



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 \geq 0 months and \leq 6 months versus PFI > 6 months and \leq 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/m ² 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/m ² 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/m ² 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/m ² 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 $\geq 2 \times$ ULN and available post-baseline data

[15] - Participants with baseline CA-125 $\geq 2 \times$ 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 occurrences (all) | 1 / 113 (0.88%) 1 | 0 / 108 (0.00%) 0 | |
| Tooth extraction subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 0 / 108 (0.00%) 0 | |
| Eye irrigation subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 0 / 108 (0.00%) 0 | |
| General disorders and administration site conditions | | | |
| Application site hypersensitivity subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 1 / 108 (0.93%) 1 | |
| Asthenia subjects affected / exposed occurrences (all) | 9 / 113 (7.96%) 16 | 12 / 108 (11.11%) 19 | |
| Axillary pain subjects affected / exposed occurrences (all) | 2 / 113 (1.77%) 2 | 0 / 108 (0.00%) 0 | |
| Catheter site erythema subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 2 | 1 / 108 (0.93%) 4 | |
| Catheter site haematoma subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 0 / 108 (0.00%) 0 | |
| Catheter site inflammation subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 1 / 108 (0.93%) 1 | |
| Catheter site pain subjects affected / exposed occurrences (all) | 2 / 113 (1.77%) 3 | 1 / 108 (0.93%) 1 | |
| Catheter site pruritus subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 1 / 108 (0.93%) 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 occurrences (all) | 4 / 113 (3.54%) 4 | 11 / 108 (10.19%) 17 | |
| Weight increased subjects affected / exposed occurrences (all) | 2 / 113 (1.77%) 3 | 0 / 108 (0.00%) 0 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 3 / 113 (2.65%) 33 | 2 / 108 (1.85%) 4 | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 0 / 108 (0.00%) 0 | |
| Contusion subjects affected / exposed occurrences (all) | 2 / 113 (1.77%) 2 | 3 / 108 (2.78%) 4 | |
| Eye injury subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 1 / 108 (0.93%) 1 | |
| Fall subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 3 / 108 (2.78%) 3 | |
| Humerus fracture subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 1 / 108 (0.93%) 1 | |
| Infusion related reaction subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 3 / 108 (2.78%) 3 | |
| Joint dislocation subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 0 / 108 (0.00%) 0 | |
| Laceration subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 0 / 108 (0.00%) 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 occurrences (all) | 1 / 113 (0.88%) 1 | 2 / 108 (1.85%) 2 | |
| Wrist fracture subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 0 / 108 (0.00%) 0 | |
| Cardiac disorders | | | |
| Bundle branch block right subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 1 / 108 (0.93%) 1 | |
| Extrasystoles subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 1 / 108 (0.93%) 1 | |
| Palpitations subjects affected / exposed occurrences (all) | 3 / 113 (2.65%) 3 | 2 / 108 (1.85%) 2 | |
| Pericardial effusion subjects affected / exposed occurrences (all) | 3 / 113 (2.65%) 3 | 0 / 108 (0.00%) 0 | |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 1 / 108 (0.93%) 1 | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 1 / 108 (0.93%) 4 | |
| Ventricular arrhythmia subjects affected / exposed occurrences (all) | 0 / 113 (0.00%) 0 | 1 / 108 (0.93%) 1 | |
| Nervous system disorders | | | |
| Ageusia subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 0 / 108 (0.00%) 0 | |
| Burning sensation subjects affected / exposed occurrences (all) | 1 / 113 (0.88%) 1 | 0 / 108 (0.00%) 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 erythrodysesthesia 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 | <ul style="list-style-type: none">- 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:<ul style="list-style-type: none">- 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:<ul style="list-style-type: none">-- 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 occurring 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 | <ul style="list-style-type: none">- 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)<ul style="list-style-type: none">- 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