Clinical trial results:
Phase 3, Randomized, Double-Blind Trial of Pegylated Liposomal Doxorubicin (PLD) Plus AMG 386 or Placebo in Women With Recurrent Partially Platinum Sensitive or Resistant Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Summary

EudraCT number	2009-017946-30
Trial protocol	HU GB SK AT BE IT DK DE PL GR LV ES FR
Global end of trial date	19 April 2017

Results information

Result version number	v1 (current)
This version publication date	02 May 2018
First version publication date	02 May 2018

Trial information

Trial identification

Sponsor protocol code	20060517

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01281254
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine if trebananib plus pegylated liposomal doxorubicin (PLD) is superior to placebo plus PLD as measured by progression-free survival (PFS), defined as the time from randomization to the earliest of the dates of first radiologic disease progression per Response Evaluation Criteria in Solid Tumors 1.1 with modifications (RECIST 1.1 mod) or death from any cause in subjects with recurrent partially platinum sensitive or resistant epithelial ovarian, primary peritoneal or fallopian tube cancer.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, United States Food and Drug Administration (FDA) regulations/guidelines, and country-specific national and local laws.
A copy of the protocol, proposed informed consent form (ICF), other written subject information, and any proposed advertising material was submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for written approval. A copy of the IEC/IRB approval was received by the sponsor before recruitment of subjects into the study.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belgium: 37
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	United Kingdom: 26

Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Slovakia: 9
Worldwide total number of subjects	223
EEA total number of subjects	159

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)	147
From 65 to 84 years	76
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 69 centers worldwide. Participants were enrolled from 18 April 2011 to 12 November 2013. Enrollment was put on hold from 23 November 2011 until 10 January 2013 because of a global shortage of PLD. On 23 October 2013, Amgen closed the study to subject screening because of a further imminent shortage of PLD.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to 1 of 2 treatment groups. Randomization was stratified based on platinum-free interval (PFI) status (PFI ≥ 0 months and ≤ 6 months versus PFI > 6 months and ≤ 12 months), presence / absence of measurable disease, and region (North America, Western Europe/Australia, Rest of World [ROW]).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + PLD

Arm description:

Participants received pegylated liposomal doxorubicin (PLD) 50 mg/m² every 4 weeks (Q4W) plus placebo to trebananib administered intravenously (IV) every week (QW) until disease progression per RECIST 1.1 mod, unacceptable toxicity, withdrawal of consent, or death.

Arm type	Placebo
Investigational medicinal product name	Placebo to Trebananib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as an IV infusion

Arm title	Trebananib + PLD

Arm description:

Participants received PLD 50 mg/m² every 4 weeks (Q4W) plus trebananib 15 mg/kg administered intravenously (IV) every week (QW) until disease progression per RECIST 1.1 mod, unacceptable toxicity, withdrawal of consent, or death.

Arm type	Experimental
Investigational medicinal product name	Trebananib
Investigational medicinal product code	AMG 386
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg administered as an IV infusion

Number of subjects in period 1	Placebo + PLD	Trebananib + PLD
Started	109	114
Received Trebananib/Placebo	108	112
Completed	0	0
Not completed	109	114
Consent withdrawn by subject	2	6
Death	94	102
Other	12	5
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + PLD
Reporting group description:	
Participants received pegylated liposomal doxorubicin (PLD) 50 mg/m² every 4 weeks (Q4W) plus placebo to trebananib administered intravenously (IV) every week (QW) until disease progression per RECIST 1.1 mod, unacceptable toxicity, withdrawal of consent, or death.	
Reporting group title	Trebananib + PLD
Reporting group description:	
Participants received PLD 50 mg/m² every 4 weeks (Q4W) plus trebananib 15 mg/kg administered intravenously (IV) every week (QW) until disease progression per RECIST 1.1 mod, unacceptable toxicity, withdrawal of consent, or death.	

Reporting group values	Placebo + PLD	Trebananib + PLD	Total
Number of subjects	109	114	223
Age Categorical Units: Subjects			
Adults (18-64 years)	79	68	147
From 65-84 years	30	46	76
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	59.7	60.3	
standard deviation	± 9.2	± 9.6	-
Gender Categorical Units: Subjects			
Female	109	114	223
Male	0	0	0
Race Units: Subjects			
Asian	12	10	22
Black (or African American)	2	1	3
Native Hawaiian or Other Pacific Islander	1	0	1
White	92	102	194
Other	2	1	3
Primary Tumor Type Units: Subjects			
Fallopian tube cancer	1	8	9
Ovarian cancer	95	98	193
Primary peritoneal carcinoma	13	8	21
Eastern Cooperative Oncology Group (ECOG) Performance Status			
A scale to assess a patient's disease status. 0 = Fully active, able to carry out all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care, unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead.			
Units: Subjects			
0 (Fully active)	67	75	142
1 (Restricted but ambulatory)	41	39	80

2 (Ambulatory but unable to work)	1	0	1
Histologic Type Units: Subjects			
Mucinous	1	4	5
Serous	82	89	171
Endometrioid	7	6	13
Clear cell	4	4	8
Undifferentiated	6	3	9
Other	8	8	16
Not applicable	1	0	1
Histologic Grade Units: Subjects			
Well differentiated	5	3	8
Moderately differentiated	18	14	32
Poorly differentiated	70	77	147
Unknown	16	20	36
Number of Lines of Prior Therapy Units: Subjects			
One	40	45	85
Two	46	45	91
Three	23	24	47
Measurable Disease at Baseline Units: Subjects			
Yes	96	99	195
No	13	15	28
Region Units: Subjects			
North America	14	18	32
Western Europe/Australia	75	76	151
Rest of the World	20	20	40
Platinum-free Interval (PFI) Status			
Platinum-free interval (PFI) was defined as the time from the last dose of the last platinum-containing regimen until the first date of progression was noted following discontinuation of the last prior platinum-containing agent.			
Units: Subjects			
≤ 6 months	60	62	122
> 6 months to ≤ 12 months	49	52	101
Enrollment Period Units: Subjects			
Enrolled prior to hold	26	32	58
Enrolled after hold	83	82	165

End points

End points reporting groups

Reporting group title	Placebo + PLD
Reporting group description:	
Participants received pegylated liposomal doxorubicin (PLD) 50 mg/m² every 4 weeks (Q4W) plus placebo to trebananib administered intravenously (IV) every week (QW) until disease progression per RECIST 1.1 mod, unacceptable toxicity, withdrawal of consent, or death.	
Reporting group title	Trebananib + PLD
Reporting group description:	
Participants received PLD 50 mg/m² every 4 weeks (Q4W) plus trebananib 15 mg/kg administered intravenously (IV) every week (QW) until disease progression per RECIST 1.1 mod, unacceptable toxicity, withdrawal of consent, or death.	

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
End point description:	
PFS was defined as the time from the date of randomization to the earliest of the dates of first radiologic disease progression per RECIST 1.1 with modifications, based on investigator assessment, or death from any cause. Subjects who did not meet these criteria by the analysis data cutoff date had their PFS time censored at the latest of their last evaluable radiologic disease assessment date. Events of radiographic progression per RECIST 1.1 with modifications that occurred after initiation of subsequent anticancer therapy were not considered PFS events and were censored at the last evaluable radiographic tumor assessment before the initiation of subsequent anticancer therapy. Deaths that occurred after initiation of subsequent anticancer therapy were considered PFS events.	
End point type	Primary
End point timeframe:	
From randomization to the data cut off-date of 19 April 2017; median follow-up time was 15.2 months (interquartile range [IQR], 8.8-25.4) in the Placebo arm and 17.3 months (IQR, 8.4-27.7) in the Trebananib group	

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	114		
Units: months				
median (confidence interval 95%)	7.3 (4.8 to 8.8)	7.6 (7.3 to 9.2)		

Statistical analyses

Statistical analysis title	Primary Evaluation
Statistical analysis description:	
A stratified log-rank test was used for the primary comparison of PFS.	
Comparison groups	Trebananib + PLD v Placebo + PLD

Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54 [1]
Method	Stratified Log-rank Test

Notes:

[1] - Stratified by PFI status and enrollment before PLD shortage

Statistical analysis title	Piece-wise Cox Model Analysis of PFS

Statistical analysis description:

A stratified piecewise Cox regression model using 16-week intervals was used to estimate the PFS hazard ratio (HR) and 2-sided 95% confidence interval (CI) for trebananib in combination with PLD relative to placebo and PLD.

Comparison groups	Placebo + PLD v Trebananib + PLD
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56 [2]
Method	Cox proportional hazards model
Parameter estimate	Overall hazard ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.22

Notes:

[2] - Stratified Cox proportional hazards models fit with treatment as covariate, and additional time-dependent indicators for each additional time interval for the test arm. Stratification factors are PFI status and enrollment prior to PLD shortage.

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time from the randomization date to the date of death from any cause. Subjects who did not die by the analysis data cutoff date were censored at their last contact date prior to the data cutoff date. Subjects known to be alive prior to the data cutoff date were censored at the last contact prior to the cutoff date. Subjects known to be alive or dead after the data cutoff date were censored at the data cutoff date.

End point type	Secondary

End point timeframe:

From randomization to the data cut off-date of 19 April 2017; median follow-up time was 15.2 months (interquartile range [IQR], 8.8-25.4) in the Placebo arm and 17.3 months (IQR, 8.4-27.7) in the Trebananib group.

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	114		
Units: months				
median (confidence interval 95%)	15.8 (13.5 to 20.5)	18.5 (13.4 to 22.5)		

Statistical analyses

Statistical analysis title	Analysis of Overall Survival

Statistical analysis description:

A stratified log-rank test was used for the primary comparison of overall survival.

Comparison groups	Placebo + PLD v Trebananib + PLD
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.76 [4]
Method	Stratified Log-rank Test

Notes:

[3] - The analysis was descriptive

[4] - Stratified by PFI status and enrollment before PLD shortage.

Statistical analysis title	Cox Proportional Hazards Analysis

Statistical analysis description:

A stratified Cox regression model was also used to provide the estimated overall survival hazard ratio and 2-sided 95% CI for trebananib in combination with PLD relative to placebo and PLD.

Comparison groups	Placebo + PLD v Trebananib + PLD
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.76 [5]
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.39

Notes:

[5] - Stratified by PFI status and enrollment before PLD shortage

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Disease response was assessed using computed tomography or magnetic resonance imaging of at least the chest, abdomen and pelvis. Objective response rate (ORR) was defined as the percentage of participants with measurable disease at baseline who achieved either a complete response (CR) or partial response (PR) while on study, according to RECIST 1.1 mod assessed by the investigator.
CR: Disappearance of all target and non-target lesions and no new lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
PR: At least a 30% decrease in the size of target lesions with persistence of one or more non-target lesions and no new lesions, or, disappearance of all target lesions with persistence of one or more non-target lesions and no new lesions.

Participants with measurable disease at baseline who did not meet the criteria for objective response by the analysis cut-off date were considered non-responders.

End point type	Secondary

End point timeframe:

Disease response was assessed every 8 weeks for the first 64 weeks, then every 16 weeks for 32 weeks, and every 24 weeks thereafter until disease progression or death.

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[6]	99[7]		
Units: percentage of participants				
number (confidence interval 95%)	20.2 (12.6 to 29.8)	47.5 (37.3 to 57.8)		

Notes:

[6] - Participants with measurable disease at baseline

[7] - Participants with measurable disease at baseline

Statistical analyses

Statistical analysis title	Analysis of Objective Response Rate
Comparison groups	Placebo + PLD v Trebananib + PLD
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.95
upper limit	7.35

Notes:

[8] - Cochran-Mantel-Haenszel test adjusted for PFI status.

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response was defined as the time from the first objective response to disease progression per RECIST 1.1 with modifications or death due to any cause. Subjects not meeting criteria for disease progression by the analysis data cut-off date were censored at their last evaluable disease assessment date. The analysis of DOR was conducted on the subset of subjects with measurable disease at baseline who experienced an objective response during the study.

End point type	Secondary

End point timeframe:

Disease response was assessed every 8 weeks for the first 64 weeks, then every 16 weeks for 32 weeks, and every 24 weeks thereafter until disease progression or death.

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[9]	47[10]		
Units: months				
median (confidence interval 95%)	5.6 (2.3 to 9.2)	7.4 (5.6 to 9.1)		

Notes:

[9] - Participants with measurable disease at baseline and with an objective response during the study

[10] - Participants with measurable disease at baseline and with an objective response during the study

Statistical analyses

No statistical analyses for this end point

Secondary: CA-125 Response Rate

End point title	CA-125 Response Rate

End point description:

A confirmed CA-125 response, according to the Gynecologic Cancer Intergroup (GCIG) criteria, defined as the percentage of participants with at least a 50% reduction in CA-125 levels from baseline, confirmed and maintained for at least 28 days. Only participants with CA-125 levels at least 2 X the upper limit of normal (ULN) within 2 weeks of starting treatment were evaluated for CA-125 response. Participants evaluable for CA-125 response that did not meet the criteria for a CA-125 response were considered non-responders.

End point type	Secondary

End point timeframe:

CA-125 was measured every 4 weeks for up to 2 years and then every 6 months thereafter.

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[11]	94[12]		
Units: percentage of participants				
number (confidence interval 95%)	26.4 (17.6 to 37.0)	51.1 (40.5 to 61.5)		

Notes:

[11] - Participants with baseline CA-125 at least 2 x upper limit of normal

[12] - Participants with baseline CA-125 at least 2 x upper limit of normal

Statistical analyses

Statistical analysis title	Analysis of CA-125 Response
Comparison groups	Placebo + PLD v Trebananib + PLD

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.61
upper limit	5.79

Notes:

[13] - Cochran-Mantel-Haenszel test adjusted for PFI status.

Secondary: Maximum Percent Change from Baseline in CA-125

End point title	Maximum Percent Change from Baseline in CA-125

End point description:

End point type	Secondary

End point timeframe:

Baseline and every 4 weeks for 2 years and then every 6 months thereafter until the end of treatment.

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75[14]	85[15]		
Units: percent change				
arithmetic mean (standard error)	-13.22 (± 16.83)	-46.45 (± 9.01)		

Notes:

[14] - Participants with baseline CA-125 ≥ 2 x ULN and available post-baseline data

[15] - Participants with baseline CA-125 ≥ 2 x ULN and available post-baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

Adverse events were graded for severity using the Common Terminology Criteria for Adverse Events version 3.0.
Trebananib/placebo-related or PLD-related adverse events are those events for which the investigator considered there to be a reasonable possibility that the event may have been caused by the study treatment, trebananib/placebo or PLD, respectively.

End point type	Secondary

End point timeframe:

From the first dose of study drug until 30 days after last dose; the median duration of trebananib treatment was 156 days.

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108[16]	113[17]		
Units: participants				
Any adverse event	108	113		
AE Grade ≥ 3	78	89		
AE Grade ≥ 4	21	15		
Fatal adverse events	7	6		
Serious adverse events	50	55		
AE leading to discontinuation of trebananib	23	32		
AE leading to discontinuation of PLD	25	20		
AE leading to discontinuation from study treatment	16	12		
Trebananib/placebo-related adverse events	89	95		
Trebananib/placebo-related AE Grade ≥ 3	33	48		
Trebananib/placebo-related AE Grade ≥ 4	8	6		
Trebananib/placebo-related fatal AE	2	2		
Trebananib/placebo-related serious AE	18	27		
PLD-related adverse events	99	105		
PLD-related adverse events Grade ≥ 3	44	53		
PLD-related adverse events Grade ≥ 4	8	6		
PLD-related fatal adverse events	0	0		
PLD-related serious adverse events	14	17		

Notes:

[16] - Randomized participants who received at least 1 dose of trebananib or PLD

[17] - Randomized participants who received at least 1 dose of trebananib or PLD

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of Trebananib and Week 1 and Week 5

End point title	Maximum Observed Serum Concentration (Cmax) of Trebananib and Week 1 and Week 5

End point description:

End point type	Secondary

End point timeframe:

Week 1 and week 5 at the end of infusion

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[18]	101[19]		
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 1	()	295 (± 215)		
Week 5	()	319 (± 105)		

Notes:

[18] - Participants did not receive trebananib

[19] - Participants with evaluable trebananib concentration data; N= 70 at Week 5

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) of Trebananib and Weeks 2, 5 and 9

End point title	Minimum Observed Serum Concentration (Cmin) of Trebananib and Weeks 2, 5 and 9

End point description:

End point type	Secondary

End point timeframe:

Weeks 2, 5 and 9, predose

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[20]	101[21]		
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 2	()	13.2 (± 6.56)		
Week 5	()	28.2 (± 15.8)		
Week 9	()	27.8 (± 15.5)		

Notes:

[20] - Participants did not receive trebananib

[21] - Participants with evaluable data; N at weeks 5 and 9 was 76 and 67

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Developed Anti-trebananib Antibodies

End point title	Number of Participants who Developed Anti-trebananib Antibodies

End point description:

Two validated assays were used to detect the presence of anti-trebananib antibodies. Samples were first tested in a biosensor immunoassay to detect antibodies capable of binding to trebananib. Samples confirmed to be positive for binding antibodies were subsequently tested in a receptor-binding assay to determine neutralizing activity against trebananib. If a post-dose sample was positive for binding antibodies and demonstrated neutralizing activity at the same time point, the sample was defined as

positive for neutralizing antibodies.

End point type	Secondary

End point timeframe:

Pre-infusion of trebananib or placebo on day 1 of week 1, week 9 and at the safety follow-up visit.

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95[22]	101[23]		
Units: participants				
Binding antibody positive	0	1		
Neutralizing antibody positive	0	0		

Notes:

[22] - Participants with a postbaseline result

[23] - Participants with a postbaseline result

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Change from Baseline in Functional Assessment of Cancer Therapy – Ovary (FACT-O) Summary Score

End point title	Secondary: Change from Baseline in Functional Assessment of Cancer Therapy – Ovary (FACT-O) Summary Score

End point description:

The FACT-O evaluates the health-related quality of life (HRQOL) and symptoms in patients with ovarian cancer. It consists of the FACT-G, a 27 item general cancer questionnaire and a 12-item ovarian cancer-specific subscale (OCS). Each item is scored by the participant on a scale from 0 (not at all true) to 4 (very much true). The total score ranges from 0 to 156; a higher total score indicates better quality of life or less severe symptoms.
The patient-reported outcomes (PRO) analysis set is defined as a subset of randomized subjects who have a baseline PRO assessment and at least one post-baseline PRO assessment prior to disease progression.

End point type	Secondary

End point timeframe:

Baseline and Weeks 5, 9, 13, 17, 25, 33, 41, 49, 57, 65, 81, and the safety follow-up visit 30 days after last dose.

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90[24]	98[25]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 5 (n = 87, 91)	-2.495 (± 19.732)	-4.991 (± 13.523)		
Week 9 (n = 69, 82)	-0.116 (± 17.978)	-5.708 (± 14.545)		
Week 13 (n = 62, 72)	-2.502 (± 18.251)	-7.161 (± 17.231)		

Week 17 (n = 52, 61)	-1.554 (± 16.545)	-5.809 (± 18.753)		
Week 25 (n = 42, 44)	1.568 (± 15.889)	-5.093 (± 15.862)		
Week 33 (n = 30, 29)	0.926 (± 14.907)	0.204 (± 11.304)		
Week 41 (n = 21, 21)	1.622 (± 14.203)	-0.192 (± 1.474)		
Week 49 (n = 12, 11)	2.113 (± 12.096)	-3.970 (± 15.934)		
Week 57 (n = 9, 4)	9.333 (± 13.043)	-6.733 (± 13.244)		
Week 65 (n = 8, 4)	3.621 (± 12.060)	-2.833 (± 12.662)		
Week 81 (n = 5, 2)	11.267 (± 7.316)	1.500 (± 2.121)		
Safety follow-up (n = 13, 14)	-11.667 (± 21.698)	-8.446 (± 18.886)		

Notes:

[24] - Participants with available baseline and post-baseline FACT-O data

[25] - Participants with available baseline and post-baseline FACT-O data

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FACT-O Ovarian Cancer-specific (OCS) Subscale

End point title	Change from Baseline in FACT-O Ovarian Cancer-specific (OCS) Subscale

End point description:

The FACT-O evaluates the health-related quality of life (HRQOL) and symptoms in patients with ovarian cancer. It consists of the FACT-G, a 27 item general cancer questionnaire and a 12-item ovarian cancer-specific subscale (OCS). The OCS consists of 12 symptom items including swelling in stomach area, cramps in stomach area, weight loss, hair loss, control of bowels, appetite, vomiting, ability to get around, liking the appearance of one's body, being able to feel like a woman, interest in sex, and concern about ability to have children. Each item is scored by the participant on a scale from 0 (not at all true) to 4 (very much true). The OCS summary score ranges from 0 to 48, where a higher score indicates better quality of life or less severe symptoms.
The PRO analysis set includes a subset of randomized subjects who had a baseline PRO assessment and at least one post-baseline PRO assessment prior to disease progression.

End point type	Secondary

End point timeframe:

Baseline and Weeks 5, 9, 13, 17, 25, 33, 41, 49, 57, 65, 81, and the safety follow-up visit 30 days after last dose.

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91[26]	98[27]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 5 (n = 89, 91)	0.129 (± 6.737)	-1.430 (± 4.746)		
Week 9 (n = 71, 83)	0.494 (± 6.173)	-0.993 (± 4.999)		

Week 13 (n = 62, 73)	0.681 (± 6.341)	-1.377 (± 5.325)		
Week 17 (n = 53, 62)	0.752 (± 6.062)	-1.030 (± 6.915)		
Week 25 (n = 42, 45)	0.637 (± 6.187)	-1.108 (± 4.585)		
Week 33 (n = 30, 29)	1.207 (± 5.599)	0.497 (± 4.538)		
Week 41 (n = 21, 22)	2.917 (± 5.465)	0.415 (± 4.569)		
Week 49 (n = 12, 11)	1.296 (± 5.465)	-0.182 (± 5.528)		
Week 57 (n = 9, 4)	4.778 (± 6.741)	-1.525 (± 1.684)		
Week 65 (n = 8, 4)	4.875 (± 8.288)	-0.500 (± 2.380)		
Week 81 (n = 5, 2)	7.200 (± 7.918)	-1.500 (± 0.707)		
Safety follow-up (n = 14, 14)	-4.021 (± 8.205)	-3.250 (± 7.350)		

Notes:

[26] - Participants with available baseline and post-baseline FACT-OCS data

[27] - Participants with available baseline and post-baseline FACT-OCS data

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQOL 5-Dimension (EQ-5D) Health Index Score

End point title	Change from Baseline in EuroQOL 5-Dimension (EQ-5D) Health Index Score

End point description:

The EQ-5D is a standardized instrument for use as a generic, preference-based measure of health outcome. The EQ-5D questionnaire captures two basic types of information, a descriptive "profile," or "health state," and an overall health rating using a visual analogue scale.
The health state includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each question has 3 answer choices: 1 (no problems), 2 (moderate problems), and 3 (extreme problems). The health states for each respondent are converted into a single index number using a specified set of weights. Resulting scores can range from 1.0 and –0.594. A higher score indicates a more preferred health status with 1.0 representing perfect health.
The PRO analysis set includes a subset of randomized subjects who had a baseline assessment and at least 1 post-baseline PRO assessment prior to disease progression.

End point type	Secondary

End point timeframe:

Baseline and Weeks 5, 9, 13, 17, 25, 33, 41, 49, 57, 65, 81, and the safety follow-up visit 30 days after last dose.

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[28]	93[29]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 5 (n = 82, 83)	-0.027 (± 0.217)	-0.026 (± 0.198)		

Week 9 (n = 66, 77)	-0.057 (± 0.237)	-0.035 (± 0.263)		
Week 13 (n = 55, 69)	-0.001 (± 0.210)	-0.044 (± 0.225)		
Week 17 (n = 45, 58)	-0.043 (± 0.178)	-0.052 (± 0.269)		
Week 25 (n = 38, 39)	-0.017 (± 0.155)	-0.050 (± 0.266)		
Week 33 (n = 26, 26)	-0.015 (± 0.188)	-0.061 (± 0.206)		
Week 41 (n = 18, 20)	-0.007 (± 0.177)	-0.078 (± 0.188)		
Week 49 (n = 10, 9)	0.008 (± 0.155)	-0.166 (± 0.319)		
Week 57 (n = 8, 4)	0.060 (± 0.164)	-0.010 (± 0.020)		
Week 65 (n = 7, 4)	0.059 (± 0.178)	-0.010 (± 0.020)		
Week 81 (n = 4, 2)	0.065 (± 0.241)	0.000 (± 0.000)		
Safety follow-up (n = 13, 14)	-0.098 (± 0.158)	-0.159 (± 0.339)		

Notes:

[28] - Participants with available baseline and post-baseline EQ-5D data

[29] - Participants with available baseline and post-baseline EQ-5D data

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EQ-5D Visual Analogue Scale Score

End point title	Change from Baseline in EQ-5D Visual Analogue Scale Score

End point description:

The EQ-5D is a standardized instrument for use as a generic, preference-based measure of health outcome. The EQ-5D questionnaire captures two basic types of information, a descriptive "profile," or "health state," and an overall health rating using a visual analogue scale (VAS).
The visual analogue scale asks respondents to rate their present health status on a 0 - 100 visual analogue scale, with 0 labeled as "Worst imaginable health state" and 100 labeled as "Best imaginable health state." The VAS score is determined by observing the point at which the subjects hand drawn line intersects the scale.
The PRO analysis set includes the subset of randomized subjects who had a baseline assessment and at least 1 post-baseline PRO assessment prior to disease progression.

End point type	Secondary

End point timeframe:

Baseline and Weeks 5, 9, 13, 17, 25, 33, 41, 49, 57, 65, 81, and the safety follow-up visit 30 days after last dose.

End point values	Placebo + PLD	Trebananib + PLD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90[30]	94[31]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 5 (n = 86, 82)	-3.907 (± 21.469)	-0.622 (± 18.844)		

Week 9 (n = 69, 79)	-3.275 (± 15.224)	0.532 (± 19.367)		
Week 13 (n = 60, 69)	-2.433 (± 16.213)	-0.942 (± 17.306)		
Week 17 (n = 51, 59)	-1.569 (± 15.263)	-1.441 (± 23.219)		
Week 25 (n = 40, 44)	1.125 (± 10.013)	-0.773 (± 21.431)		
Week 33 (n = 28, 28)	2.607 (± 12.467)	4.714 (± 15.224)		
Week 41 (n = 21, 22)	2.000 (± 12.542)	5.682 (± 18.198)		
Week 49 (n = 12, 11)	-2.083 (± 14.656)	1.909 (± 13.472)		
Week 57 (n = 9, 4)	5.000 (± 10.770)	-4.000 (± 4.899)		
Week 65 (n = 8, 4)	1.625 (± 12.727)	-0.750 (± 1.500)		
Week 81 (n = 5, 2)	-0.200 (± 10.257)	0.000 (± 0.000)		
Safety follow-up (n = 15, 14)	-5.867 (± 11.154)	-7.571 (± 18.029)		

Notes:

[30] - Participants with available baseline and post-baseline EQ-5D VAS data

[31] - Participants with available baseline and post-baseline EQ-5D VAS data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug until 30 days after last dose; the median duration of trebananib treatment was 156 days.

Adverse event reporting additional description:

One subject randomized to the placebo group received trebananib and was counted in the trebananib group for safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Trebananib + PLD

Reporting group description:

Participants received PLD 50 mg/m² every 4 weeks (Q4W) plus trebananib 15 mg/kg administered intravenously (IV) every week (QW) until disease progression per RECIST 1.1 mod, unacceptable toxicity, withdrawal of consent, or death.

Reporting group title	Placebo + PLD

Reporting group description:

Participants received pegylated liposomal doxorubicin (PLD) 50 mg/m² every 4 weeks (Q4W) plus placebo to trebananib administered intravenously (IV) every week (QW) until disease progression per RECIST 1.1 mod, unacceptable toxicity, withdrawal of consent, or death.

Serious adverse events	Trebananib + PLD	Placebo + PLD	
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 113 (48.67%)	50 / 108 (46.30%)	
number of deaths (all causes)	102	93	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant ascites			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			

subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer metastatic			
subjects affected / exposed	0 / 113 (0.00%)	3 / 108 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			

subjects affected / exposed	2 / 113 (1.77%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 113 (4.42%)	4 / 108 (3.70%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suprapubic pain			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Alveolitis allergic			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 113 (2.65%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	8 / 113 (7.08%)	4 / 108 (3.70%)	
occurrences causally related to treatment / all	6 / 8	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleurisy			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 113 (1.77%)	3 / 108 (2.78%)	
occurrences causally related to treatment / all	1 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory failure			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine increased			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine abnormal			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eastern cooperative oncology group performance status worsened			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Weight decreased			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 113 (1.77%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 113 (0.00%)	3 / 108 (2.78%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 113 (0.00%)	3 / 108 (2.78%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	7 / 113 (6.19%)	6 / 108 (5.56%)	
occurrences causally related to treatment / all	2 / 11	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	11 / 113 (9.73%)	5 / 108 (4.63%)	
occurrences causally related to treatment / all	14 / 23	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 5	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enteritis			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal oedema			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival pain			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 113 (1.77%)	6 / 108 (5.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal fluid collection			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 113 (2.65%)	4 / 108 (3.70%)	
occurrences causally related to treatment / all	3 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	4 / 113 (3.54%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis necrotising			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	9 / 113 (7.96%)	3 / 108 (2.78%)	
occurrences causally related to treatment / all	4 / 14	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Dermatitis allergic			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Decreased appetite			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trebananib + PLD	Placebo + PLD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 113 (99.12%)	103 / 108 (95.37%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Pyogenic granuloma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Tumour pain			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Deep vein thrombosis			
subjects affected / exposed	4 / 113 (3.54%)	1 / 108 (0.93%)	
occurrences (all)	4	1	
Diastolic hypertension			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	3 / 113 (2.65%)	4 / 108 (3.70%)	
occurrences (all)	3	4	
Embolism			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Haematoma			
subjects affected / exposed	2 / 113 (1.77%)	2 / 108 (1.85%)	
occurrences (all)	2	3	
Hot flush			

subjects affected / exposed	5 / 113 (4.42%)	1 / 108 (0.93%)	
occurrences (all)	5	1	
Hypertension			
subjects affected / exposed	12 / 113 (10.62%)	9 / 108 (8.33%)	
occurrences (all)	17	9	
Jugular vein distension			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Jugular vein thrombosis			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Lymphocele			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Peripheral venous disease			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Lymphoedema			
subjects affected / exposed	10 / 113 (8.85%)	2 / 108 (1.85%)	
occurrences (all)	16	2	
Phlebitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Thrombosis			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Thrombophlebitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Venous thrombosis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Surgical and medical procedures			

Central venous catheter removal			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Tooth extraction			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Eye irrigation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Application site hypersensitivity			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	9 / 113 (7.96%)	12 / 108 (11.11%)	
occurrences (all)	16	19	
Axillary pain			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Catheter site erythema			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	2	4	
Catheter site haematoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Catheter site inflammation			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Catheter site pain			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	3	1	
Catheter site pruritus			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	3	
Catheter site rash			

subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Catheter site vesicles			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Chest discomfort			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Chest pain			
subjects affected / exposed	2 / 113 (1.77%)	5 / 108 (4.63%)	
occurrences (all)	2	5	
Chills			
subjects affected / exposed	7 / 113 (6.19%)	2 / 108 (1.85%)	
occurrences (all)	10	5	
Complication associated with device			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Discomfort			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Drug intolerance			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Early satiety			
subjects affected / exposed	0 / 113 (0.00%)	4 / 108 (3.70%)	
occurrences (all)	0	5	
Fatigue			
subjects affected / exposed	61 / 113 (53.98%)	48 / 108 (44.44%)	
occurrences (all)	112	105	
Gait disturbance			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
General physical health deterioration			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences (all)	3	1	
Generalised oedema			

subjects affected / exposed	8 / 113 (7.08%)	2 / 108 (1.85%)	
occurrences (all)	13	2	
Hernia pain			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Impaired healing			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	11	
Influenza like illness			
subjects affected / exposed	6 / 113 (5.31%)	2 / 108 (1.85%)	
occurrences (all)	7	2	
Infusion site extravasation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Injection site haematoma			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Injection site rash			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Injection site reaction			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Localised oedema			
subjects affected / exposed	67 / 113 (59.29%)	32 / 108 (29.63%)	
occurrences (all)	133	45	
Malaise			
subjects affected / exposed	5 / 113 (4.42%)	2 / 108 (1.85%)	
occurrences (all)	5	2	
Mucosal dryness			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Mucosal inflammation			
subjects affected / exposed	20 / 113 (17.70%)	26 / 108 (24.07%)	
occurrences (all)	40	64	
Non-cardiac chest pain			

subjects affected / exposed	4 / 113 (3.54%)	1 / 108 (0.93%)	
occurrences (all)	5	1	
Oedema peripheral			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Pain			
subjects affected / exposed	4 / 113 (3.54%)	8 / 108 (7.41%)	
occurrences (all)	4	12	
Peripheral swelling			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	20 / 113 (17.70%)	15 / 108 (13.89%)	
occurrences (all)	28	19	
Sensation of foreign body			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Temperature intolerance			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Ulcer			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Visceral oedema			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Drug hypersensitivity			

subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Hypersensitivity			
subjects affected / exposed	2 / 113 (1.77%)	5 / 108 (4.63%)	
occurrences (all)	2	5	
Seasonal allergy			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Reproductive system and breast disorders			
Genital rash			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Pelvic discomfort			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Vaginal discharge			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences (all)	4	2	
Vaginal haemorrhage			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	2	
Vaginal lesion			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	2	
Vulva cyst			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Vulval disorder			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Vulvovaginal discomfort			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal dryness			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal inflammation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal pruritus			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 113 (19.47%)	17 / 108 (15.74%)	
occurrences (all)	30	25	
Dysphonia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	25 / 113 (22.12%)	16 / 108 (14.81%)	
occurrences (all)	51	23	
Dyspnoea at rest			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Dyspnoea exertional			
subjects affected / exposed	3 / 113 (2.65%)	6 / 108 (5.56%)	
occurrences (all)	4	9	
Epistaxis			
subjects affected / exposed	3 / 113 (2.65%)	3 / 108 (2.78%)	
occurrences (all)	3	4	
Haemoptysis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Hiccups			

subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Hypoxia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Nasal dryness			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	15 / 113 (13.27%)	11 / 108 (10.19%)	
occurrences (all)	16	13	
Pleural effusion			
subjects affected / exposed	13 / 113 (11.50%)	7 / 108 (6.48%)	
occurrences (all)	14	8	
Pneumonitis			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Pneumothorax			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Pulmonary embolism			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Pulmonary pain			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Pulmonary sarcoidosis			

subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Respiratory alkalosis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	5 / 113 (4.42%)	1 / 108 (0.93%)	
occurrences (all)	5	1	
Sinus congestion			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Throat irritation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 113 (6.19%)	5 / 108 (4.63%)	
occurrences (all)	7	7	
Anxiety disorder			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Confusional state			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	2	
Depressed mood			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Depression			
subjects affected / exposed	10 / 113 (8.85%)	3 / 108 (2.78%)	
occurrences (all)	10	3	
Disorientation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	

Hallucination			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	13 / 113 (11.50%)	11 / 108 (10.19%)	
occurrences (all)	14	14	
Mood altered			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Mood swings			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Panic attack			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Somnambulism			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Stress			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Thrombosis in device			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 113 (2.65%)	3 / 108 (2.78%)	
occurrences (all)	3	4	
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 113 (1.77%)	4 / 108 (3.70%)		
occurrences (all)	2	6		
Blood albumin decreased				
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)		
occurrences (all)	3	0		
Blood alkaline phosphatase increased				
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)		
occurrences (all)	5	1		
Blood creatinine increased				
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)		
occurrences (all)	3	1		
Blood folate decreased				
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)		
occurrences (all)	0	1		
Blood magnesium decreased				
subjects affected / exposed	2 / 113 (1.77%)	2 / 108 (1.85%)		
occurrences (all)	2	2		
Blood potassium decreased				
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)		
occurrences (all)	2	0		
Blood potassium increased				
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)		
occurrences (all)	0	1		
Blood pressure increased				
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)		
occurrences (all)	0	1		
C-reactive protein increased				
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)		
occurrences (all)	1	1		
Eastern cooperative oncology group performance status				
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)		
occurrences (all)	0	1		
Ejection fraction decreased				
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)		
occurrences (all)	1	0		

Electrocardiogram qt prolonged				
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)		
occurrences (all)	0	1		
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)		
occurrences (all)	1	2		
Glomerular filtration rate decreased				
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)		
occurrences (all)	2	0		
Haemoglobin decreased				
subjects affected / exposed	3 / 113 (2.65%)	2 / 108 (1.85%)		
occurrences (all)	4	2		
Human epidermal growth factor receptor decreased				
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)		
occurrences (all)	0	1		
Intraocular pressure increased				
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)		
occurrences (all)	2	0		
Lymphocyte count decreased				
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)		
occurrences (all)	15	1		
Neutrophil count decreased				
subjects affected / exposed	5 / 113 (4.42%)	6 / 108 (5.56%)		
occurrences (all)	36	7		
Platelet count abnormal				
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)		
occurrences (all)	1	0		
Platelet count decreased				
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)		
occurrences (all)	5	3		
Platelet count increased				
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)		
occurrences (all)	1	0		
Weight decreased				

subjects affected / exposed	4 / 113 (3.54%)	11 / 108 (10.19%)	
occurrences (all)	4	17	
Weight increased			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
White blood cell count decreased			
subjects affected / exposed	3 / 113 (2.65%)	2 / 108 (1.85%)	
occurrences (all)	33	4	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	2 / 113 (1.77%)	3 / 108 (2.78%)	
occurrences (all)	2	4	
Eye injury			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	0 / 113 (0.00%)	3 / 108 (2.78%)	
occurrences (all)	0	3	
Humerus fracture			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Infusion related reaction			
subjects affected / exposed	0 / 113 (0.00%)	3 / 108 (2.78%)	
occurrences (all)	0	3	
Joint dislocation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Laceration			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			

subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Procedural dizziness			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Procedural pneumothorax			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Radiation skin injury			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Rib fracture			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Skin abrasion			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Stoma site discomfort			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Stoma site irritation			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Tendon rupture			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Thermal burn			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	3	2	
Vaginal laceration			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Wound			

subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Wrist fracture			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Extrasystoles			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	3 / 113 (2.65%)	2 / 108 (1.85%)	
occurrences (all)	3	2	
Pericardial effusion			
subjects affected / exposed	3 / 113 (2.65%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Sinus tachycardia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	4	
Ventricular arrhythmia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Burning sensation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Cerebral ischaemia			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	14 / 113 (12.39%)	15 / 108 (13.89%)	
occurrences (all)	15	23	
Dizziness postural			
subjects affected / exposed	5 / 113 (4.42%)	1 / 108 (0.93%)	
occurrences (all)	5	1	
Dysaesthesia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	9 / 113 (7.96%)	7 / 108 (6.48%)	
occurrences (all)	10	9	
Extrapyramidal disorder			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	15 / 113 (13.27%)	17 / 108 (15.74%)	
occurrences (all)	17	25	
Hydrocephalus			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences (all)	4	1	
Lethargy			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Memory impairment			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	2	
Meningism			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Migraine			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Motor dysfunction			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Myoclonus			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	8 / 113 (7.08%)	11 / 108 (10.19%)	
occurrences (all)	10	15	
Paraesthesia			
subjects affected / exposed	9 / 113 (7.96%)	10 / 108 (9.26%)	
occurrences (all)	13	13	
Parosmia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Partial seizures			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Peripheral sensory neuropathy			
subjects affected / exposed	9 / 113 (7.96%)	3 / 108 (2.78%)	
occurrences (all)	17	3	
Polyneuropathy			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Polyneuropathy in malignant disease			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Restless legs syndrome			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Sciatica			

subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Syncope			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Tension headache			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 113 (10.62%)	13 / 108 (12.04%)	
occurrences (all)	25	29	
Anaemia folate deficiency			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Aplastic anaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Haemorrhagic diathesis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Leukocytosis			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	3	
Leukopenia			
subjects affected / exposed	8 / 113 (7.08%)	8 / 108 (7.41%)	
occurrences (all)	13	13	
Lymphadenopathy			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	3	0	

Neutropenia			
subjects affected / exposed	16 / 113 (14.16%)	23 / 108 (21.30%)	
occurrences (all)	43	68	
Neutrophilia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Splenomegaly			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	3 / 113 (2.65%)	2 / 108 (1.85%)	
occurrences (all)	17	14	
Thrombocytosis			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
White blood cell disorder			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Hypoacusis			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Tinnitus			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Vertigo			
subjects affected / exposed	6 / 113 (5.31%)	3 / 108 (2.78%)	
occurrences (all)	6	4	
Eye disorders			

Asthenopia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Blepharitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Dry eye			
subjects affected / exposed	2 / 113 (1.77%)	4 / 108 (3.70%)	
occurrences (all)	2	4	
Eye discharge			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Eye disorder			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Eye irritation			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	2	
Eyelid function disorder			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Eyelid oedema			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Eyelid pain			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	5 / 113 (4.42%)	3 / 108 (2.78%)	
occurrences (all)	7	3	
Ocular hyperaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Ocular surface disease			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	

Photopsia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Scleral discolouration			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	7 / 113 (6.19%)	3 / 108 (2.78%)	
occurrences (all)	7	3	
Visual impairment			
subjects affected / exposed	2 / 113 (1.77%)	2 / 108 (1.85%)	
occurrences (all)	2	4	
Vitreous floaters			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 113 (2.65%)	3 / 108 (2.78%)	
occurrences (all)	3	3	
Abdominal distension			
subjects affected / exposed	9 / 113 (7.96%)	10 / 108 (9.26%)	
occurrences (all)	10	11	
Abdominal hernia			
subjects affected / exposed	3 / 113 (2.65%)	0 / 108 (0.00%)	
occurrences (all)	4	0	
Abdominal pain			
subjects affected / exposed	35 / 113 (30.97%)	36 / 108 (33.33%)	
occurrences (all)	58	67	
Abdominal pain lower			
subjects affected / exposed	5 / 113 (4.42%)	7 / 108 (6.48%)	
occurrences (all)	6	9	
Abdominal pain upper			
subjects affected / exposed	18 / 113 (15.93%)	16 / 108 (14.81%)	
occurrences (all)	21	25	
Abdominal tenderness			

subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Abnormal faeces			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Anal hypoaesthesia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Anal incontinence			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Anorectal discomfort			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Aphthous ulcer			
subjects affected / exposed	6 / 113 (5.31%)	2 / 108 (1.85%)	
occurrences (all)	9	4	
Ascites			
subjects affected / exposed	27 / 113 (23.89%)	8 / 108 (7.41%)	
occurrences (all)	57	16	
Cheilitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	39 / 113 (34.51%)	36 / 108 (33.33%)	
occurrences (all)	63	66	
Diarrhoea			
subjects affected / exposed	32 / 113 (28.32%)	28 / 108 (25.93%)	
occurrences (all)	62	43	
Diverticulum intestinal			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	6 / 113 (5.31%)	5 / 108 (4.63%)	
occurrences (all)	7	5	
Dyschezia			

subjects affected / exposed	3 / 113 (2.65%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Dyspepsia			
subjects affected / exposed	21 / 113 (18.58%)	15 / 108 (13.89%)	
occurrences (all)	26	17	
Dysphagia			
subjects affected / exposed	6 / 113 (5.31%)	5 / 108 (4.63%)	
occurrences (all)	6	5	
Enteritis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Epigastric discomfort			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Eructation			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Flatulence			
subjects affected / exposed	3 / 113 (2.65%)	3 / 108 (2.78%)	
occurrences (all)	3	3	
Gastric disorder			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Gastric stenosis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Gastritis erosive			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal pain			

subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	4	2	
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 113 (3.54%)	8 / 108 (7.41%)	
occurrences (all)	4	9	
Gingival bleeding			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Gingival pain			
subjects affected / exposed	4 / 113 (3.54%)	3 / 108 (2.78%)	
occurrences (all)	4	3	
Glossodynia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Haematemesis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Haematochezia			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Haemorrhoids			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Hiatus hernia			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Hyperchlorhydria			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Ileus			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Intestinal obstruction			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Intra-abdominal fluid collection			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Mouth ulceration			
subjects affected / exposed	4 / 113 (3.54%)	6 / 108 (5.56%)	
occurrences (all)	6	13	
Nausea			
subjects affected / exposed	66 / 113 (58.41%)	61 / 108 (56.48%)	
occurrences (all)	134	113	
Odynophagia			
subjects affected / exposed	1 / 113 (0.88%)	3 / 108 (2.78%)	
occurrences (all)	2	3	
Oesophagitis			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences (all)	3	1	
Oral dysaesthesia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	2 / 113 (1.77%)	6 / 108 (5.56%)	
occurrences (all)	2	7	
Paraesthesia oral			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Periodontal disease			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Proctalgia			
subjects affected / exposed	2 / 113 (1.77%)	2 / 108 (1.85%)	
occurrences (all)	4	3	
Rectal discharge			

subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Rectal haemorrhage			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Reflux gastritis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Small intestinal obstruction			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Stomatitis			
subjects affected / exposed	58 / 113 (51.33%)	55 / 108 (50.93%)	
occurrences (all)	112	137	
Swollen tongue			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Tongue coated			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Tongue disorder			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Tooth discolouration			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Tooth loss			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 113 (0.88%)	3 / 108 (2.78%)	
occurrences (all)	1	4	
Vomiting			
subjects affected / exposed	49 / 113 (43.36%)	35 / 108 (32.41%)	
occurrences (all)	76	75	
Skin and subcutaneous tissue disorders			

Acanthosis nigricans			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Acne			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	7 / 113 (6.19%)	4 / 108 (3.70%)	
occurrences (all)	10	5	
Alopecia			
subjects affected / exposed	21 / 113 (18.58%)	12 / 108 (11.11%)	
occurrences (all)	27	15	
Dermatitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Decubitus ulcer			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Dermatitis acneiform			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			
subjects affected / exposed	3 / 113 (2.65%)	2 / 108 (1.85%)	
occurrences (all)	8	2	
Dermatitis exfoliative			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	2	
Eczema			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences (all)	3	2	
Dry skin			
subjects affected / exposed	10 / 113 (8.85%)	13 / 108 (12.04%)	
occurrences (all)	11	13	
Erythema			
subjects affected / exposed	3 / 113 (2.65%)	5 / 108 (4.63%)	
occurrences (all)	9	10	

Exfoliative rash				
subjects affected / exposed	4 / 113 (3.54%)	1 / 108 (0.93%)		
occurrences (all)	6	1		
Generalised erythema				
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)		
occurrences (all)	0	1		
Hyperhidrosis				
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)		
occurrences (all)	1	3		
Nail discolouration				
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)		
occurrences (all)	1	1		
Nail disorder				
subjects affected / exposed	2 / 113 (1.77%)	4 / 108 (3.70%)		
occurrences (all)	2	4		
Nail dystrophy				
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)		
occurrences (all)	1	0		
Night sweats				
subjects affected / exposed	4 / 113 (3.54%)	2 / 108 (1.85%)		
occurrences (all)	4	4		
Pain of skin				
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)		
occurrences (all)	2	0		
Onycholysis				
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)		
occurrences (all)	1	0		
Palmar erythema				
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)		
occurrences (all)	1	2		
Panniculitis				
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)		
occurrences (all)	1	0		
Palmar-plantar erythrodysaesthesia syndrome				

subjects affected / exposed	70 / 113 (61.95%)	61 / 108 (56.48%)	
occurrences (all)	247	177	
Plantar erythema			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Pigmentation disorder			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Pruritus			
subjects affected / exposed	11 / 113 (9.73%)	8 / 108 (7.41%)	
occurrences (all)	17	10	
Pruritus generalised			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences (all)	5	1	
Psoriasis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	30 / 113 (26.55%)	28 / 108 (25.93%)	
occurrences (all)	59	67	
Pustular psoriasis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Rash erythematous			
subjects affected / exposed	2 / 113 (1.77%)	3 / 108 (2.78%)	
occurrences (all)	2	3	
Rash generalised			
subjects affected / exposed	3 / 113 (2.65%)	0 / 108 (0.00%)	
occurrences (all)	4	0	
Rash macular			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			
subjects affected / exposed	4 / 113 (3.54%)	4 / 108 (3.70%)	
occurrences (all)	6	26	
Rash pruritic			

subjects affected / exposed	2 / 113 (1.77%)	2 / 108 (1.85%)	
occurrences (all)	2	2	
Rash vesicular			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Scar pain			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Skin discolouration			
subjects affected / exposed	2 / 113 (1.77%)	2 / 108 (1.85%)	
occurrences (all)	2	2	
Skin disorder			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Skin exfoliation			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	4	1	
Skin fissures			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Skin hyperpigmentation			
subjects affected / exposed	7 / 113 (6.19%)	11 / 108 (10.19%)	
occurrences (all)	8	14	
Skin irritation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	0 / 113 (0.00%)	3 / 108 (2.78%)	
occurrences (all)	0	3	
Skin reaction			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	4	
Skin mass			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Skin tightness			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Stasis dermatitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Anuria			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Dysuria			
subjects affected / exposed	6 / 113 (5.31%)	5 / 108 (4.63%)	
occurrences (all)	6	6	
Haematuria			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	2	
Hydronephrosis			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Kidney enlargement			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Nocturia			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Obstructive uropathy			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Oliguria			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences (all)	3	1	

Proteinuria			
subjects affected / exposed	6 / 113 (5.31%)	4 / 108 (3.70%)	
occurrences (all)	6	10	
Renal colic			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Renal pain			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Renal vein thrombosis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Urinary hesitation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	3 / 113 (2.65%)	2 / 108 (1.85%)	
occurrences (all)	3	2	
Urinary retention			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Urinary tract obstruction			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 113 (9.73%)	7 / 108 (6.48%)	
occurrences (all)	18	8	
Arthritis			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	12 / 113 (10.62%)	17 / 108 (15.74%)	
occurrences (all)	13	20	
Bone pain			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Bursitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Coccydynia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Enthesopathy			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Flank pain			
subjects affected / exposed	3 / 113 (2.65%)	4 / 108 (3.70%)	
occurrences (all)	5	6	
Fracture pain			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Groin pain			
subjects affected / exposed	2 / 113 (1.77%)	2 / 108 (1.85%)	
occurrences (all)	3	2	
Intervertebral disc displacement			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Limb discomfort			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Muscle fatigue			

subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	9 / 113 (7.96%)	11 / 108 (10.19%)	
occurrences (all)	10	20	
Muscle tightness			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	0 / 113 (0.00%)	3 / 108 (2.78%)	
occurrences (all)	0	3	
Musculoskeletal chest pain			
subjects affected / exposed	3 / 113 (2.65%)	8 / 108 (7.41%)	
occurrences (all)	4	9	
Musculoskeletal discomfort			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Musculoskeletal disorder			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	4 / 113 (3.54%)	7 / 108 (6.48%)	
occurrences (all)	4	9	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	4 / 113 (3.54%)	2 / 108 (1.85%)	
occurrences (all)	4	3	
Neck pain			
subjects affected / exposed	4 / 113 (3.54%)	3 / 108 (2.78%)	
occurrences (all)	4	3	
Osteopenia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Pain in extremity			

subjects affected / exposed	13 / 113 (11.50%)	4 / 108 (3.70%)	
occurrences (all)	17	4	
Spinal osteoarthritis			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Spinal pain			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Tendon disorder			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Trismus			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Appendicitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	2 / 113 (1.77%)	3 / 108 (2.78%)	
occurrences (all)	2	3	
Candida infection			
subjects affected / exposed	2 / 113 (1.77%)	3 / 108 (2.78%)	
occurrences (all)	3	3	
Carbuncle			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	

Conjunctivitis			
subjects affected / exposed	4 / 113 (3.54%)	3 / 108 (2.78%)	
occurrences (all)	4	3	
Cystitis			
subjects affected / exposed	3 / 113 (2.65%)	3 / 108 (2.78%)	
occurrences (all)	6	3	
Device related infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Enterocolitis infectious			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Erysipelas			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Eye infection			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Folliculitis			
subjects affected / exposed	3 / 113 (2.65%)	4 / 108 (3.70%)	
occurrences (all)	5	5	
Fungal cystitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Fungal infection			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Fungal skin infection			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	

Gastroenteritis			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	5	
Gastrointestinal infection			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Gingivitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Herpes virus infection			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Herpes zoster			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Hordeolum			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	2	2	
Influenza			
subjects affected / exposed	1 / 113 (0.88%)	4 / 108 (3.70%)	
occurrences (all)	1	4	
Lice infestation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Localised infection			
subjects affected / exposed	2 / 113 (1.77%)	1 / 108 (0.93%)	
occurrences (all)	3	2	
Lower respiratory tract infection			
subjects affected / exposed	2 / 113 (1.77%)	4 / 108 (3.70%)	
occurrences (all)	3	4	

Lung abscess			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Lung infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Lymphangitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Mastoiditis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Nail infection			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Onychomycosis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	6 / 113 (5.31%)	9 / 108 (8.33%)	
occurrences (all)	6	10	
Oral fungal infection			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Oral herpes			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences (all)	3	1	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	

Paronychia			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	3	
Periorbital cellulitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	3 / 113 (2.65%)	3 / 108 (2.78%)	
occurrences (all)	3	3	
Pneumonia			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Post procedural cellulitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Pseudomonas infection			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Pyuria			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Rash pustular			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	4 / 113 (3.54%)	4 / 108 (3.70%)	
occurrences (all)	6	5	
Skin infection			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Soft tissue infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	

Staphylococcal infection			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	2	
Tinea infection			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Tooth abscess			
subjects affected / exposed	1 / 113 (0.88%)	2 / 108 (1.85%)	
occurrences (all)	1	2	
Tooth infection			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	12 / 113 (10.62%)	7 / 108 (6.48%)	
occurrences (all)	13	10	
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	7 / 113 (6.19%)	9 / 108 (8.33%)	
occurrences (all)	7	14	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 113 (0.88%)	1 / 108 (0.93%)	
occurrences (all)	2	1	
Viral pharyngitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			

subjects affected / exposed	11 / 113 (9.73%)	11 / 108 (10.19%)	
occurrences (all)	14	13	
Vulvovaginal candidiasis			
subjects affected / exposed	3 / 113 (2.65%)	3 / 108 (2.78%)	
occurrences (all)	3	3	
Wound infection			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Decreased appetite			
subjects affected / exposed	27 / 113 (23.89%)	24 / 108 (22.22%)	
occurrences (all)	33	36	
Dehydration			
subjects affected / exposed	2 / 113 (1.77%)	4 / 108 (3.70%)	
occurrences (all)	2	4	
Diabetes mellitus			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Glucose tolerance impaired			
subjects affected / exposed	0 / 113 (0.00%)	2 / 108 (1.85%)	
occurrences (all)	0	2	
Hypercalcaemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	3 / 113 (2.65%)	1 / 108 (0.93%)	
occurrences (all)	8	1	
Hyperkalaemia			
subjects affected / exposed	2 / 113 (1.77%)	0 / 108 (0.00%)	
occurrences (all)	4	0	
Hypermagnesaemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	

Hyperuricaemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	4 / 113 (3.54%)	3 / 108 (2.78%)	
occurrences (all)	9	3	
Hypocalcaemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Hypochloraemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	3	0	
Hypokalaemia			
subjects affected / exposed	23 / 113 (20.35%)	11 / 108 (10.19%)	
occurrences (all)	37	14	
Hypomagnesaemia			
subjects affected / exposed	11 / 113 (9.73%)	3 / 108 (2.78%)	
occurrences (all)	25	7	
Hyponatraemia			
subjects affected / exposed	4 / 113 (3.54%)	6 / 108 (5.56%)	
occurrences (all)	4	9	
Hypophosphataemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Hypoproteinaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	1	0	
Hypovolaemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 108 (0.00%)	
occurrences (all)	2	0	
Iron deficiency			
subjects affected / exposed	0 / 113 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2012	- To provide current language for the management of trebananib related toxicities. Pleural effusion and ascites are known identified risks of trebananib, and thus a new toxicity management section was added to provide guidance to participating investigators of the study. - Statistical changes rationale are as follows: - The accrual assumptions for this study were modified to reflect the initial accrual of 58 subjects and the accrual hold. Accrual is most commonly modeled with a 2-stage accrual curve, with 50% of the accrual occurring in the last 30% of the accrual time. To reflect the initial accrual, the accrual hold, and the future accrual for this study, accrual is modeled with a 4-part accrual curve: -- Part 1 reflects linear accrual of the first 58 patients over 7 months -- Part 2 reflects the hold of 15 months -- Parts 3 and 4 are the typical 2-stage accrual used; part 3 reflects accrual of the remaining 322 patients, with 47% of this accrual occurring over the 16 months and the remaining 53% of accrual occuring over the last 6 months. - the operating characteristics of this futility analysis are based on the hypothesis testing being set up as 1-sided 2.5% testing. Therefore, the references to 2-sided 5% tests have been changed to 1-sided 2.5% tests throughout. - The primary analysis was modified to reflect the inclusion of the time of accrual (before or after the accrual hold) as a stratification factor - To reword and move hypertension from exclusion to inclusion criteria - To add guidelines regarding immune modulators as excluded medications during the study - To add the new pregnancy and lactation reporting guidance - To update language on the reporting of adverse events by Investigators and the use of Appendix B in the Investigator's Brochure for the determination of adverse event expectedness - Update the trebananib Investigator's Brochure version number and date - Administrative and typographical corrections throughout
23 January 2014	- To address the decisions to close the study to further randomization last 23 October 2013 due to global supply shortages of DOXIL® (doxorubicin HCl liposome injection)/CAELYX® (pegylated liposomal doxorubicin hydrochloride) - A total of 223 subjects were randomized to the study - Statistical analyses plans were amended to reflect the change in the number of subjects on study - To add language on how to address and report serious adverse events occurring outside the protocol required reporting period and provide serious adverse events sample forms - Update key contact information of the Clinical Research Medical Director (Medical Monitor) and study management for the study - Update toxicity management guidelines - Update the references in Section 13 - Correct any typographical and/or grammatical errors in the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

23 November 2011	Due to a global shortage of PLD, enrollment was put on hold from 23 November 2011 (last subject enrolled date pre-hold) until 10 January 2013 (first subjected enrolled date post-hold).	10 January 2013

Notes:

Limitations and caveats

None reported