / exposed        | 1 / 11 (9.09%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Hyperglycaemia                     |                |  |  |
| subjects affected / exposed        | 0 / 11 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Hyperkalaemia                      |                |  |  |
| subjects affected / exposed        | 0 / 11 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Hypertriglyceridaemia              |                |  |  |
| subjects affected / exposed        | 1 / 11 (9.09%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Hypoglycaemia                      |                |  |  |
| subjects affected / exposed        | 1 / 11 (9.09%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Hypokalaemia                       |                |  |  |
| subjects affected / exposed        | 0 / 11 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 06 September 2011 | Core: Amendment 1 was issued to exclude patients with NETs of GI or lung origin. After implementation of this amendment, only patients with advanced pNETs were enrolled in this trial. This change was being made in view of decisions to amend the regulatory filings in the US and EU to patients with NET of pancreatic origin only. All patients enrolled in this study including previously enrolled patient with NET of GI or lung origin, remained on study until 30-May-2012, disease progression or any reason as allowed by the protocol, whichever came first. Additionally, the following changes were made to the original protocol: the overview of everolimus was updated; regarding the data collection, the references to eCRF and electronic data capture (EDC) were deleted and updated to reflect data collection on paper CRF; the amendment provided changes based on recent updates of the most recent Afinitor® (everolimus) Core Data Sheet and included: Guidance was revised for dosing patients with hepatic impairment and information regarding the midazolam drug-drug interaction was added; the estimated number of patients in this trial had decreased from 400 patients to 200 patients, due to exclusion of patients with NET of GI or lung origin which represents more than 50% of advanced NET population; interim analysis was removed due to lack of sufficient data i.e., at the rate of enrollment before the amendment 1, it was deemed not possible to enroll 100 patients with four months of treatment completed prior to 30-May-2012; and clarification of Child-Pugh class C was added. |
| 21 February 2013  | Extension: Primary reason for the first amendment was to update dosing recommendations for patients with hepatic impairment and the contraceptive methods in line with Novartis guidance for prevention of pregnancy in clinical trials.   |
| 14 January 2014   | Extension: The main rationale for amendment 2 was to extend the study duration from 31 May 2014 until 31 May 2015 in order to provide access to patients who were continuously benefitting from the study treatment.   |
| 27 October 2014   | Extension: The main rationale for amendment 3 was to update sections related to adverse drug reactions, handling of specific toxicities and concomitant medication according to the RAD001 IB version 13. Furthermore, the study duration was extended from 31 May 2015 until 31 May 2016 in order to provide access to patients who were continuously benefitting from the study treatment.   |
| 25 January 2016   | Extension: The rationale for amendment 4 was to extend study duration from 31 May 2016 until 31 May 2017 in order to provide access to patients who were continuously benefitting from the study treatment. Additionally, commercial availability of the study drug in the respective indication was added as a reason for end of treatment. Furthermore, minor errors in Amendment 3 were corrected.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: