



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
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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
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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
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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
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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)
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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
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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)
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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
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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
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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
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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
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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)
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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
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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
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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)

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
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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
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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
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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
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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
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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
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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
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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)
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	PF-05280586
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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
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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 occurrences (all)	2 / 196 (1.02%) 2	3 / 197 (1.52%) 3	
Polyneuropathy subjects affected / exposed occurrences (all)	1 / 196 (0.51%) 1	0 / 197 (0.00%) 0	
Presyncope subjects affected / exposed occurrences (all)	0 / 196 (0.00%) 0	1 / 197 (0.51%) 1	
Somnolence subjects affected / exposed occurrences (all)	2 / 196 (1.02%) 5	3 / 197 (1.52%) 6	
Restless legs syndrome subjects affected / exposed occurrences (all)	3 / 196 (1.53%) 3	1 / 197 (0.51%) 1	
Speech disorder subjects affected / exposed occurrences (all)	0 / 196 (0.00%) 0	1 / 197 (0.51%) 1	
Syncope subjects affected / exposed occurrences (all)	1 / 196 (0.51%) 1	0 / 197 (0.00%) 0	
Tension headache subjects affected / exposed occurrences (all)	0 / 196 (0.00%) 0	1 / 197 (0.51%) 1	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 196 (0.51%) 1	1 / 197 (0.51%) 1	
Lymph node pain subjects affected / exposed occurrences (all)	1 / 196 (0.51%) 1	0 / 197 (0.00%) 0	
Lymphopenia subjects affected / exposed occurrences (all)	1 / 196 (0.51%) 1	1 / 197 (0.51%) 1	
Neutropenia subjects affected / exposed occurrences (all)	1 / 196 (0.51%) 1	3 / 197 (1.52%) 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