



Clinical trial results:

A Phase 3, Randomized, Double-Blind Study of PF-05280586 Versus Rituximab for the First-Line Treatment of Patients With CD20-Positive, Low Tumor Burden, Follicular Lymphoma

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2014-000132-41 |
| Trial protocol | BE GB DE ES IT PT AT HR GR |
| Global end of trial date | 19 April 2018 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v2 (current) |
| This version publication date | 31 March 2019 |
| First version publication date | 18 October 2018 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | B3281006 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02213263 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Study Name: REFLECTIONS |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pfizer Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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 | 25 June 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 October 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 April 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to compare the efficacy of PF-05280586 to rituximab-EU when administered as a first-line treatment to subjects with cluster of differentiation 20 (CD20)-positive, low tumor burden (LTB) follicular lymphoma (FL).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 30 September 2014 |
| 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 | Austria: 2 |
| Country: Number of subjects enrolled | Belarus: 3 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Brazil: 26 |
| Country: Number of subjects enrolled | Croatia: 6 |
| Country: Number of subjects enrolled | France: 14 |
| Country: Number of subjects enrolled | Georgia: 3 |
| Country: Number of subjects enrolled | Germany: 14 |
| Country: Number of subjects enrolled | Greece: 8 |
| Country: Number of subjects enrolled | India: 5 |
| Country: Number of subjects enrolled | Italy: 63 |
| Country: Number of subjects enrolled | Japan: 51 |
| Country: Number of subjects enrolled | Korea, Republic of: 11 |
| Country: Number of subjects enrolled | Lebanon: 3 |
| Country: Number of subjects enrolled | Mexico: 6 |
| Country: Number of subjects enrolled | Peru: 5 |
| Country: Number of subjects enrolled | Poland: 4 |
| Country: Number of subjects enrolled | Portugal: 13 |
| Country: Number of subjects enrolled | Puerto Rico: 1 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Romania: 6 |
| Country: Number of subjects enrolled | Russian Federation: 19 |
| Country: Number of subjects enrolled | South Africa: 7 |
| Country: Number of subjects enrolled | Spain: 35 |
| Country: Number of subjects enrolled | Switzerland: 4 |
| Country: Number of subjects enrolled | Thailand: 4 |
| Country: Number of subjects enrolled | Turkey: 16 |
| Country: Number of subjects enrolled | Ukraine: 10 |
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Country: Number of subjects enrolled | United States: 44 |
| Worldwide total number of subjects | 394 |
| EEA total number of subjects | 176 |

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) | 259 |
| From 65 to 84 years | 132 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 394 subjects were enrolled and randomized in 1:1 ratio to 1 of the 2 study treatment arms: PF-05280586 (Rituximab-Pfizer) and Rituximab-EU (MabThera®).

Period 1

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

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Rituximab-EU |

Arm description:

Subjects received Rituximab-EU intravenous (IV) infusion at a dose of 375 milligrams per meter square (mg/m²) on Days 1, 8, 15, and 22. The maximum dose that could be infused in 1 day was 1125 mg.

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

Dosage and administration details:

Subjects received Rituximab-EU IV infusion at a dose of 375 mg/m² on Days 1, 8, 15 and 22.

| | |
|------------------|-------------|
| Arm title | PF-05280586 |
|------------------|-------------|

Arm description:

Subjects received PF-05280586 IV infusion at a dose of 375 mg/m² on Days 1, 8, 15, and 22. The maximum dose that could be infused in 1 day was 1125 mg.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | PF-05280586 |
| Investigational medicinal product code | |
| Other name | Rituximab-Pfizer |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received PF-05280586 IV infusion at a dose of 375 mg/m² on Days 1, 8, 15 and 22.

| Number of subjects in period 1 | Rituximab-EU | PF-05280586 |
|--|--------------|-------------|
| Started | 198 | 196 |
| Treated | 197 | 196 |
| Completed | 170 | 170 |
| Not completed | 28 | 26 |
| Adverse events(AE) related to study drug | - | 2 |
| No longer willing to participate | 3 | 4 |
| Progressive disease | 20 | 14 |
| Lost to follow-up | - | 1 |
| AE not related to study drug | 1 | 1 |
| Insufficient clinical response | 4 | 3 |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Rituximab-EU |
|-----------------------|--------------|

Reporting group description:

Subjects received Rituximab-EU intravenous (IV) infusion at a dose of 375 milligrams per meter square (mg/m²) on Days 1, 8, 15, and 22. The maximum dose that could be infused in 1 day was 1125 mg.

| | |
|-----------------------|-------------|
| Reporting group title | PF-05280586 |
|-----------------------|-------------|

Reporting group description:

Subjects received PF-05280586 IV infusion at a dose of 375 mg/m² on Days 1, 8, 15, and 22. The maximum dose that could be infused in 1 day was 1125 mg.

| Reporting group values | Rituximab-EU | PF-05280586 | Total |
|------------------------|--------------|-------------|-------|
| Number of subjects | 198 | 196 | 394 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|-----|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 58.3 | 58.7 | |
| standard deviation | ± 12.8 | ± 12.1 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 106 | 110 | 216 |
| Male | 92 | 86 | 178 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 44 | 30 | 74 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 1 | 1 |
| White | 146 | 158 | 304 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 8 | 7 | 15 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 26 | 31 | 57 |
| Not Hispanic or Latino | 172 | 165 | 337 |
| Unknown or Not Reported | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|---|--------------|
| Reporting group title | Rituximab-EU |
| Reporting group description: Subjects received Rituximab-EU intravenous (IV) infusion at a dose of 375 milligrams per meter square (mg/m ²) on Days 1, 8, 15, and 22. The maximum dose that could be infused in 1 day was 1125 mg. | |
| Reporting group title | PF-05280586 |
| Reporting group description: Subjects received PF-05280586 IV infusion at a dose of 375 mg/m ² on Days 1, 8, 15, and 22. The maximum dose that could be infused in 1 day was 1125 mg. | |

Primary: Overall Response Rate (ORR): Percentage of Subjects With Overall Response (OR) at Week 26

| | |
|--|---|
| End point title | Overall Response Rate (ORR): Percentage of Subjects With Overall Response (OR) at Week 26 |
| End point description: ORR was defined as the percentage of subjects who achieved complete response (CR) or partial response (PR) in accordance with the revised response criteria for malignant lymphoma (Cheson 2007). CR was defined as disappearance of all evidence of disease. PR was defined as regression of measurable disease and no new sites. Intent to treatment (ITT) population included all subjects who were randomized. | |
| End point type | Primary |
| End point timeframe: Week 26 | |

| End point values | Rituximab-EU | PF-05280586 | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198 | 196 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 70.7 (63.8 to 76.9) | 75.5 (68.9 to 81.4) | | |

Statistical analyses

| | |
|--|---------------------------------|
| Statistical analysis title | PF-05280586 versus Rituximab-EU |
| Statistical analysis description: Difference in ORR between PF-05280586 and rituximab-EU was computed using the stratified Mantel-Haenszel method. The 95 percent (%) confidence interval (CI) for the difference was calculated using the asymptotic stratified method proposed by Miettinen and Nurminen. | |
| Comparison groups | Rituximab-EU v PF-05280586 |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 394 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[1] |
| Parameter estimate | Difference in ORR |
| Point estimate | 4.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.16 |
| upper limit | 13.47 |

Notes:

[1] - Equivalence was tested within the pre-specified margins of (-16%, 16%) 95% confidence interval.

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

An AE was any untoward medical occurrence in subjects who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events after first dose of study drug that were absent before treatment or that worsened relative to pretreatment state. AEs included both serious and non-serious AEs. Safety population included all subjects who received at least 1 dose of any study drug.

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

End point timeframe:

Baseline up to Week 52

| End point values | Rituximab-EU | PF-05280586 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 197 | 196 | | |
| Units: subjects | | | | |
| AEs | 145 | 156 | | |
| SAEs | 15 | 17 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Related Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment-Related Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience

(immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events after first dose of study drug that were absent before treatment or that worsened relative to pretreatment state. Relatedness to treatment was assessed by investigator. AEs included both serious and non-serious AEs. Safety population included all subjects who received at least 1 dose of any study drug.

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Week 52 | |

| End point values | Rituximab-EU | PF-05280586 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 197 | 196 | | |
| Units: subjects | | | | |
| AEs | 94 | 86 | | |
| SAEs | 2 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 3 or Higher Treatment-Emergent Adverse Events (AEs) as Graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03

| | |
|-----------------|--|
| End point title | Number of Subjects With Grade 3 or Higher Treatment-Emergent Adverse Events (AEs) as Graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 |
|-----------------|--|

End point description:

An AE was any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. Grade 1=Mild, asymptomatic or mild symptoms, Grade 2=Moderate; minimal, local or noninvasive intervention indicated, Grade 3 (Severe) events=unacceptable or intolerable events, significantly interrupting usual daily activity, require systemic drug therapy/other treatment, Grade 4 (Life threatening) events caused subject to be in imminent danger of death, Grade 5 = death. Treatment-emergent were events after first dose of study drug that were absent before treatment or that worsened relative to pretreatment state. Safety population included all subjects who received at least 1 dose of any study drug.

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Week 52 | |

| End point values | Rituximab-EU | PF-05280586 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 197 | 196 | | |
| Units: subjects | 26 | 28 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events (AEs) as Graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03

| | |
|-----------------|--|
| End point title | Number of Subjects With Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events (AEs) as Graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 |
|-----------------|--|

End point description:

Treatment-related AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. Grade 1=Mild, asymptomatic or mild symptoms, Grade 2=Moderate; minimal, local or noninvasive intervention indicated; Grade 3 (Severe) events=unacceptable or intolerable events, significantly interrupting usual daily activity, require systemic drug therapy/other treatment. Grade 4 (Life-threatening) events caused subject to be in imminent danger of death. Grade 5 = death. Treatment-emergent were events after first dose of study drug that were absent before treatment or that worsened relative to pretreatment state. Safety population included all subjects who received at least 1 dose of any study drug.

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Week 52 | |

| | | | | |
|-----------------------------|-----------------|-----------------|--|--|
| End point values | Rituximab-EU | PF-05280586 | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 197 | 196 | | |
| Units: subjects | 8 | 9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Laboratory Abnormalities

| | |
|-----------------|---|
| End point title | Number of Subjects With Clinically Significant Laboratory Abnormalities |
|-----------------|---|

End point description:

Criteria for clinically significant laboratory abnormalities included total bilirubin (TB) less than (<) 2*upper limit of normal (ULN), alanine aminotransferase (ALT)<3*ULN; TB<2*ULN, ALT more than (>) 3 equal to (=) *ULN; TB<2*ULN, aspartate aminotransferase (AST)<3*ULN; TB<2*ULN, AST>=3*ULN. Data for only those categories are reported for which at least one subject had clinically significant laboratory abnormality. Safety population included all subjects who received at least 1 dose of any study drug. Here, 'Number of subjects analysed' signifies number of subjects evaluable for this endpoint.

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

End point timeframe:
Baseline up to Week 52

| End point values | Rituximab-EU | PF-05280586 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 197 | 195 | | |
| Units: subjects | | | | |
| TB<2*ULN, ALT<3*ULN | 194 | 192 | | |
| TB<2*ULN, ALT>=3*ULN | 3 | 3 | | |
| TB<2*ULN, AST<3*ULN | 196 | 195 | | |
| TB<2*ULN, AST>=3*ULN | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure (TTF)

| | |
|-----------------|---------------------------------|
| End point title | Time to Treatment Failure (TTF) |
|-----------------|---------------------------------|

End point description:

TTF was defined as the time (in months) from date of randomization to first progression of disease based on central review, death due to any cause, or permanent discontinuation from treatment, or discontinuation from study for any reason, whichever came first. Progression was defined as any new lesion or increase by greater than equal to (\geq) 50 percent (%) of previously involved sites from nadir. TTF was calculated using Kaplan-Meier method. ITT population included all subjects who were randomized. Here, '99999' signifies that due to smaller number of subjects with an event, median and upper limit of 95% CI could not be calculated. Here, 'Number of subjects analysed' signifies number of subjects evaluable for this endpoint.

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

End point timeframe:

From randomization until disease progression, death or permanent discontinuation from treatment/study due to any reason, or up to Week 52

| End point values | Rituximab-EU | PF-05280586 | | |
|----------------------------------|---------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 54 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 18.9 (12.6 to 18.9) | 99999 (12.3 to 99999) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | PF-05280586 versus Rituximab-EU |
|----------------------------|---------------------------------|

Statistical analysis description:

Hazard ratio and its confidence intervals (CIs) were estimated from Cox Proportional hazards model stratified by FLIPI2 risk categorization.

| | |
|---|----------------------------|
| Comparison groups | Rituximab-EU v PF-05280586 |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.45 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.163 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.786 |
| upper limit | 1.72 |

Notes:

[2] - A log-rank test stratified by Follicular Lymphoma International Prognostic Index 2 (FLIPI2) risk was used to compare the treatment groups with respect to TTF at a 2-sided alpha level of 0.05.

Secondary: Progression-Free Survival (PFS)

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|---|---------------------------------|
| End point title | Progression-Free Survival (PFS) |
| End point description: | |
| PFS was defined as the time (in months) from date of randomization to first progression of disease (PD) based on central review or death due to any cause in the absence of documented PD. PD was defined as any new lesion or increase by $\geq 50\%$ of previously involved sites from nadir. PFS was calculated using Kaplan-Meier method. ITT population included all subjects who were randomized. Here, '99999' signifies that due to smaller number of subjects with an event, median and 95% CI could not be calculated. Here, 'Number of subjects analysed' signifies number of subjects evaluable for this endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until disease progression or death due to any cause or up to Week 52 | |

| End point values | Rituximab-EU | PF-05280586 | | |
|----------------------------------|---------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 37 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 18.9 (12.6 to 18.9) | 99999 (99999 to 99999) | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | PF-05280586 versus Rituximab-EU |
| Statistical analysis description: | |
| Hazard ratio and its CIs were estimated from Cox Proportional hazards model stratified by FLIPI2 risk categorization. | |
| Comparison groups | Rituximab-EU v PF-05280586 |

| | |
|---|------------------------|
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.189 ^[3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.393 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.847 |
| upper limit | 2.291 |

Notes:

[3] - A log-rank test stratified by FLIPI2 risk was used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.05.

Secondary: Percentage of Subjects With Complete Remission (CR) at Week 26

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Complete Remission (CR) at Week 26 |
|-----------------|--|

End point description:

Complete Remission (CR) was defined as disappearance of all evidence of disease. CR was assessed by central review based on scans done at Week 26. ITT population included all subjects who were randomized.

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

End point timeframe:

Week 26

| End point values | Rituximab-EU | PF-05280586 | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198 | 196 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 28.3 (22.1 to 35.1) | 26.0 (20.0 to 32.8) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | PF-05280586 versus Rituximab-EU |
|----------------------------|---------------------------------|

Statistical analysis description:

Difference in CR between PF-05280586 and rituximab-EU was computed using the stratified Mantel-Haenszel method. The 95% confidence interval for the difference was calculated using the asymptotic stratified method proposed by Miettinen and Nurminen.

| | |
|-------------------|----------------------------|
| Comparison groups | Rituximab-EU v PF-05280586 |
|-------------------|----------------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 394 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.09 |
| upper limit | 6.5 |

Secondary: Duration of Response (DOR)

| | |
|---|----------------------------|
| End point title | Duration of Response (DOR) |
| End point description: | |
| DOR was defined as the time (in months) from date of the first documentation of overall response (CR or PR) to the first documentation of progressive disease (PD) based on central review or to death due to any cause in the absence of documented PD. CR was defined as disappearance of all evidence of disease. PR was defined as regression of measureable disease and no new sites. PD was defined as any new lesion or increase by $\geq 50\%$ of previously involved sites from nadir. DOR was calculated using Kaplan-Meier method. The response-evaluable population was defined as all randomized subjects who received at least 1 dose of study drug, had adequate disease assessment at baseline, and at least 1 post baseline response assessment. Here, '99999' signifies that due to small number of subjects with an event, median and upper limit of 95% CI could not be calculated. Here, 'Number of subjects analysed' signifies number of subjects evaluable for this endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of first documentation of overall response to first documentation of PD or to death due to any cause in absence of PD or up to Week 52 | |

| End point values | Rituximab-EU | PF-05280586 | | |
|----------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 28 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 15.4 (10.4 to 15.4) | 99999 (9.6 to 99999) | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | PF-05280586 versus Rituximab-EU |
| Statistical analysis description: | |
| Hazard ratio and its CIs were estimated from Cox Proportional hazards model stratified by FLIPI2 risk categorization. | |
| Comparison groups | Rituximab-EU v PF-05280586 |

| | |
|---|------------------------|
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.185 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.492 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.823 |
| upper limit | 2.704 |

Notes:

[4] - A log-rank test stratified by FLIPI2 risk was used to compare the treatment groups with respect to DOR at a 2-sided alpha level of 0.05.

Secondary: Overall Survival

| | |
|--|------------------|
| End point title | Overall Survival |
| End point description: | |
| Overall survival was defined as the time (in months) from date of randomization to death due to any cause. For subjects who were alive, overall survival was censored at the last contact. Overall survival was calculated using Kaplan-Meier method. ITT population included all subjects who were randomized. Here, '99999' signifies that due to single subject with an event, median and 95% CI could not be calculated. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until death due to any cause or up to Week 52 | |

| End point values | Rituximab-EU | PF-05280586 | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198 | 196 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 18.9 (-99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | PF-05280586 versus Rituximab EU |
| Statistical analysis description: | |
| Hazard ratio and its CIs were estimated from Cox Proportional hazards model stratified by FLIPI2 risk categorization. | |
| Comparison groups | Rituximab-EU v PF-05280586 |

| | |
|---|------------------------|
| Number of subjects included in analysis | 394 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.319 ^[5] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 2.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 99999 |

Notes:

[5] - A log-rank test stratified by FLIPI2 risk was used to compare the treatment groups with respect to overall survival at a 2-sided alpha level of 0.05.

Secondary: Maximum Observed Serum Concentration (Cmax) of PF-05280586 and Rituximab-EU

| | |
|-----------------|---|
| End point title | Maximum Observed Serum Concentration (Cmax) of PF-05280586 and Rituximab-EU |
|-----------------|---|

End point description:

The pharmacokinetic analysis set (PKAS) included subjects who received at least 1 dose of any study drug and who provided at least one post-dose pharmacokinetic concentration. Here, 'Number of subjects analysed' signifies number of subjects evaluable for this endpoint.

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

End point timeframe:

Predose (within 4 hours prior to start of infusion) on Days 1, 8, 15 and 22; within 15 minutes prior to end of infusion on Days 1 and 22

| End point values | Rituximab-EU | PF-05280586 | | |
|---|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 132 | 138 | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | 334848.88 (± 33) | 337708.05 (± 36) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed (Trough) Serum Concentration (Ctrough) of PF-05280586 and Rituximab-EU

| | |
|-----------------|---|
| End point title | Minimum Observed (Trough) Serum Concentration (Ctrough) of PF-05280586 and Rituximab-EU |
|-----------------|---|

End point description:

The pharmacokinetic analysis set (PKAS) included subjects who received at least 1 dose of any study drug and who provided at least one post-dose pharmacokinetic concentration. Here, 'Number of subjects analysed' signifies number of subjects evaluable for this endpoint and "n" signifies subjects evaluable for this endpoint at specified time points.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Predose (within 4 hours prior to the start of dosing) on Days 1, 8, 15, and 22 | |

| End point values | Rituximab-EU | PF-05280586 | | |
|---|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 197 | 196 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Day 1 (n=195,192) | 0.01 (± 577) | 0.01 (± 1320) | | |
| Day 8 (n=197,194) | 62311.74 (± 47) | 66669.15 (± 45) | | |
| Day 15 (n=194,193) | 109619.73 (± 43) | 119026.91 (± 29) | | |
| Day 22 (n=194,194) | 144650.79 (± 68) | 158294.91 (± 32) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cluster of Differentiation (CD) 19-Positive B-Cell Counts

| | |
|--|---|
| End point title | Cluster of Differentiation (CD) 19-Positive B-Cell Counts |
| End point description: | |
| The modified ITT (mITT) Population included all subjects who were randomized and received at least 1 dose of any study drug. Here, 'Number of subjects analysed' signifies number of subjects evaluable for this endpoint and "n" signifies subjects evaluable for this endpoint at specified time points. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 2, 3, 4, 5, 13, 26, 39 and 52 | |

| End point values | Rituximab-EU | PF-05280586 | | |
|-------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 197 | 196 | | |
| Units: cells per microliter | | | | |
| median (full range (min-max)) | | | | |
| Baseline (n= 174,175) | 114.2 (0.6 to 2313.1) | 119.9 (10.9 to 1310.1) | | |
| Week 2 (n=168,159) | 1.0 (0.2 to 44.8) | 0.8 (0.2 to 136.0) | | |
| Week 3 (n= 149,149) | 0.6 (0.2 to 19.5) | 0.6 (0.2 to 248.1) | | |
| Week 4 (n=143,114) | 0.5 (0.2 to 8.7) | 0.4 (0.2 to 144.5) | | |

| | | | | |
|---------------------|---------------------|---------------------|--|--|
| Week 5 (n=118,128) | 0.5 (0.2 to 19.0) | 0.4 (0.2 to 19.0) | | |
| Week 13 (n=106,103) | 0.5 (0.2 to 130.7) | 0.5 (0.2 to 183.7) | | |
| Week 26 (n=142,123) | 1.2 (0.2 to 496.5) | 0.9 (0.2 to 329.8) | | |
| Week 39 (n=157,135) | 21.7 (0.3 to 341.0) | 10.7 (0.2 to 442.7) | | |
| Week 52 (n=151,147) | 60.8 (1.4 to 413.0) | 51.6 (0.3 to 597.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Anti-Drug Antibodies (ADAs) and Neutralizing Antibodies (NABs)

| | |
|-----------------|---|
| End point title | Number of Subjects With Positive Anti-Drug Antibodies (ADAs) and Neutralizing Antibodies (NABs) |
|-----------------|---|

End point description:

Human serum ADA samples were analysed for the presence or absence of anti-rituximab antibodies or anti-PF-05280586 antibodies using the validated drug-specific assay with a tiered approach using screening, confirmation and titer/quantitation. Human NAb serum samples testing ADA positive were analysed for the presence or absence of neutralizing anti-rituximab antibody and neutralizing anti-PF-05280586 antibody using the validated drug-specific assay with a tiered approach using screening, confirmation and titer/quantitation. Subjects with their ADA titer ≥ 1.88 were considered to be ADA positive. Only subjects with a positive ADA result were further tested for NAb. Safety population included all subjects who received at least 1 dose of any study drug. Here, 'Number of subjects analysed' signifies number of subjects evaluable for this endpoint. Here, 'n' signifies number of subjects evaluable for this endpoint for specified categories.

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

End point timeframe:

Baseline up to Week 52

| End point values | Rituximab-EU | PF-05280586 | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 197 | 195 | | |
| Units: subjects | | | | |
| ADA Positive (n = 197, 195) | 39 | 43 | | |
| NAB Positive (n = 39, 43) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Immune-Based Adverse Effects

| | |
|-----------------|---|
| End point title | Number of Subjects Reporting Immune-Based Adverse Effects |
|-----------------|---|

End point description:

Immune-based adverse effects included infusion related reaction (IRR), adverse events which fulfill Sampson's criteria, and adverse events which belong to the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) anaphylaxis or hypersensitivity reactions. The Safety analysis population include all subjects who received at least 1 dose of any study treatment. Potential allergic and anaphylactic reactions were identified programmatically based on the criteria of Sampson et al, (2006).

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

End point timeframe:

Baseline up to Week 52

| End point values | Rituximab-EU | PF-05280586 | | |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 197 | 196 | | |
| Units: subjects | | | | |
| IRR reported | 59 | 49 | | |
| AE based on Sampson's criteria | 17 | 17 | | |
| Anaphylaxis/Hypersensitivity (SMQ) | 48 | 39 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of study (up to 52 weeks)

Adverse event reporting additional description:

Same event may appear as both an adverse event (AE) and serious adverse event (SAE). However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event. Analysis was performed on safety population.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | PF-05280586 |
|-----------------------|-------------|

Reporting group description:

Subjects received PF-05280586 IV infusion at a dose of 375 mg/m² on Day 1, 8, 15, and 22. The maximum dose that could be infused in 1 day was 1125 mg.

| | |
|-----------------------|--------------|
| Reporting group title | Rituximab-EU |
|-----------------------|--------------|

Reporting group description:

Subjects received Rituximab-EU IV infusion at a dose of 375 mg/m² on Day 1, 8, 15, and 22. The maximum dose that could be infused in 1 day was 1125 mg.

| Serious adverse events | PF-05280586 | Rituximab-EU | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 17 / 196 (8.67%) | 15 / 197 (7.61%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma stage I | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine cancer | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon adenoma | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Intracardiac thrombus | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Disease progression | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Serum sickness | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesenteric artery stenosis | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyarthritis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Spinal column stenosis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis B | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney infection | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral sinusitis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | PF-05280586 | Rituximab-EU | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 153 / 196 (78.06%) | 143 / 197 (72.59%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 2 / 197 (1.02%) | |
| occurrences (all) | 1 | 2 | |
| Infected neoplasm | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Lung adenocarcinoma stage I | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Non-Hodgkin's lymphoma | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Meningioma | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) | |
| occurrences (all) | 0 | 2 | |
| Flushing | | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed | 1 / 196 (0.51%) | 4 / 197 (2.03%) | |
| occurrences (all) | 1 | 4 | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 2 / 197 (1.02%) | |
| occurrences (all) | 1 | 2 | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 196 (2.55%) | 7 / 197 (3.55%) | |
| occurrences (all) | 9 | 13 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 197 (0.51%) | |
| occurrences (all) | 2 | 1 | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 9 / 196 (4.59%) | 13 / 197 (6.60%) | |
| occurrences (all) | 11 | 15 | |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Catheter site related reaction | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Chest discomfort | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 197 (0.51%) | |
| occurrences (all) | 2 | 1 | |
| Chest pain | | | |

| | | |
|---------------------------------------|------------------|------------------|
| subjects affected / exposed | 2 / 196 (1.02%) | 3 / 197 (1.52%) |
| occurrences (all) | 2 | 3 |
| Chills | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 3 / 197 (1.52%) |
| occurrences (all) | 4 | 4 |
| Discomfort | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Face oedema | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Facial pain | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 2 |
| Fatigue | | |
| subjects affected / exposed | 12 / 196 (6.12%) | 13 / 197 (6.60%) |
| occurrences (all) | 15 | 16 |
| Feeling abnormal | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 2 |
| Feeling cold | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Feeling hot | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 2 / 197 (1.02%) |
| occurrences (all) | 3 | 2 |
| Generalised oedema | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 0 / 197 (0.00%) |
| occurrences (all) | 2 | 0 |
| Influenza like illness | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 4 / 197 (2.03%) |
| occurrences (all) | 2 | 4 |
| Infusion site bruising | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| General physical health deterioration | | |

| | | |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Infusion site erythema | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Infusion site extravasation | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Infusion site pain | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 2 | 0 |
| Malaise | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 0 / 197 (0.00%) |
| occurrences (all) | 6 | 0 |
| Non-cardiac chest pain | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Oedema | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 197 (0.51%) |
| occurrences (all) | 2 | 1 |
| Oedema peripheral | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 7 / 197 (3.55%) |
| occurrences (all) | 2 | 7 |
| Pain | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 3 / 197 (1.52%) |
| occurrences (all) | 3 | 7 |
| Peripheral swelling | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Pyrexia | | |
| subjects affected / exposed | 11 / 196 (5.61%) | 11 / 197 (5.58%) |
| occurrences (all) | 11 | 12 |
| Suprapubic pain | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Swelling | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Immune system disorders | | | |
| Contrast media allergy | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 197 (0.51%) | |
| occurrences (all) | 2 | 1 | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Hypogammaglobulinaemia | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Social circumstances | | | |
| Menopause | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Breast pain | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Breast tenderness | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) | |
| occurrences (all) | 1 | 1 | |
| Genital burning sensation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) | |
| occurrences (all) | 1 | 2 | |
| Prostatitis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Scrotal pain | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Testicular pain | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 0 / 197 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Vulvovaginal inflammation | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vulvovaginal pain | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Cough | | | |

| | | |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 11 / 196 (5.61%) | 11 / 197 (5.58%) |
| occurrences (all) | 13 | 11 |
| Dry throat | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 197 (0.51%) |
| occurrences (all) | 2 | 1 |
| Dysphonia | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) |
| occurrences (all) | 0 | 2 |
| Dyspnoea | | |
| subjects affected / exposed | 6 / 196 (3.06%) | 8 / 197 (4.06%) |
| occurrences (all) | 6 | 8 |
| Dyspnoea exertional | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Emphysema | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Epistaxis | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Hiccups | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hyperventilation | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Laryngeal discomfort | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Laryngeal inflammation | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Laryngeal oedema | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) |
| occurrences (all) | 0 | 2 |
| Laryngeal pain | | |

| | | |
|-------------------------------------|-----------------|------------------|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Lung disorder | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Nasal congestion | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 197 (0.51%) |
| occurrences (all) | 2 | 1 |
| Nasal discomfort | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Nasal pruritus | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Oropharyngeal discomfort | | |
| subjects affected / exposed | 4 / 196 (2.04%) | 1 / 197 (0.51%) |
| occurrences (all) | 4 | 1 |
| Paranasal sinus mucosal hypertrophy | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Oropharyngeal pain | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 10 / 197 (5.08%) |
| occurrences (all) | 2 | 12 |
| Pharyngeal erythema | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 0 / 197 (0.00%) |
| occurrences (all) | 3 | 0 |
| Pharyngeal inflammation | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pharyngeal oedema | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Pharyngeal paraesthesia | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 197 (0.51%) |
| occurrences (all) | 2 | 1 |
| Productive cough | | |

| | | |
|--------------------------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 197 (0.51%) |
| occurrences (all) | 2 | 1 |
| Pulmonary embolism | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Respiratory disorder | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Rhinalgia | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Rhinitis allergic | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Rhinorrhoea | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Sleep apnoea syndrome | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Suffocation feeling | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Throat tightness | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Tonsillar disorder | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Tonsillar erythema | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Tonsillar hypertrophy | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Upper respiratory tract inflammation | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 196 (0.51%) | 3 / 197 (1.52%) | |
| occurrences (all) | 1 | 4 | |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sneezing | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinus disorder | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Throat irritation | | | |
| subjects affected / exposed | 14 / 196 (7.14%) | 10 / 197 (5.08%) | |
| occurrences (all) | 15 | 10 | |
| Psychiatric disorders | | | |
| Affect lability | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Agitation | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Anxiety | | | |
| subjects affected / exposed | 6 / 196 (3.06%) | 7 / 197 (3.55%) | |
| occurrences (all) | 6 | 8 | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Depression | | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 2 / 197 (1.02%) | |
| occurrences (all) | 4 | 2 | |
| Gastrointestinal somatic symptom disorder | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Irritability | | | |

| | | | |
|---|----------------------|-----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 1 / 197 (0.51%) 1 | |
| Insomnia subjects affected / exposed occurrences (all) | 5 / 196 (2.55%) 6 | 8 / 197 (4.06%) 18 | |
| Panic attack subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Restlessness subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 | |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 3 / 197 (1.52%) 3 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 1 / 197 (0.51%) 1 | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Blood glucose increased subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 3 / 196 (1.53%) 3 | 1 / 197 (0.51%) 1 | |
| Blood potassium increased subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 2 | |
| Blood pressure decreased | | | |

| | | |
|---|-----------------|-----------------|
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) |
| occurrences (all) | 0 | 2 |
| Blood pressure increased | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 2 | 1 |
| Blood thyroid stimulating hormone increased | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood urine present | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| C-reactive protein increased | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Gamma-glutamyltransferase increased | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Lymphocyte count decreased | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 2 |
| Neutrophil count decreased | | |
| subjects affected / exposed | 5 / 196 (2.55%) | 0 / 197 (0.00%) |
| occurrences (all) | 5 | 0 |
| Neutrophil count increased | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Serum ferritin decreased | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Weight decreased | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| White blood cell count decreased | | |

| | | | |
|--|-------------------|-------------------|--|
| subjects affected / exposed | 4 / 196 (2.04%) | 1 / 197 (0.51%) | |
| occurrences (all) | 4 | 1 | |
| Breath sounds abnormal | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) | |
| occurrences (all) | 1 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Bone contusion | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Chest injury | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) | |
| occurrences (all) | 1 | 1 | |
| Contusion | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 197 (0.51%) | |
| occurrences (all) | 2 | 1 | |
| Fall | | | |
| subjects affected / exposed | 5 / 196 (2.55%) | 2 / 197 (1.02%) | |
| occurrences (all) | 5 | 2 | |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) | |
| occurrences (all) | 0 | 2 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 49 / 196 (25.00%) | 58 / 197 (29.44%) | |
| occurrences (all) | 58 | 63 | |
| Laceration | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) | |
| occurrences (all) | 0 | 2 | |
| Limb injury | | | |

| | | |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 196 (1.02%) | 0 / 197 (0.00%) |
| occurrences (all) | 2 | 0 |
| Neck injury | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Post procedural haemorrhage | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Road traffic accident | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Skin abrasion | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Suture related complication | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Suture rupture | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Tendon rupture | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Thermal burn | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Upper limb fracture | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Wound complication | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) |
| occurrences (all) | 0 | 2 |
| Wrist fracture | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Incision site pain | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 0 / 197 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Palpitations | | | |
| subjects affected / exposed | 5 / 196 (2.55%) | 2 / 197 (1.02%) | |
| occurrences (all) | 6 | 2 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) | |
| occurrences (all) | 0 | 2 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 6 / 197 (3.05%) | |
| occurrences (all) | 2 | 8 | |
| Burning sensation | | | |

| | | |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Dysgeusia | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Head discomfort | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Headache | | |
| subjects affected / exposed | 16 / 196 (8.16%) | 19 / 197 (9.64%) |
| occurrences (all) | 18 | 31 |
| Hypoaesthesia | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Hypotonia | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Intercostal neuralgia | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 2 | 0 |
| Migraine | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Lethargy | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 3 | 0 |
| Neuralgia | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Nerve compression | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Neuropathy peripheral | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Paraesthesia | | |

| | | | |
|--------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 196 (1.02%) | 3 / 197 (1.52%) | |
| occurrences (all) | 2 | 3 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Somnolence | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 3 / 197 (1.52%) | |
| occurrences (all) | 5 | 6 | |
| Restless legs syndrome | | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 1 / 197 (0.51%) | |
| occurrences (all) | 3 | 1 | |
| Speech disorder | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tension headache | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) | |
| occurrences (all) | 1 | 1 | |
| Lymph node pain | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) | |
| occurrences (all) | 1 | 1 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 3 / 197 (1.52%) | |
| occurrences (all) | 1 | 3 | |

| | | | |
|--|----------------------|----------------------|--|
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 | |
| Ear and labyrinth disorders | | | |
| Ear discomfort subjects affected / exposed occurrences (all) | 2 / 196 (1.02%) 3 | 0 / 197 (0.00%) 0 | |
| Ear disorder subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Ear pain subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 1 / 197 (0.51%) 1 | |
| Ear pruritus subjects affected / exposed occurrences (all) | 3 / 196 (1.53%) 4 | 2 / 197 (1.02%) 2 | |
| Hypoacusis subjects affected / exposed occurrences (all) | 2 / 196 (1.02%) 2 | 2 / 197 (1.02%) 2 | |
| Tinnitus subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 1 / 197 (0.51%) 1 | |
| Vertigo subjects affected / exposed occurrences (all) | 2 / 196 (1.02%) 2 | 3 / 197 (1.52%) 3 | |
| Vertigo positional subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 | |
| Eye disorders | | | |
| Accommodation disorder subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Cataract subjects affected / exposed occurrences (all) | 2 / 196 (1.02%) 2 | 1 / 197 (0.51%) 2 | |
| Conjunctival disorder | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Dry eye | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) | |
| occurrences (all) | 0 | 2 | |
| Erythema of eyelid | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye pruritus | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 3 / 197 (1.52%) | |
| occurrences (all) | 0 | 3 | |
| Lacrimation increased | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Meibomianitis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Entropion | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) | |
| occurrences (all) | 1 | 1 | |
| Abdominal pain | | | |
| subjects affected / exposed | 7 / 196 (3.57%) | 3 / 197 (1.52%) | |
| occurrences (all) | 12 | 3 | |

| | | |
|---|------------------------|------------------------|
| Abdominal pain lower subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 9 / 196 (4.59%) 9 | 5 / 197 (2.54%) 7 |
| Cheilitis subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 |
| Chronic gastritis subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 |
| Colitis subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 8 / 196 (4.08%) 9 | 8 / 197 (4.06%) 9 |
| Dental caries subjects affected / exposed occurrences (all) | 2 / 196 (1.02%) 2 | 0 / 197 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 14 / 196 (7.14%) 16 | 12 / 197 (6.09%) 15 |
| Diverticulum intestinal subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 |
| Dry mouth subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 |
| Dyspepsia subjects affected / exposed occurrences (all) | 5 / 196 (2.55%) 6 | 2 / 197 (1.02%) 2 |
| Dysphagia subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 |

| | | |
|--------------------------------------|-----------------|-----------------|
| Enterocolitis | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Faeces soft | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Flatulence | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Functional gastrointestinal disorder | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Gastritis | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gastrointestinal disorder | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 0 / 197 (0.00%) |
| occurrences (all) | 3 | 0 |
| Gastrooesophageal reflux disease | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gingival pain | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Gingival swelling | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Haematochezia | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Haemorrhoids | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) |
| occurrences (all) | 0 | 2 |
| Inguinal hernia | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |

| | | |
|-----------------------------|------------------|------------------|
| Lip oedema | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Mouth swelling | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nausea | | |
| subjects affected / exposed | 15 / 196 (7.65%) | 17 / 197 (8.63%) |
| occurrences (all) | 19 | 22 |
| Odynophagia | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 2 |
| Oral discomfort | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Oral mucosal erythema | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Paraesthesia oral | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Periodontal disease | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Rectal haemorrhage | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Salivary gland pain | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Stomatitis | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 3 / 197 (1.52%) |
| occurrences (all) | 0 | 6 |
| Swollen tongue | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | | |
|--|----------------------|----------------------|--|
| Tooth disorder subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Toothache subjects affected / exposed occurrences (all) | 2 / 196 (1.02%) 3 | 2 / 197 (1.02%) 2 | |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 196 (1.53%) 4 | 7 / 197 (3.55%) 7 | |
| Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 | |
| Hepatocellular injury subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Angioedema subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Asteatosis subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 | |
| Blister subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 | |
| Dermatitis subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 | |
| Dermatitis contact | | | |

| | | |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Drug eruption | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Dry skin | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Eczema | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 3 / 197 (1.52%) |
| occurrences (all) | 1 | 3 |
| Erythema | | |
| subjects affected / exposed | 7 / 196 (3.57%) | 2 / 197 (1.02%) |
| occurrences (all) | 7 | 2 |
| Hyperhidrosis | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 3 / 197 (1.52%) |
| occurrences (all) | 4 | 4 |
| Hyperkeratosis | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Intertrigo | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nail disorder | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Neurodermatitis | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Night sweats | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Pruritus allergic | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Rash | | |

| | | |
|-----------------------------|------------------|-------------------|
| subjects affected / exposed | 10 / 196 (5.10%) | 8 / 197 (4.06%) |
| occurrences (all) | 14 | 9 |
| Rash erythematous | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Rash maculo-papular | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Rash pruritic | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 0 / 197 (0.00%) |
| occurrences (all) | 2 | 0 |
| Scab | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Seborrhoeic dermatitis | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Skin burning sensation | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Skin lesion | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 2 / 197 (1.02%) |
| occurrences (all) | 1 | 2 |
| Swelling face | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Urticaria | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 6 / 197 (3.05%) |
| occurrences (all) | 3 | 6 |
| Pruritus | | |
| subjects affected / exposed | 13 / 196 (6.63%) | 22 / 197 (11.17%) |
| occurrences (all) | 14 | 23 |
| Pruritus generalised | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Scar pain | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 | |
| Renal and urinary disorders | | | |
| Bladder spasm | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Calculus bladder | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Dysuria | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 1 / 197 (0.51%) | |
| occurrences (all) | 2 | 1 | |
| Nocturia | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Renal pain | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Strangury | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Urinary tract pain | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Hypothyroidism | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) | |
| occurrences (all) | 0 | 2 | |
| Thyroid cyst | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 7 / 196 (3.57%) | 6 / 197 (3.05%) | |
| occurrences (all) | 8 | 8 | |
| Bone loss | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Back pain | | | |
| subjects affected / exposed | 8 / 196 (4.08%) | 10 / 197 (5.08%) | |
| occurrences (all) | 8 | 11 | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 3 / 197 (1.52%) | |
| occurrences (all) | 0 | 3 | |
| Costochondritis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Groin pain | | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 2 / 197 (1.02%) | |
| occurrences (all) | 3 | 3 | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 2 / 197 (1.02%) | |
| occurrences (all) | 1 | 3 | |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Joint effusion | | | |

| | | |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Joint stiffness | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Joint swelling | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Muscle contracture | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Muscle spasms | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Muscle twitching | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Muscular weakness | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 2 / 197 (1.02%) |
| occurrences (all) | 1 | 2 |
| Musculoskeletal chest pain | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Musculoskeletal discomfort | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 0 / 197 (0.00%) |
| occurrences (all) | 2 | 0 |
| Musculoskeletal pain | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 2 / 197 (1.02%) |
| occurrences (all) | 1 | 2 |
| Musculoskeletal stiffness | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 2 / 197 (1.02%) |
| occurrences (all) | 2 | 2 |
| Myalgia | | |
| subjects affected / exposed | 9 / 196 (4.59%) | 5 / 197 (2.54%) |
| occurrences (all) | 10 | 5 |
| Neck pain | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 196 (1.02%) | 3 / 197 (1.52%) | |
| occurrences (all) | 2 | 3 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 2 | |
| Pain in extremity | | | |
| subjects affected / exposed | 7 / 196 (3.57%) | 4 / 197 (2.03%) | |
| occurrences (all) | 9 | 4 | |
| Posture abnormal | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Pubic pain | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Spinal pain | | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 2 / 197 (1.02%) | |
| occurrences (all) | 2 | 2 | |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Tendon calcification | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tendonitis | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) | |
| occurrences (all) | 1 | 1 | |
| Periarthritis | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Acarodermatitis | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | |
|----------------------------------|-----------------|-----------------|
| Acute sinusitis | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) |
| occurrences (all) | 1 | 1 |
| Atypical mycobacterial infection | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Bronchitis | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 7 / 197 (3.55%) |
| occurrences (all) | 3 | 7 |
| Cellulitis | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Conjunctivitis | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 3 / 197 (1.52%) |
| occurrences (all) | 0 | 4 |
| Cystitis | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 3 / 197 (1.52%) |
| occurrences (all) | 1 | 3 |
| Cystitis bacterial | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Diverticulitis | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Enteritis infectious | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Folliculitis | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Gastroenteritis | | |
| subjects affected / exposed | 2 / 196 (1.02%) | 3 / 197 (1.52%) |
| occurrences (all) | 2 | 3 |
| Genital herpes | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | |
|-----------------------------|-----------------|-----------------|
| Gingivitis | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Herpes zoster | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 3 / 197 (1.52%) |
| occurrences (all) | 1 | 3 |
| Infected bite | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Influenza | | |
| subjects affected / exposed | 4 / 196 (2.04%) | 6 / 197 (3.05%) |
| occurrences (all) | 5 | 7 |
| Laryngitis | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 2 |
| Nasopharyngitis | | |
| subjects affected / exposed | 5 / 196 (2.55%) | 9 / 197 (4.57%) |
| occurrences (all) | 8 | 9 |
| Oral herpes | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 2 / 197 (1.02%) |
| occurrences (all) | 3 | 2 |
| Otitis externa fungal | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Paronychia | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pertussis | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Pharyngitis | | |
| subjects affected / exposed | 4 / 196 (2.04%) | 4 / 197 (2.03%) |
| occurrences (all) | 4 | 4 |
| Pneumonia | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | |
|-----------------------------------|-----------------|-----------------|
| Purulence | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Respiratory tract infection | | |
| subjects affected / exposed | 3 / 196 (1.53%) | 1 / 197 (0.51%) |
| occurrences (all) | 3 | 1 |
| Rhinitis | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 3 / 197 (1.52%) |
| occurrences (all) | 1 | 3 |
| Sinusitis | | |
| subjects affected / exposed | 5 / 196 (2.55%) | 2 / 197 (1.02%) |
| occurrences (all) | 5 | 2 |
| Skin infection | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 2 / 197 (1.02%) |
| occurrences (all) | 0 | 2 |
| Sycosis barbae | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Systemic infection | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 2 |
| Tracheitis | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |
| Trichophytosis | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) |
| occurrences (all) | 0 | 1 |
| Upper respiratory tract infection | | |
| subjects affected / exposed | 9 / 196 (4.59%) | 5 / 197 (2.54%) |
| occurrences (all) | 14 | 5 |
| Urinary tract infection | | |
| subjects affected / exposed | 4 / 196 (2.04%) | 5 / 197 (2.54%) |
| occurrences (all) | 4 | 5 |
| Viral infection | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 0 / 197 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | | |
|---|----------------------|----------------------|--|
| Viral pharyngitis subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 2 / 197 (1.02%) 3 | |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 2 / 196 (1.02%) 2 | 1 / 197 (0.51%) 2 | |
| Dehydration subjects affected / exposed occurrences (all) | 2 / 196 (1.02%) 2 | 0 / 197 (0.00%) 0 | |
| Diabetes mellitus subjects affected / exposed occurrences (all) | 2 / 196 (1.02%) 2 | 0 / 197 (0.00%) 0 | |
| Dyslipidaemia subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 0 / 197 (0.00%) 0 | |
| Fluid retention subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 1 / 197 (0.51%) 1 | |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 1 / 197 (0.51%) 1 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 1 / 196 (0.51%) 1 | 4 / 197 (2.03%) 4 | |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 3 / 196 (1.53%) 3 | 1 / 197 (0.51%) 1 | |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 0 / 196 (0.00%) 0 | 2 / 197 (1.02%) 2 | |
| Hypoglycaemia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 196 (0.00%) | 1 / 197 (0.51%) | |
| occurrences (all) | 0 | 1 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) | |
| occurrences (all) | 1 | 1 | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 1 / 196 (0.51%) | 1 / 197 (0.51%) | |
| occurrences (all) | 1 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 08 May 2014 | Updated Section 8.2 to extend the SAE reporting period to 28 days after the last study visit. |
| 04 December 2014 | 1. Deleted ADR table in Section 1.2.1.2 for MabThera and instead referenced the MabThera SPC to avoid any inconsistencies. 2. Updated Section 7.2.4 to clarify which laboratory tests were performed centrally and which were performed locally. 3. Clarified the vital signs which should be collected every 30 minutes during IP infusion (heart rate, seated blood pressure, respiratory rate, and oral or tympanic body temperature) and specified that a every 5 minute window is acceptable for the collection of vital signs during IP infusion. Sections impacted: Schedule of Assessments, Section 5.3.3 and Section 7.2.2. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported