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)

Summary

EudraCT number	2010-023032-17
Trial protocol	DE AT CZ SE GR BE DK PT IT
Global end of trial date	09 August 2016

Results information

Result version number	v1 (current)
This version publication date	07 October 2018
First version publication date	07 October 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001K24133 / CRAD001K24133

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, CRAD001K24133, 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
Arm title	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.

Arm title	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.

Number of subjects in period 1	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:	
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.	
Subject analysis set title	GI NET
Subject analysis set type	Full analysis
Subject analysis set description:	
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:	
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:	
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:	
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)[1]
End point description:	
The number of participants with AEs, SAEs and deaths were assessed.	
End point type	Primary
End point timeframe:	
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)[2]

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: 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 o 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)		
Appetitie loss, week 4 (n=102,102)	25.16 (± 31.618)	21.9 (± 29.849)		
Appetitie loss, week 8 (n=73,87)	24.66 (± 30.946)	25.67 (± 31.623)		
Appetitie loss, week 24 (n29,57)	18.39 (± 27.583)	20.47 (± 27.998)		
Appetitie loss, week 36 (n=5,39)	20 (± 18.257)	23.93 (± 30.54)		
Appetitie loss, week 44 (n=3,14)	11.11 (± 19.245)	26.19 (± 29.753)		
Appetitie 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: 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 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 actvities, 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 activties, 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, Anxiry/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 toWeek 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 toWeek 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

No statistical analyses for this end point

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	11	4		
Units: units on a scale				
arithmetic mean (standard deviation)				
Social function	7.41 (± 22.951)	11.11 (± 9999)		
Disease-related worries	-0.93 (± 7.384)	44.44 (± 9999)		
Sexual function	50 (± 43.033)	9999 (± 9999)		
Communicative functioning	11.11 (± 17.213)	0 (± 9999)		
Endocrine scale	5.56 (± 18.257)	11.11 (± 9999)		
G.I. scale	14.44 (± 23.633)	0 (± 9999)		
Treatment scale	5.56 (± 12.423)	-16.67 (± 9999)		
Muscle/bone pain symptom	33.33 (± 29.814)	9999 (± 9999)		
Body image	0 (± 21.082)	0 (± 9999)		

Statistical analyses

No statistical analyses for this end point

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

End point values	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	GI NET (E1)
Reporting group description:	
GI NET (E1)	
Reporting group title	Lung NET (E1)
Reporting group description:	
Lung NET (E1)	
Reporting group title	Non-pNET (Core)
Reporting group description:	
Non-pNET (Core)	

Serious adverse events	pNET (Core)	GI NET (E1)	Lung NET (E1)
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 123 (20.33%)	4 / 11 (36.36%)	1 / 4 (25.00%)
number of deaths (all causes)	4	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Metastases to liver			

subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (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
Neoplasm progression			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (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
Prostate cancer			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Vipoma			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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

Chills			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Death			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	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
Device occlusion			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (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
Fatigue			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
General physical health deterioration			
subjects affected / exposed	2 / 123 (1.63%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Multi-organ failure			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Oedema			

subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Oedema peripheral			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Pyrexia			
subjects affected / exposed	2 / 123 (1.63%)	0 / 11 (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
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (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
Epistaxis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Lung infiltration			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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

Pleural effusion			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Pulmonary oedema			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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 / 11 (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%)	0 / 11 (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
Major depression			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Investigations			
Antineutrophil cytoplasmic antibody increased			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Blood cholesterol increased			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
C-reactive protein increased			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Weight decreased			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count increased			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Limb traumatic amputation			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Ulna fracture			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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

Cardiac failure			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Mitral valve incompetence			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Right ventricular failure			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Tricuspid valve incompetence			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (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
Ischaemic stroke			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Loss of consciousness			

subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	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
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobinaemia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Thrombocytopenia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Eye disorders			
Retinal vascular thrombosis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	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 disorders			
Abdominal hernia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	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
Abdominal pain			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	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

Ascites			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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
Constipation			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	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
Diarrhoea			
subjects affected / exposed	3 / 123 (2.44%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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 / 11 (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%)	0 / 11 (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
Gastric ulcer perforation			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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
Gastritis haemorrhagic			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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 haemorrhage			

subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Ileitis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Inguinal hernia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	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
Intestinal obstruction			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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
Nausea			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Pancreatitis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Peptic ulcer			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (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
Stomatitis			

subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (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
Tongue oedema			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Varices oesophageal			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Vomiting			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (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
Cholecystocholangitis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Cholestasis			

subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Hepatic failure			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Hyperbilirubinaemia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Cystitis haemorrhagic			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Renal failure acute			
subjects affected / exposed	3 / 123 (2.44%)	0 / 11 (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
Musculoskeletal and connective tissue disorders			
Hypercreatinaemia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (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
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Arthritis infective			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Cholecystitis infective			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Cystitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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 / 11 (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%)	0 / 11 (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
Infection			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Peritonitis			

subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Peritonitis bacterial			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (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
Pneumonia			
subjects affected / exposed	2 / 123 (1.63%)	0 / 11 (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
Pyelonephritis acute			
subjects affected / exposed	2 / 123 (1.63%)	0 / 11 (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%)	0 / 11 (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
Septic shock			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	0 / 11 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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 / 11 (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%)	0 / 11 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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
Diabetic ketoacidosis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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 / 11 (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 / 11 (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 / 11 (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%)	0 / 11 (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
Hypoglycaemia			

subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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%)	1 / 11 (9.09%)	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
Hypophosphataemia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (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

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

Neuroendocrine tumour				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vipoma				
subjects affected / exposed	0 / 117 (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	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device occlusion				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Euthanasia			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Fatigue			
subjects affected / exposed	5 / 117 (4.27%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	7 / 117 (5.98%)		
occurrences causally related to treatment / all	2 / 7		
deaths causally related to treatment / all	0 / 1		
Impaired healing			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multi-organ failure			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			

Metrorrhagia				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lung infiltration				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Respiratory failure			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Antineutrophil cytoplasmic antibody increased			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood cholesterol increased			
subjects affected / exposed	0 / 117 (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	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

White blood cell count increased			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb traumatic amputation			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mitral valve incompetence			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Right ventricular failure			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tricuspid valve incompetence			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemic seizure			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

Haemoglobinaemia			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal vascular thrombosis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	5 / 117 (4.27%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	4 / 117 (3.42%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		

Dysphagia				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Faecal incontinence				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer perforation				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis haemorrhagic				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ileitis				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				

subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peptic ulcer				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Proctalgia				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Tongue oedema				
subjects affected / exposed	2 / 117 (1.71%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Varices oesophageal				

subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystocholangitis			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholestasis			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis haemorrhagic			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Hypercreatinaemia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis infective			

subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis infective			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Peritonitis bacterial			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	6 / 117 (5.13%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 117 (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 / 117 (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	1 / 117 (0.85%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				

subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			

subjects affected / exposed	0 / 117 (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 %

Non-serious adverse events	pNET (Core)	GI NET (E1)	Lung NET (E1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 123 (59.35%)	11 / 11 (100.00%)	4 / 4 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hypertension			
subjects affected / exposed	5 / 123 (4.07%)	5 / 11 (45.45%)	0 / 4 (0.00%)
occurrences (all)	5	5	0
Hypotension			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 123 (9.76%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	12	1	0
Chest pain			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Fatigue			
subjects affected / exposed	1 / 123 (0.81%)	3 / 11 (27.27%)	0 / 4 (0.00%)
occurrences (all)	1	4	0
Generalised oedema			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Inflammation			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Injection site reaction			

subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Mucosal inflammation			
subjects affected / exposed	12 / 123 (9.76%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	13	0	0
Oedema			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Oedema peripheral			
subjects affected / exposed	5 / 123 (4.07%)	4 / 11 (36.36%)	0 / 4 (0.00%)
occurrences (all)	5	10	0
Peripheral swelling			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	8 / 123 (6.50%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	11	2	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	3 / 123 (2.44%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	3	2	0
Dyspnoea			
subjects affected / exposed	5 / 123 (4.07%)	2 / 11 (18.18%)	1 / 4 (25.00%)
occurrences (all)	5	3	1
Dyspnoea exertional			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Epistaxis			

subjects affected / exposed	2 / 123 (1.63%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Pleural effusion			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Sleep disorder			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 123 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Blood glucose increased			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood uric acid increased			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 123 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			

Incisional hernia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	0 / 123 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Tachyarrhythmia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	4 / 123 (3.25%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 123 (5.69%)	3 / 11 (27.27%)	1 / 4 (25.00%)
occurrences (all)	7	3	1
Thrombocytopenia			
subjects affected / exposed	12 / 123 (9.76%)	1 / 11 (9.09%)	1 / 4 (25.00%)
occurrences (all)	18	1	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eyelid oedema			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			

Abdominal hernia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	4 / 123 (3.25%)	5 / 11 (45.45%)	0 / 4 (0.00%)
occurrences (all)	4	7	0
Abdominal pain upper			
subjects affected / exposed	3 / 123 (2.44%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Anal haemorrhage			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Ascites			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Bowel movement irregularity			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
Diarrhoea			
subjects affected / exposed	10 / 123 (8.13%)	3 / 11 (27.27%)	0 / 4 (0.00%)
occurrences (all)	10	3	0
Dry mouth			
subjects affected / exposed	1 / 123 (0.81%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Flatulence			
subjects affected / exposed	0 / 123 (0.00%)	3 / 11 (27.27%)	2 / 4 (50.00%)
occurrences (all)	0	4	2
Frequent bowel movements			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Inguinal hernia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Mouth ulceration			
subjects affected / exposed	2 / 123 (1.63%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	10 / 123 (8.13%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	11	0	1
Stomatitis			
subjects affected / exposed	11 / 123 (8.94%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	11	6	0
Vomiting			
subjects affected / exposed	2 / 123 (1.63%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 123 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Dry skin			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Dermatitis			
subjects affected / exposed	3 / 123 (2.44%)	1 / 11 (9.09%)	1 / 4 (25.00%)
occurrences (all)	3	1	2
Hair growth abnormal			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nail dystrophy			
subjects affected / exposed	0 / 123 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Onychoclasis			
subjects affected / exposed	0 / 123 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Panniculitis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pityriasis rosea			

subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	9 / 123 (7.32%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	10	2	0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Haematuria			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nephrolithiasis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Renal cyst haemorrhage			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 123 (1.63%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Arthritis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 123 (0.00%)	4 / 11 (36.36%)	0 / 4 (0.00%)
occurrences (all)	0	5	0
Muscle spasms			
subjects affected / exposed	1 / 123 (0.81%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Muscle tightness			

subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	5	0
Osteitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 123 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 11 (0.00%)	2 / 4 (50.00%)
occurrences (all)	1	0	5
Conjunctivitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	1 / 123 (0.81%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Erysipelas			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrointestinal infection			
subjects affected / exposed	0 / 123 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	2 / 123 (1.63%)	5 / 11 (45.45%)	2 / 4 (50.00%)
occurrences (all)	2	10	2

Otitis media acute			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Paronychia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Pulpitis dental			
subjects affected / exposed	0 / 123 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Pyelonephritis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pyelonephritis acute			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	2 / 123 (1.63%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Sinusitis			
subjects affected / exposed	2 / 123 (1.63%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Urinary tract infection			
subjects affected / exposed	1 / 123 (0.81%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 123 (4.88%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	6	0	0
Diabetes mellitus			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolaemia			

subjects affected / exposed	3 / 123 (2.44%)	1 / 11 (9.09%)	1 / 4 (25.00%)
occurrences (all)	3	2	1
Hyperglycaemia			
subjects affected / exposed	13 / 123 (10.57%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	15	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	3 / 123 (2.44%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	2 / 123 (1.63%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	Non-pNET (Core)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 117 (76.07%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	6 / 117 (5.13%)		
occurrences (all)	6		
Hypotension			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 117 (5.13%)		
occurrences (all)	6		
Chest pain			

subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	13 / 117 (11.11%)		
occurrences (all)	15		
Generalised oedema			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Inflammation			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Injection site reaction			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Mucosal inflammation			
subjects affected / exposed	5 / 117 (4.27%)		
occurrences (all)	7		
Oedema			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	15 / 117 (12.82%)		
occurrences (all)	18		
Peripheral swelling			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	5 / 117 (4.27%)		
occurrences (all)	6		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	6 / 117 (5.13%)		
occurrences (all)	6		
Dyspnoea			
subjects affected / exposed	6 / 117 (5.13%)		
occurrences (all)	7		
Dyspnoea exertional			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences (all)	3		
Pleural effusion			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences (all)	3		
Sleep disorder			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Blood glucose increased			

subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Blood uric acid increased			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Incisional hernia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Cardiac disorders			
Tachyarrhythmia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	9 / 117 (7.69%)		
occurrences (all)	11		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 117 (8.55%)		
occurrences (all)	11		
Thrombocytopenia			
subjects affected / exposed	5 / 117 (4.27%)		
occurrences (all)	8		

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Eyelid oedema			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	10 / 117 (8.55%)		
occurrences (all)	12		
Abdominal pain upper			
subjects affected / exposed	4 / 117 (3.42%)		
occurrences (all)	4		
Anal haemorrhage			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Bowel movement irregularity			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	4 / 117 (3.42%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	34 / 117 (29.06%)		
occurrences (all)	38		
Dry mouth			

subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Frequent bowel movements			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Inguinal hernia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	10 / 117 (8.55%)		
occurrences (all)	10		
Stomatitis			
subjects affected / exposed	13 / 117 (11.11%)		
occurrences (all)	16		
Vomiting			
subjects affected / exposed	5 / 117 (4.27%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Dermatitis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Hair growth abnormal			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		

Nail dystrophy subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0		
Onychoclasis subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0		
Panniculitis subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0		
Pityriasis rosea subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	4 / 117 (3.42%) 6		
Rash subjects affected / exposed occurrences (all)	7 / 117 (5.98%) 8		
Renal and urinary disorders Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0		
Haematuria subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0		
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0		
Renal cyst haemorrhage subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 117 (1.71%) 2		
Arthritis			

subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	6 / 117 (5.13%)		
occurrences (all)	7		
Muscle spasms			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Muscle tightness			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Osteitis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences (all)	3		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Erysipelas			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		

Laryngitis				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences (all)	1			
Gastrointestinal infection				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	5 / 117 (4.27%)			
occurrences (all)	6			
Otitis media acute				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences (all)	0			
Paronychia				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences (all)	0			
Pulpitis dental				
subjects affected / exposed	3 / 117 (2.56%)			
occurrences (all)	3			
Pyelonephritis				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences (all)	0			
Pyelonephritis acute				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences (all)	0			
Respiratory tract infection				
subjects affected / exposed	4 / 117 (3.42%)			
occurrences (all)	4			
Rhinitis				
subjects affected / exposed	0 / 117 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	1 / 117 (0.85%)			
occurrences (all)	1			
Urinary tract infection				
subjects affected / exposed	5 / 117 (4.27%)			
occurrences (all)	6			

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 117 (7.69%)		
occurrences (all)	9		
Diabetes mellitus			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences (all)	2		
Hypercholesterolaemia			
subjects affected / exposed	5 / 117 (4.27%)		
occurrences (all)	6		
Hyperglycaemia			
subjects affected / exposed	6 / 117 (5.13%)		
occurrences (all)	7		
Hyperkalaemia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	6 / 117 (5.13%)		
occurrences (all)	6		

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

None reported