



Clinical trial results:

A randomized, controlled, double-blind Phase III trial to compare the efficacy, safety and pharmacokinetics of GP2013 plus cyclophosphamide, vincristine, prednisone vs. MabThera® plus cyclophosphamide, vincristine, prednisone, followed by GP2013 or MabThera® maintenance therapy in patients with previously untreated, advanced stage follicular lymphoma

Summary

| | |
|--------------------------|--|
| EudraCT number | 2010-019522-13 |
| Trial protocol | NL PT FR HU DE AT BG ES PL GR IT GB IE |
| Global end of trial date | 22 January 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 06 February 2019 |
| First version publication date | 06 February 2019 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CIGG013A2301J |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01419665 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Hexal AG/ Novartis Pharmaceuticals |
| Sponsor organisation address | Industriestr. 25, Holzkirchen, Germany, D-83607 |
| Public contact | Study Director, Hexal AG / Novartis, 41 613241111, novartis.email@novartis.com |
| Scientific contact | Study Director, Hexal AG / Novartis Pharmaceuticals, +41 613241111, novartis.email@novartis.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 | 22 January 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 January 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate comparability of the overall response rate (ORR) in patients with previously untreated, advanced stage follicular lymphoma who received GP2013-CVP combination treatment to patients who received MabThera-CVP combination treatment.

Protection of trial subjects:

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

Background therapy:

cyclophosphamide, vincristine, prednisone

Evidence for comparator:

MabThera

| | |
|---|------------------|
| Actual start date of recruitment | 01 December 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Australia: 27 |
| Country: Number of subjects enrolled | Argentina: 5 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | Bulgaria: 15 |
| Country: Number of subjects enrolled | Brazil: 102 |
| Country: Number of subjects enrolled | Colombia: 2 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Greece: 9 |
| Country: Number of subjects enrolled | Hungary: 14 |
| Country: Number of subjects enrolled | India: 94 |
| Country: Number of subjects enrolled | Ireland: 2 |
| Country: Number of subjects enrolled | Israel: 12 |
| Country: Number of subjects enrolled | Italy: 23 |
| Country: Number of subjects enrolled | Japan: 29 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Malaysia: 30 |
| Country: Number of subjects enrolled | Netherlands: 17 |
| Country: Number of subjects enrolled | Peru: 9 |
| Country: Number of subjects enrolled | Poland: 41 |
| Country: Number of subjects enrolled | Portugal: 33 |
| Country: Number of subjects enrolled | Romania: 13 |
| Country: Number of subjects enrolled | Russian Federation: 46 |
| Country: Number of subjects enrolled | South Africa: 28 |
| Country: Number of subjects enrolled | Spain: 37 |
| Country: Number of subjects enrolled | Ukraine: 21 |
| Worldwide total number of subjects | 627 |
| EEA total number of subjects | 222 |

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) | 461 |
| From 65 to 84 years | 166 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 629 patients were randomized at 159 centers in 26 countries, 314 patients to GP2013 (312 patients treated) and 315 to MabThera. Of those 314 patients in the GP2013 group, 2 patients were randomized by error and discontinued before any treatment with GP2013. The number of patients in both treatment groups remained similar.

Pre-assignment

Screening details:

full analysis set participants :

GP2013 312 MabThera 315

safety set participants :

GP2013 312 MabThera 315

per protocol set participants: GP2013 310 MabThera 312

pharmacokinetic analysis set 1 : GP2013 119 MabThera 120

immunogenicity analysis set: GP2013 275 MabThera 287

pharmacodynamic analysis set : GP2013 24 MabThera 24

Period 1

| | |
|------------------------------|---|
| Period 1 title | combination treatment |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes |
| Arm title | GP2013 |

Arm description:

Experimental Type: Biological/Vaccine

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | GP2013 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

GP2013 was provided as sterile, colorless, preservative-free liquid concentrate for solution for i.v. infusion. It was supplied at a concentration of 10 mg/mL in 500 mg (50 mL) single use vials.

| | |
|------------------|----------|
| Arm title | MabThera |
|------------------|----------|

Arm description:

Comparator Type: Biological/Vaccine

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | MabThera |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

MabThera (Roche Registration Ltd.) was provided as sterile, colorless, preservative-free liquid concentrate for solution for i.v. infusion. It was supplied at a concentration of 10 mg/mL in 500 mg (50 mL) single use vials.

| Number of subjects in period 1 | GP2013 | MabThera |
|---------------------------------------|--------|----------|
| Started | 312 | 315 |
| Completed | 274 | 274 |
| Not completed | 38 | 41 |
| Adverse event, serious fatal | 5 | 7 |
| Physician decision | 5 | 8 |
| Consent withdrawn by subject | 5 | 4 |
| Adverse event, non-fatal | 7 | 10 |
| administrative problems | - | 1 |
| disease progression | 10 | 9 |
| Protocol deviation | 6 | 2 |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Maintenance treatment and/or follow up |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes |
| Arm title | GP2013 |

Arm description:

Experimental Type: Biological/Vaccine

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | GP2013 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

GP2013 was provided as sterile, colorless, preservative-free liquid concentrate for solution for i.v. infusion. It was supplied at a concentration of 10 mg/mL in 500 mg (50 mL) single use vials.

| | |
|------------------|----------|
| Arm title | MabThera |
|------------------|----------|

Arm description:

Comparator Type: Biological/Vaccine

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|---------------------------------------|
| Investigational medicinal product name | MabThera |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

MabThera (Roche Registration Ltd.) was provided as sterile, colorless, preservative-free liquid concentrate for solution for i.v. infusion. It was supplied at a concentration of 10 mg/mL in 500 mg (50 mL) single use vials.

| Number of subjects in period 2^[1] | GP2013 | MabThera |
|---|--------|----------|
| Started | 254 | 252 |
| Completed | 132 | 150 |
| Not completed | 122 | 102 |
| Adverse event, serious fatal | 1 | 2 |
| Consent withdrawn by subject | 6 | 6 |
| Physician decision | 5 | 2 |
| Adverse event, non-fatal | 11 | 7 |
| switch to open label | 44 | 39 |
| administrative problems | - | 6 |
| Lost to follow-up | 1 | 2 |
| disease progression | 53 | 37 |
| Protocol deviation | 1 | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: numbers are correct

Period 3

| | |
|------------------------------|------------------|
| Period 3 title | open label phase |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | MabThera |

Arm description:

Experimental Type: Biological/Vaccine, all patients switched to MabThera

| | |
|---|--|
| Arm type | all patients in this phase received MabThera |
| No investigational medicinal product assigned in this arm | |
| Arm title | MabThera |

Arm description:

Comparator Type: Biological/Vaccine

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | MabThera |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

MabThera (Roche Registration Ltd.) was provided as sterile, colorless, preservative-free liquid concentrate for solution for i.v. infusion. It was supplied at a concentration of 10 mg/mL in 500 mg (50 mL) single use vials.

| Number of subjects in period 3^[2] | MabThera | MabThera |
|---|----------|----------|
| Started | 44 | 39 |
| Completed | 43 | 38 |
| Not completed | 1 | 1 |
| Adverse event, serious fatal | 1 | - |
| disease progression | - | 1 |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: numbers are correct

Baseline characteristics

Reporting groups

| | |
|---------------------------------------|----------|
| Reporting group title | GP2013 |
| Reporting group description: | |
| Experimental Type: Biological/Vaccine | |
| Reporting group title | MabThera |
| Reporting group description: | |
| Comparator Type: Biological/Vaccine | |

| Reporting group values | GP2013 | MabThera | Total |
|--|---------|----------|-------|
| Number of subjects | 312 | 315 | 627 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 226 | 235 | 461 |
| From 65-84 years | 86 | 80 | 166 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 57.5 | 56.4 | |
| standard deviation | ± 11.86 | ± 11.72 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 181 | 169 | 350 |
| Male | 131 | 146 | 277 |
| Race, Customized | | | |
| Race | | | |
| Units: Subjects | | | |
| Asian | 71 | 85 | 156 |
| Black | 6 | 3 | 9 |
| Caucasian | 214 | 207 | 421 |
| Native American | 2 | 5 | 7 |
| Other | 19 | 15 | 34 |
| Ethnicity, Customized | | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Chinese | 5 | 6 | 11 |
| Hispanic / Latino | 59 | 68 | 127 |
| Indian (Indian Subcontinent) | 40 | 54 | 94 |
| Mixed Ethnicity | 8 | 3 | 11 |
| Other | 183 | 170 | 353 |

| | | | |
|-------------------|----|----|----|
| Unknown / missing | 1 | 0 | 1 |
| Japanese | 16 | 14 | 30 |

End points

End points reporting groups

| | |
|--|----------|
| Reporting group title | GP2013 |
| Reporting group description: | |
| Experimental Type: Biological/Vaccine | |
| Reporting group title | MabThera |
| Reporting group description: | |
| Comparator Type: Biological/Vaccine | |
| Reporting group title | GP2013 |
| Reporting group description: | |
| Experimental Type: Biological/Vaccine | |
| Reporting group title | MabThera |
| Reporting group description: | |
| Comparator Type: Biological/Vaccine | |
| Reporting group title | MabThera |
| Reporting group description: | |
| Experimental Type: Biological/Vaccine, all patients switched to MabThera | |
| Reporting group title | MabThera |
| Reporting group description: | |
| Comparator Type: Biological/Vaccine | |

Primary: Overall response rate (ORR)

| | |
|---|-----------------------------|
| End point title | Overall response rate (ORR) |
| End point description: | |
| ORR is defined as the proportion of patients whose best overall disease response was either CR or PR during the combination treatment period based on blinded independent central radiology review. Per protocol set. | |
| End point type | Primary |
| End point timeframe: | |
| 24 weeks | |

| End point values | GP2013 | MabThera | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 311 | 313 | | |
| Units: percentage | | | | |
| number (confidence interval 90%) | 87.1 (83.59 to 90.15) | 87.5 (84.04 to 90.49) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | comparison of ORR between the 2 arms |
| Statistical analysis description: | |
| Equivalence to be concluded if the entire 95% CI of the difference in ORR between both groups is within | |

the pre-specified margin of (-12%, 12%).

| | |
|---|---------------------------------------|
| Comparison groups | GP2013 v MabThera |
| Number of subjects included in analysis | 624 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[1] |
| Method | Binomial approximation |
| Parameter estimate | difference in ORR (GP2013 –MabThera) |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.94 |
| upper limit | 5.14 |

Notes:

[1] - The equivalence margin of + or - 12% was determined considering the variability of the point estimate of the add-on effect by taking a value lower than the lower boundary of the 95% CI for Rituximab+chemotherapy versus chemotherapy obtained from historical data.

Secondary: To evaluate the Complete Response (CR) rate during the combination treatment period

| | |
|------------------------|---|
| End point title | To evaluate the Complete Response (CR) rate during the combination treatment period |
| End point description: | |
| Per protocol set | |
| End point type | Secondary |
| End point timeframe: | |
| 24 weeks | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | GP2013 | MabThera | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 311 | 313 | | |
| Units: participants | 46 | 42 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate the Partial Response (PR) rate during the combination treatment period

| | |
|------------------------|--|
| End point title | To evaluate the Partial Response (PR) rate during the combination treatment period |
| End point description: | |
| Per protocol set | |
| End point type | Secondary |
| End point timeframe: | |
| 24 weeks | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | GP2013 | MabThera | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 311 | 313 | | |
| Units: participants | 225 | 232 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate the progression free survival (PFS) with up to 3 years of follow-up post randomization

| | |
|---|--|
| End point title | To evaluate the progression free survival (PFS) with up to 3 years of follow-up post randomization |
| End point description: | |
| Number of participants with progression free survival events. PFS was defined as the time from the date of randomization to the date of event defined as the first observation of documented disease progression or death due to any cause. | |
| full analysis set | |
| End point type | Secondary |
| End point timeframe: | |
| 3 years | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | GP2013 | MabThera | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 315 | | |
| Units: participants | 97 | 78 | | |

Statistical analyses

| | |
|--|-------------------|
| Statistical analysis title | PFS |
| Statistical analysis description: | |
| PFS evaluation was based on the investigators' assessment of documented disease Progression. | |
| If a patient did not have an event, PFS was censored at the date of last adequate Tumor assessment. The PFS analysis contained data from the Combination Phase, the Maintenance Phase, the Open-label Phase, and the Follow-up Phase of the study. | |
| Comparison groups | GP2013 v MabThera |

| | |
|---|-------------------|
| Number of subjects included in analysis | 627 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.97 |
| upper limit | 1.76 |

Secondary: Overall survival (OS) with up to 3 years of follow- up post randomization, as assessed by the number of deaths

| | |
|--|--|
| End point title | Overall survival (OS) with up to 3 years of follow- up post randomization, as assessed by the number of deaths |
| End point description: | |
| OS was defined as the time from date of randomization to date of death due to any cause. If a patient was not known to have died, OS was censored at the date of last contact. | |
| full analysis set | |
| End point type | Secondary |
| End point timeframe: | |
| 3 years | |

| End point values | GP2013 | MabThera | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 312 | 315 | | |
| Units: participants | 29 | 31 | | |

Statistical analyses

| | |
|---|-------------------|
| Statistical analysis title | Overall Survival |
| Comparison groups | GP2013 v MabThera |
| Number of subjects included in analysis | 627 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.52 |

Secondary: To evaluate the incidence of immunogenicity (ADA formation) against GP2013 and MabThera (rituximab)

| | |
|-----------------|---|
| End point title | To evaluate the incidence of immunogenicity (ADA formation) against GP2013 and MabThera (rituximab) |
|-----------------|---|

End point description:

number of participants with confirmed positive ADA
immunogenicity analysis set

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

End point timeframe:

24 weeks, 3 years

| End point values | GP2013 | MabThera | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 287 | | |
| Units: participants | | | | |
| end of treatment combination phase (24 weeks) | 1 | 2 | | |
| end of treatment maintenance phase (3 years) | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate a PK marker following the treatment with GP2013-Chemotherapy and MabThera-Chemotherapy (Cmax)

| | |
|-----------------|---|
| End point title | To evaluate a PK marker following the treatment with GP2013-Chemotherapy and MabThera-Chemotherapy (Cmax) |
|-----------------|---|

End point description:

Cmax

PK analysis set 1

Day 63 is the C4D1 (cycle 4 day 1) of the combination phase

For descriptive purposes only, no hypothesis testing

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

End point timeframe:

day 63

| End point values | GP2013 | MabThera | | |
|---|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 119 ^[2] | 120 ^[3] | | |
| Units: microg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 333.59 (± 41.09) | 331.93 (± 35.32) | | |

Notes:

[2] - number of participants with data : 108

[3] - number of participants with data : 111

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate a PK marker following the treatment with GP2013-Chemotherapy and MabThera-Chemotherapy (Ctrough)

| | |
|--|--|
| End point title | To evaluate a PK marker following the treatment with GP2013-Chemotherapy and MabThera-Chemotherapy (Ctrough) |
| End point description: | |
| Cthrough | |
| PK analysis set 1 | |
| For descriptive purposes only, no hypothesis testing | |
| End point type | Secondary |
| End point timeframe: | |
| day 63 | |

| End point values | GP2013 | MabThera | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 119 ^[4] | 120 ^[5] | | |
| Units: microg/mL | | | | |
| arithmetic mean (standard deviation) | 66.42 (± 47.593) | 82.13 (± 61.526) | | |

Notes:

[4] - number of participants with data : 104

[5] - number of participants with data : 110

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate a PD marker (peripheral CD19+ B-cell counts) following the treatment with GP2013 + Chemotherapy and MabThera- Chemotherapy

| | |
|--|--|
| End point title | To evaluate a PD marker (peripheral CD19+ B-cell counts) following the treatment with GP2013 + Chemotherapy and MabThera- Chemotherapy |
| End point description: | |
| AUEC (0-21d) | |
| PD analysis set | |
| For descriptive purposes only, no hypothesis testing | |
| End point type | Secondary |
| End point timeframe: | |
| 21 days | |

| End point values | GP2013 | MabThera | | |
|---|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 ^[6] | 24 ^[7] | | |
| Units: %*day | | | | |
| geometric mean (geometric coefficient of variation) | 1790 (\pm 23.5) | 1910 (\pm 13.3) | | |

Notes:

[6] - number of participants with data : 19

[7] - number of participants with data : 18

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description :

Note that maintenance treatment phase data include the open label phase

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Combination GP2013+CVP |
|-----------------------|------------------------|

Reporting group description:

Combination GP2013+CVP

| | |
|-----------------------|--------------------------|
| Reporting group title | Combination MabThera+CVP |
|-----------------------|--------------------------|

Reporting group description:

Combination MabThera+CVP

| | |
|-----------------------|--------------------|
| Reporting group title | Maintenance GP2013 |
|-----------------------|--------------------|

Reporting group description:

Maintenance GP2013

| | |
|-----------------------|----------------------|
| Reporting group title | Maintenance MabThera |
|-----------------------|----------------------|

Reporting group description:

Maintenance MabThera

| Serious adverse events | Combination GP2013+CVP | Combination MabThera+CVP | Maintenance GP2013 |
|---|------------------------|--------------------------|--------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 71 / 312 (22.76%) | 63 / 315 (20.00%) | 24 / 254 (9.45%) |
| number of deaths (all causes) | 4 | 5 | 2 |
| number of deaths resulting from adverse events | 3 | 2 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Lung neoplasm malignant subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Circulatory collapse subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension subjects affected / exposed | 1 / 312 (0.32%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery stenosis subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chills subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Hypothermia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 315 (0.63%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 312 (1.28%) | 7 / 315 (2.22%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 1 / 4 | 2 / 8 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatism | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Scrotal swelling | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Asthma | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthmatic crisis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis chronic | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 6 / 315 (1.90%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngeal pain | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiogenic pulmonary oedema | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 3 / 315 (0.95%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 3 / 315 (0.95%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pulmonary mass | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental disorder | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coagulation test abnormal | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 3 / 312 (0.96%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Patella fracture | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pubis fracture | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Congenital cystic kidney disease | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocele | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Polycystic liver disease | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Extrasystoles | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palpitations | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prinzmetal angina | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical cord compression | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dementia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 2 / 254 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Meningeal disorder | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Occipital neuralgia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 312 (0.64%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular dementia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 315 (0.63%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 15 / 312 (4.81%) | 9 / 315 (2.86%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 14 / 17 | 12 / 13 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 2 / 315 (0.63%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Microcytic anaemia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 312 (1.28%) | 5 / 315 (1.59%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 5 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 312 (1.28%) | 6 / 315 (1.90%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4 | 2 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute abdomen | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis microscopic | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 3 / 312 (0.96%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 3 / 315 (0.95%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erosive duodenitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal hypomotility | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 3 / 315 (0.95%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 315 (0.63%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 2 / 315 (0.63%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxic skin eruption | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Anuria | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 2 / 254 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oliguria | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 2 / 315 (0.63%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess limb | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometritis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia infection | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Genital herpes | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Helicobacter infection | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis B | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 315 (0.32%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaria | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 312 (0.96%) | 4 / 315 (1.27%) | 3 / 254 (1.18%) |
| occurrences causally related to treatment / all | 3 / 4 | 3 / 5 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 0 / 315 (0.00%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 2 / 254 (0.79%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 5 / 315 (1.59%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 3 / 312 (0.96%) | 1 / 315 (0.32%) | 1 / 254 (0.39%) |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 312 (0.96%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypervolaemia | | | |
| subjects affected / exposed | 0 / 312 (0.00%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypocalcaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 312 (0.64%) | 1 / 315 (0.32%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 312 (0.32%) | 0 / 315 (0.00%) | 0 / 254 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Maintenance MabThera | | |
|---|----------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 252 (8.33%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------|--|--|
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chills | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Malaise | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cytokine release syndrome | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostatism | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Scrotal swelling | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | | |
|---|-----------------|--|--|--|
| Acute pulmonary oedema | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute respiratory distress syndrome | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute respiratory failure | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Asthma | | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Asthmatic crisis | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchitis chronic | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cough | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Interstitial lung disease | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Laryngeal pain | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-cardiogenic pulmonary oedema | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary oedema | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mental disorder | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase | | | |

| | | | |
|---|-----------------|--|--|
| increased | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coagulation test abnormal | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Patella fracture | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pubis fracture | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Congenital cystic kidney disease | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydrocele | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Polycystic liver disease | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Extrasystoles | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prinzmetal angina | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervical cord compression | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dementia | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meningeal disorder | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Occipital neuralgia | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular dementia | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Febrile neutropenia | | | | |
| subjects affected / exposed | 2 / 252 (0.79%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Leukocytosis | | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Leukopenia | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lymphadenopathy | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Microcytic anaemia | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neutropenia | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancytopenia | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thrombocytopenia | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute abdomen | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis microscopic | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erosive duodenitis | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal hypomotility | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhoidal haemorrhage | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxic skin eruption | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anuria | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oliguria | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|-----------------|--|--|
| Back pain | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal abscess | | | |
| subjects affected / exposed | 2 / 252 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometritis | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia infection | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia sepsis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Genital herpes | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Helicobacter infection | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis B | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaria | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 252 (0.79%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus inadequate control | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hyperglycaemia | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hyperkalaemia | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hyperuricaemia | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypervolaemia | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypocalcaemia | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoglycaemia | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hyponatraemia | | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metabolic acidosis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 252 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Combination GP2013+CVP | Combination MabThera+CVP | Maintenance GP2013 |
|---|---------------------------|-----------------------------|-----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 262 / 312 (83.97%) | 255 / 315 (80.95%) | 141 / 254 (55.51%) |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 41 / 312 (13.14%) | 37 / 315 (11.75%) | 5 / 254 (1.97%) |
| occurrences (all) | 73 | 61 | 9 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 22 / 312 (7.05%) | 15 / 315 (4.76%) | 12 / 254 (4.72%) |
| occurrences (all) | 28 | 17 | 15 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 18 / 312 (5.77%) | 12 / 315 (3.81%) | 5 / 254 (1.97%) |
| occurrences (all) | 19 | 12 | 6 |
| Headache | | | |
| subjects affected / exposed | 29 / 312 (9.29%) | 34 / 315 (10.79%) | 12 / 254 (4.72%) |
| occurrences (all) | 45 | 51 | 19 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 49 / 312 (15.71%) | 30 / 315 (9.52%) | 8 / 254 (3.15%) |
| occurrences (all) | 78 | 43 | 8 |
| Paraesthesia | | | |
| subjects affected / exposed | 24 / 312 (7.69%) | 44 / 315 (13.97%) | 7 / 254 (2.76%) |
| occurrences (all) | 33 | 61 | 7 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 26 / 312 (8.33%) | 23 / 315 (7.30%) | 6 / 254 (2.36%) |
| occurrences (all) | 39 | 33 | 7 |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|-------------------|-------------------|-------------------|
| Anaemia | | | |
| subjects affected / exposed | 25 / 312 (8.01%) | 28 / 315 (8.89%) | 2 / 254 (0.79%) |
| occurrences (all) | 55 | 58 | 2 |
| Leukopenia | | | |
| subjects affected / exposed | 23 / 312 (7.37%) | 25 / 315 (7.94%) | 11 / 254 (4.33%) |
| occurrences (all) | 56 | 57 | 15 |
| Neutropenia | | | |
| subjects affected / exposed | 78 / 312 (25.00%) | 91 / 315 (28.89%) | 32 / 254 (12.60%) |
| occurrences (all) | 177 | 220 | 41 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 30 / 312 (9.62%) | 31 / 315 (9.84%) | 12 / 254 (4.72%) |
| occurrences (all) | 40 | 46 | 14 |
| Fatigue | | | |
| subjects affected / exposed | 35 / 312 (11.22%) | 31 / 315 (9.84%) | 6 / 254 (2.36%) |
| occurrences (all) | 59 | 41 | 6 |
| Oedema peripheral | | | |
| subjects affected / exposed | 13 / 312 (4.17%) | 24 / 315 (7.62%) | 4 / 254 (1.57%) |
| occurrences (all) | 13 | 37 | 4 |
| Pyrexia | | | |
| subjects affected / exposed | 27 / 312 (8.65%) | 32 / 315 (10.16%) | 12 / 254 (4.72%) |
| occurrences (all) | 38 | 44 | 15 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 28 / 312 (8.97%) | 35 / 315 (11.11%) | 6 / 254 (2.36%) |
| occurrences (all) | 35 | 46 | 6 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 20 / 312 (6.41%) | 16 / 315 (5.08%) | 4 / 254 (1.57%) |
| occurrences (all) | 24 | 17 | 4 |
| Constipation | | | |
| subjects affected / exposed | 69 / 312 (22.12%) | 64 / 315 (20.32%) | 8 / 254 (3.15%) |
| occurrences (all) | 95 | 98 | 8 |
| Diarrhoea | | | |
| subjects affected / exposed | 39 / 312 (12.50%) | 33 / 315 (10.48%) | 11 / 254 (4.33%) |
| occurrences (all) | 55 | 48 | 14 |
| Nausea | | | |

| | | | |
|---|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 51 / 312 (16.35%) 77 | 42 / 315 (13.33%) 66 | 11 / 254 (4.33%) 11 |
| Vomiting subjects affected / exposed occurrences (all) | 22 / 312 (7.05%) 34 | 26 / 315 (8.25%) 38 | 6 / 254 (2.36%) 9 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 32 / 312 (10.26%) 40 | 37 / 315 (11.75%) 44 | 33 / 254 (12.99%) 38 |
| Dyspnoea subjects affected / exposed occurrences (all) | 16 / 312 (5.13%) 18 | 17 / 315 (5.40%) 24 | 5 / 254 (1.97%) 5 |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 31 / 312 (9.94%) 34 | 26 / 315 (8.25%) 27 | 1 / 254 (0.39%) 1 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 15 / 312 (4.81%) 17 | 19 / 315 (6.03%) 22 | 3 / 254 (1.18%) 5 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 19 / 312 (6.09%) 20 | 21 / 315 (6.67%) 27 | 9 / 254 (3.54%) 11 |
| Back pain subjects affected / exposed occurrences (all) | 26 / 312 (8.33%) 30 | 30 / 315 (9.52%) 45 | 14 / 254 (5.51%) 17 |
| Myalgia subjects affected / exposed occurrences (all) | 17 / 312 (5.45%) 22 | 20 / 315 (6.35%) 27 | 4 / 254 (1.57%) 4 |
| Pain in extremity subjects affected / exposed occurrences (all) | 19 / 312 (6.09%) 22 | 24 / 315 (7.62%) 31 | 7 / 254 (2.76%) 10 |
| Infections and infestations Influenza | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 16 / 312 (5.13%) 17 | 7 / 315 (2.22%) 8 | 7 / 254 (2.76%) 9 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 22 / 312 (7.05%) 25 | 22 / 315 (6.98%) 35 | 12 / 254 (4.72%) 15 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 27 / 312 (8.65%) 34 | 22 / 315 (6.98%) 33 | 14 / 254 (5.51%) 19 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 8 / 312 (2.56%) 9 | 10 / 315 (3.17%) 10 | 5 / 254 (1.97%) 7 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 17 / 312 (5.45%) 20 | 21 / 315 (6.67%) 25 | 3 / 254 (1.18%) 3 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 17 / 312 (5.45%) 28 | 22 / 315 (6.98%) 48 | 4 / 254 (1.57%) 4 |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 8 / 312 (2.56%) 9 | 18 / 315 (5.71%) 22 | 5 / 254 (1.97%) 5 |

| | | | |
|---|-------------------------|--|--|
| Non-serious adverse events | Maintenance MabThera | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 144 / 252 (57.14%) | | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction subjects affected / exposed occurrences (all) | 4 / 252 (1.59%) 11 | | |
| Vascular disorders | | | |
| Hypertension subjects affected / exposed occurrences (all) | 12 / 252 (4.76%) 13 | | |
| Nervous system disorders | | | |
| Dizziness | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 2 / 252 (0.79%) | | |
| occurrences (all) | 2 | | |
| Headache | | | |
| subjects affected / exposed | 14 / 252 (5.56%) | | |
| occurrences (all) | 18 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 2 / 252 (0.79%) | | |
| occurrences (all) | 3 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 4 / 252 (1.59%) | | |
| occurrences (all) | 5 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 5 / 252 (1.98%) | | |
| occurrences (all) | 7 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 252 (1.98%) | | |
| occurrences (all) | 5 | | |
| Leukopenia | | | |
| subjects affected / exposed | 5 / 252 (1.98%) | | |
| occurrences (all) | 9 | | |
| Neutropenia | | | |
| subjects affected / exposed | 16 / 252 (6.35%) | | |
| occurrences (all) | 21 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 11 / 252 (4.37%) | | |
| occurrences (all) | 11 | | |
| Fatigue | | | |
| subjects affected / exposed | 10 / 252 (3.97%) | | |
| occurrences (all) | 12 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 11 / 252 (4.37%) | | |
| occurrences (all) | 13 | | |
| Pyrexia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 13 / 252 (5.16%) | | |
| occurrences (all) | 15 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 7 / 252 (2.78%) | | |
| occurrences (all) | 9 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 7 / 252 (2.78%) | | |
| occurrences (all) | 9 | | |
| Constipation | | | |
| subjects affected / exposed | 10 / 252 (3.97%) | | |
| occurrences (all) | 13 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 18 / 252 (7.14%) | | |
| occurrences (all) | 19 | | |
| Nausea | | | |
| subjects affected / exposed | 8 / 252 (3.17%) | | |
| occurrences (all) | 8 | | |
| Vomiting | | | |
| subjects affected / exposed | 12 / 252 (4.76%) | | |
| occurrences (all) | 12 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 23 / 252 (9.13%) | | |
| occurrences (all) | 28 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 252 (1.59%) | | |
| occurrences (all) | 4 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 4 / 252 (1.59%) | | |
| occurrences (all) | 4 | | |

| | | | |
|---|---|--|--|
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 21 / 252 (8.33%) 26 14 / 252 (5.56%) 20 3 / 252 (1.19%) 4 14 / 252 (5.56%) 19 | | |
| Infections and infestations Influenza subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 8 / 252 (3.17%) 11 17 / 252 (6.75%) 29 25 / 252 (9.92%) 35 15 / 252 (5.95%) 28 | | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) Hyperuricaemia subjects affected / exposed occurrences (all) | 4 / 252 (1.59%) 4 9 / 252 (3.57%) 11 10 / 252 (3.97%) 14 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 27 February 2012 | The key purpose of this protocol amendment was to update and clearly define the attributes of the study inclusion and exclusion criteria, revise the recommended dose modification per current clinical practice, and change the primary ORR analysis from local to central blinded review of radiological response. |
| 21 January 2013 | The primary purpose of this amendment was to allow lymph node biopsy samples collected within 5 months of screening to establish and confirm the diagnosis of follicular lymphoma. As follicular lymphoma is a slowly progressing disease and lymph node biopsy is considered an invasive procedure, lymph node biopsy samples collected within 5 months of screening were allowed to confirm patient eligibility. To simplify the assessment and interpretation of tuberculosis testing at Screening, the status of active tuberculosis infection was assessed as per the local standard of care for patient eligibility. Furthermore, the population PK of GP2013 and MabThera was removed in the amendment as this analysis was not deemed necessary to compare the PK of GP2013 and MabThera. |
| 26 September 2013 | The primary reason for this protocol amendment was to add a planned interim analysis (based on specific health authority feedback) to support the regulatory filing of GP2013 with EMA and potentially other health authorities. |
| 10 November 2014 | this amendment was based on health authority feedback received in Feb-2014, which led to the removal of the planned interim analysis added in protocol amendment version 4.0. |
| 09 June 2016 | The amendment text clarified that blinded monitors, medical monitors, data management, investigator site staff, and patients would be kept blinded (with the exception of the coordinating investigator who has to sign the CSR for the Combination Phase) until the final DBL. |
| 23 February 2017 | This amendment described a Urgent Safety Measure that was issued on 22-Dec-2016. The clinical batch of GP2013 was quarantined due to out-of-specification findings in routine stability testing. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported