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	v1
This version publication date	18 October 2018
First version publication date	18 October 2018

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 one of the 2 study treatment arms: PF-05280586 (Rituximab-Pfizer) and Rituximab-EU (MabThera®). Data reported is based on primary analysis data cut-off date of 23 October 2017.

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/m^2) 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/m^2 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/m^2 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/m^2 on Days 1, 8, 15 and 22.

Number of subjects in period 1	Rituximab-EU	PF-05280586
Started	198	196
Treated	197	196
Completed	132	131
Not completed	66	65
Ongoing in study	39	43
Adverse event	1	2
No longer willing to participate	2	3
Progressive disease	20	13
Lost to follow-up	-	1
Insufficient clinical response	4	3

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/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.	

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 measureable disease and no new sites. 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% confidence interval for the difference was calculated using the asymptotic stratified method proposed by Miettinen and Nurminen.	
Comparison groups	PF-05280586 v Rituximab-EU

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 data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

End point values	Rituximab-EU	PF-05280586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	196		
Units: subjects				
AEs	142	154		
SAEs	13	15		

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 data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

End point values	Rituximab-EU	PF-05280586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	196		
Units: subjects				
AEs	94	84		
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 data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

End point values	Rituximab-EU	PF-05280586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	196		
Units: subjects	25	27		

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 data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

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 analyzed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

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	193		
TB<2*ULN, ALT>=3*ULN	3	2		
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 or equal to (>=) 50% 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.

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 data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

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 (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	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.581 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.742
upper limit	1.701

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 >=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.

End point type	Secondary

End point timeframe:

From randomization until disease progression or death due to any cause or up to data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

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 (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	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.192 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.418
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.837
upper limit	2.402

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 >=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.

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 data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

End point values	Rituximab-EU	PF-05280586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	192		
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	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.206 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.515
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.792
upper limit	2.9

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 data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

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 analyzed' 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 analyzed' 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 analyzed' 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 and 26

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= 173,175)	114.4 (9.8 to 2313.1)	119.9 (10.9 to 1310.1)		
Week 2 (n=124,112)	1.2 (0.2 to 44.8)	0.9 (0.2 to 136.0)		
Week 3 (n= 106,114)	0.6 (0.2 to 19.5)	0.6 (0.2 to 248.1)		
Week 4 (n=100,81)	0.5 (0.2 to 9.0)	0.5 (0.2 to 144.5)		

Week 5 (n=85,87)	0.5 (0.2 to 19.0)	0.4 (0.2 to 19.0)		
Week 13 (n=78,74)	0.5 (0.2 to 130.7)	0.5 (0.2 to 183.7)		
Week 26 (n=122,100)	1.5 (0.2 to 496.5)	0.9 (0.2 to 329.8)		

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 analyzed 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 analyzed 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 analyzed' 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 data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

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)	37	38		
NAB Positive (n = 0, 0)	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 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 data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

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	50		
AE based on Sampson’s criteria	17	16		
Anaphylaxis/Hypersensitivity (SMQ)	48	38		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to data cut-off date (data cut-off occurred when the last subject randomized reached Week 26 or discontinued early)

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 one 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	Rituximab-EU

Reporting group description:

Subjects received Rituximab-EU IV infusion at a dose of 375 mg/m^2 on Day 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 Day 1, 8, 15, and 22. The maximum dose that could be infused in 1 day was 1125 mg.

Serious adverse events	Rituximab-EU	PF-05280586	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 197 (6.60%)	15 / 196 (7.65%)	
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	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage I			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

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

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

subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			

subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sinusitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rituximab-EU	PF-05280586	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	140 / 197 (71.07%)	151 / 196 (77.04%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 197 (1.02%)	1 / 196 (0.51%)	
occurrences (all)	2	1	
Infected neoplasm			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Lung adenocarcinoma stage I			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Meningioma			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Non-Hodgkin’s lymphoma			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 197 (1.02%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Flushing			
subjects affected / exposed	4 / 197 (2.03%)	1 / 196 (0.51%)	
occurrences (all)	4	1	
Hot flush			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	7 / 197 (3.55%)	5 / 196 (2.55%)	
occurrences (all)	13	6	
Hypotension			

subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Lymphoedema			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 197 (6.09%)	9 / 196 (4.59%)	
occurrences (all)	14	11	
Axillary pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Catheter site pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Catheter site related reaction			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Chest discomfort			
subjects affected / exposed	1 / 197 (0.51%)	2 / 196 (1.02%)	
occurrences (all)	1	2	
Chest pain			
subjects affected / exposed	3 / 197 (1.52%)	2 / 196 (1.02%)	
occurrences (all)	3	2	
Chills			
subjects affected / exposed	3 / 197 (1.52%)	3 / 196 (1.53%)	
occurrences (all)	4	4	
Discomfort			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Face oedema			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Facial pain			

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

subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	2	
Malaise			
subjects affected / exposed	0 / 197 (0.00%)	3 / 196 (1.53%)	
occurrences (all)	0	6	
Non-cardiac chest pain			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Oedema			
subjects affected / exposed	1 / 197 (0.51%)	2 / 196 (1.02%)	
occurrences (all)	1	2	
Oedema peripheral			
subjects affected / exposed	6 / 197 (3.05%)	2 / 196 (1.02%)	
occurrences (all)	6	2	
Pain			
subjects affected / exposed	3 / 197 (1.52%)	3 / 196 (1.53%)	
occurrences (all)	7	3	
Peripheral swelling			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	10 / 197 (5.08%)	11 / 196 (5.61%)	
occurrences (all)	11	11	
Suprapubic pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Swelling			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 197 (0.51%)	2 / 196 (1.02%)	
occurrences (all)	1	2	
Cytokine release syndrome			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	

Drug hypersensitivity			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Hypersensitivity			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Social circumstances			
Menopause			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Breast pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Breast tenderness			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Genital burning sensation			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Menorrhagia			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Metrorrhagia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Ovarian cyst			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	2	1	
Prostatitis			

subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Scrotal pain			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Testicular pain			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Vaginal haemorrhage			
subjects affected / exposed	0 / 197 (0.00%)	3 / 196 (1.53%)	
occurrences (all)	0	3	
Vulvovaginal inflammation			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Vulvovaginal pain			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	11 / 197 (5.58%)	11 / 196 (5.61%)	
occurrences (all)	11	13	
Dysphonia			
subjects affected / exposed	2 / 197 (1.02%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Dry throat			
subjects affected / exposed	1 / 197 (0.51%)	2 / 196 (1.02%)	
occurrences (all)	1	2	
Dyspnoea			
subjects affected / exposed	8 / 197 (4.06%)	6 / 196 (3.06%)	
occurrences (all)	8	6	
Dyspnoea exertional			

subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Emphysema			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Hiccups			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Hyperventilation			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Laryngeal inflammation			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Laryngeal discomfort			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Laryngeal oedema			
subjects affected / exposed	2 / 197 (1.02%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Laryngeal pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Lung disorder			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Nasal discomfort			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Nasal pruritus			

subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal discomfort			
subjects affected / exposed	1 / 197 (0.51%)	4 / 196 (2.04%)	
occurrences (all)	1	4	
Oropharyngeal pain			
subjects affected / exposed	10 / 197 (5.08%)	2 / 196 (1.02%)	
occurrences (all)	12	2	
Pharyngeal erythema			
subjects affected / exposed	0 / 197 (0.00%)	2 / 196 (1.02%)	
occurrences (all)	0	3	
Paranasal sinus mucosal hypertrophy			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Pharyngeal inflammation			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Pharyngeal oedema			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Pharyngeal paraesthesia			
subjects affected / exposed	1 / 197 (0.51%)	2 / 196 (1.02%)	
occurrences (all)	1	2	
Productive cough			
subjects affected / exposed	1 / 197 (0.51%)	2 / 196 (1.02%)	
occurrences (all)	1	2	
Pulmonary embolism			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Respiratory disorder			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Rhinalgia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			

subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Suffocation feeling			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Throat tightness			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Tonsillar disorder			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Tonsillar erythema			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract inflammation			
subjects affected / exposed	2 / 197 (1.02%)	1 / 196 (0.51%)	
occurrences (all)	2	1	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Sinus disorder			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	2	
Sneezing			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Throat irritation			

subjects affected / exposed	10 / 197 (5.08%)	14 / 196 (7.14%)	
occurrences (all)	10	15	
Psychiatric disorders			
Affect lability			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Agitation			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	6 / 197 (3.05%)	6 / 196 (3.06%)	
occurrences (all)	7	6	
Confusional state			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	2 / 197 (1.02%)	3 / 196 (1.53%)	
occurrences (all)	2	3	
Gastrointestinal somatic symptom disorder			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	8 / 197 (4.06%)	5 / 196 (2.55%)	
occurrences (all)	18	6	
Irritability			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Panic attack			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	3 / 197 (1.52%)	0 / 196 (0.00%)	
occurrences (all)	3	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Blood bilirubin increased			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 197 (0.51%)	3 / 196 (1.53%)	
occurrences (all)	1	3	
Blood potassium increased			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Blood pressure decreased			
subjects affected / exposed	2 / 197 (1.02%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Blood pressure increased			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	2	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Blood urine present			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			

subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Lymphocyte count decreased			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	2	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 197 (0.00%)	5 / 196 (2.55%)	
occurrences (all)	0	5	
Neutrophil count increased			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Serum ferritin decreased			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
White blood cell count decreased			
subjects affected / exposed	1 / 197 (0.51%)	4 / 196 (2.04%)	
occurrences (all)	1	4	
Breath sounds abnormal			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Chest injury			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Contusion			

subjects affected / exposed	1 / 197 (0.51%)	2 / 196 (1.02%)	
occurrences (all)	1	2	
Fall			
subjects affected / exposed	2 / 197 (1.02%)	4 / 196 (2.04%)	
occurrences (all)	2	4	
Hand fracture			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	2 / 197 (1.02%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Humerus fracture			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Infusion related reaction			
subjects affected / exposed	58 / 197 (29.44%)	50 / 196 (25.51%)	
occurrences (all)	63	62	
Laceration			
subjects affected / exposed	2 / 197 (1.02%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Limb injury			
subjects affected / exposed	0 / 197 (0.00%)	2 / 196 (1.02%)	
occurrences (all)	0	2	
Neck injury			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Road traffic accident			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Suture related complication			

subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Suture rupture			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Tendon rupture			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Upper limb fracture			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Wound complication			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Wrist fracture			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Angina unstable			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	0 / 197 (0.00%)	2 / 196 (1.02%)	
occurrences (all)	0	2	
Bradycardia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Cardiac failure congestive			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	

Palpitations			
subjects affected / exposed	2 / 197 (1.02%)	5 / 196 (2.55%)	
occurrences (all)	2	6	
Sinus bradycardia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	2 / 197 (1.02%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	6 / 197 (3.05%)	2 / 196 (1.02%)	
occurrences (all)	7	2	
Dysgeusia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Head discomfort			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	19 / 197 (9.64%)	16 / 196 (8.16%)	
occurrences (all)	31	18	
Hypoaesthesia			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Hypotonia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Intercostal neuralgia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	2	
Lethargy			

subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	3	
Migraine			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Nerve compression			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Neuralgia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Paraesthesia			
subjects affected / exposed	3 / 197 (1.52%)	2 / 196 (1.02%)	
occurrences (all)	3	2	
Polyneuropathy			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Restless legs syndrome			
subjects affected / exposed	1 / 197 (0.51%)	3 / 196 (1.53%)	
occurrences (all)	1	3	
Somnolence			
subjects affected / exposed	3 / 197 (1.52%)	2 / 196 (1.02%)	
occurrences (all)	6	5	
Speech disorder			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Tension headache			

subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Lymph node pain			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Lymphopenia			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Neutropenia			
subjects affected / exposed	3 / 197 (1.52%)	1 / 196 (0.51%)	
occurrences (all)	3	1	
Thrombocytopenia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 197 (0.00%)	2 / 196 (1.02%)	
occurrences (all)	0	3	
Ear disorder			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Ear pruritus			
subjects affected / exposed	2 / 197 (1.02%)	3 / 196 (1.53%)	
occurrences (all)	2	4	
Hypoacusis			
subjects affected / exposed	1 / 197 (0.51%)	2 / 196 (1.02%)	
occurrences (all)	1	2	
Tinnitus			

subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	3 / 197 (1.52%)	2 / 196 (1.02%)	
occurrences (all)	3	2	
Vertigo positional			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Accommodation disorder			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Cataract			
subjects affected / exposed	1 / 197 (0.51%)	2 / 196 (1.02%)	
occurrences (all)	2	2	
Conjunctival disorder			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Diplopia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Dry eye			
subjects affected / exposed	2 / 197 (1.02%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Erythema of eyelid			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Eye pruritus			
subjects affected / exposed	3 / 197 (1.52%)	0 / 196 (0.00%)	
occurrences (all)	3	0	
Lacrimation increased			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Meibomianitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	

Ocular hyperaemia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	3 / 197 (1.52%)	7 / 196 (3.57%)	
occurrences (all)	3	12	
Abdominal pain lower			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	5 / 197 (2.54%)	9 / 196 (4.59%)	
occurrences (all)	7	9	
Cheilitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Chronic gastritis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Colitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	8 / 197 (4.06%)	8 / 196 (4.08%)	
occurrences (all)	9	9	
Dental caries			
subjects affected / exposed	0 / 197 (0.00%)	2 / 196 (1.02%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	12 / 197 (6.09%)	14 / 196 (7.14%)	
occurrences (all)	14	16	
Diverticulum intestinal			

subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	2 / 197 (1.02%)	5 / 196 (2.55%)	
occurrences (all)	2	6	
Dysphagia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Enterocolitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Faeces soft			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Functional gastrointestinal disorder			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Gastrointestinal disorder			
subjects affected / exposed	0 / 197 (0.00%)	3 / 196 (1.53%)	
occurrences (all)	0	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Gingival pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Gingival swelling			

subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	2 / 197 (1.02%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Inguinal hernia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Lip oedema			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Mouth swelling			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	17 / 197 (8.63%)	15 / 196 (7.65%)	
occurrences (all)	22	19	
Odynophagia			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	2	1	
Oral discomfort			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Oral mucosal erythema			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Paraesthesia oral			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Periodontal disease			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			

subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Salivary gland pain			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	3 / 197 (1.52%)	0 / 196 (0.00%)	
occurrences (all)	6	0	
Swollen tongue			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Tooth disorder			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	2 / 197 (1.02%)	2 / 196 (1.02%)	
occurrences (all)	2	3	
Vomiting			
subjects affected / exposed	7 / 197 (3.55%)	3 / 196 (1.53%)	
occurrences (all)	7	4	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Hepatocellular injury			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Angioedema			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Asteatosis			

subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Dermatitis allergic			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Dermatitis contact			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Drug eruption			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	3 / 197 (1.52%)	1 / 196 (0.51%)	
occurrences (all)	3	1	
Erythema			
subjects affected / exposed	2 / 197 (1.02%)	7 / 196 (3.57%)	
occurrences (all)	2	7	
Hyperhidrosis			
subjects affected / exposed	3 / 197 (1.52%)	2 / 196 (1.02%)	
occurrences (all)	4	4	
Hyperkeratosis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Intertrigo			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Nail disorder			

subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Neurodermatitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Pruritus allergic			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	8 / 197 (4.06%)	10 / 196 (5.10%)	
occurrences (all)	9	14	
Rash erythematous			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Rash pruritic			
subjects affected / exposed	0 / 197 (0.00%)	2 / 196 (1.02%)	
occurrences (all)	0	2	
Scab			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Skin burning sensation			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	2 / 197 (1.02%)	1 / 196 (0.51%)	
occurrences (all)	2	1	
Swelling face			

subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	6 / 197 (3.05%)	3 / 196 (1.53%)	
occurrences (all)	6	3	
Pruritus			
subjects affected / exposed	22 / 197 (11.17%)	13 / 196 (6.63%)	
occurrences (all)	23	14	
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Calculus bladder			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	1 / 197 (0.51%)	2 / 196 (1.02%)	
occurrences (all)	1	2	
Nocturia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Renal pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Strangury			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Urinary tract pain			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	

Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Thyroid cyst			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 197 (3.05%)	6 / 196 (3.06%)	
occurrences (all)	7	7	
Back pain			
subjects affected / exposed	9 / 197 (4.57%)	8 / 196 (4.08%)	
occurrences (all)	10	8	
Bone loss			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Bone pain			
subjects affected / exposed	3 / 197 (1.52%)	0 / 196 (0.00%)	
occurrences (all)	3	0	
Costochondritis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Flank pain			
subjects affected / exposed	2 / 197 (1.02%)	1 / 196 (0.51%)	
occurrences (all)	3	1	
Groin pain			
subjects affected / exposed	2 / 197 (1.02%)	3 / 196 (1.53%)	
occurrences (all)	3	3	
Haemarthrosis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc protrusion			

subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)		
occurrences (all)	1	0		
Joint effusion				
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)		
occurrences (all)	1	0		
Joint stiffness				
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)		
occurrences (all)	1	0		
Joint swelling				
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)		
occurrences (all)	1	1		
Muscle contracture				
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)		
occurrences (all)	0	1		
Muscle spasms				
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)		
occurrences (all)	1	0		
Muscle twitching				
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)		
occurrences (all)	0	1		
Muscular weakness				
subjects affected / exposed	2 / 197 (1.02%)	1 / 196 (0.51%)		
occurrences (all)	2	1		
Musculoskeletal chest pain				
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)		
occurrences (all)	1	0		
Musculoskeletal discomfort				
subjects affected / exposed	0 / 197 (0.00%)	2 / 196 (1.02%)		
occurrences (all)	0	2		
Musculoskeletal pain				
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)		
occurrences (all)	1	1		
Musculoskeletal stiffness				
subjects affected / exposed	2 / 197 (1.02%)	2 / 196 (1.02%)		
occurrences (all)	2	2		
Myalgia				

subjects affected / exposed	5 / 197 (2.54%)	9 / 196 (4.59%)	
occurrences (all)	5	10	
Neck pain			
subjects affected / exposed	3 / 197 (1.52%)	2 / 196 (1.02%)	
occurrences (all)	3	2	
Osteoarthritis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Pain in extremity			
subjects affected / exposed	2 / 197 (1.02%)	7 / 196 (3.57%)	
occurrences (all)	2	9	
Posture abnormal			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Pubic pain			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Spinal pain			
subjects affected / exposed	2 / 197 (1.02%)	2 / 196 (1.02%)	
occurrences (all)	2	2	
Spondylolisthesis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Tendon calcification			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	

Acute sinusitis			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Atypical mycobacterial infection			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	5 / 197 (2.54%)	3 / 196 (1.53%)	
occurrences (all)	5	3	
Cellulitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	3 / 197 (1.52%)	0 / 196 (0.00%)	
occurrences (all)	4	0	
Cystitis			
subjects affected / exposed	2 / 197 (1.02%)	1 / 196 (0.51%)	
occurrences (all)	2	1	
Cystitis bacterial			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Diverticulitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Enteritis infectious			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	3 / 197 (1.52%)	2 / 196 (1.02%)	
occurrences (all)	3	2	
Genital herpes			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	

Gingivitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	3 / 197 (1.52%)	1 / 196 (0.51%)	
occurrences (all)	3	1	
Infected bite			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	3 / 197 (1.52%)	3 / 196 (1.53%)	
occurrences (all)	4	4	
Laryngitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	8 / 197 (4.06%)	5 / 196 (2.55%)	
occurrences (all)	8	7	
Oral herpes			
subjects affected / exposed	2 / 197 (1.02%)	3 / 196 (1.53%)	
occurrences (all)	2	3	
Otitis externa fungal			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	
Pertussis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	4 / 197 (2.03%)	4 / 196 (2.04%)	
occurrences (all)	4	4	
Pneumonia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 196 (0.51%)	
occurrences (all)	0	1	

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

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

subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 196 (0.00%)	
occurrences (all)	1	0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (0.51%)	
occurrences (all)	1	1	
Vitamin D deficiency			
subjects affected / exposed	1 / 197 (0.51%)	1 / 196 (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 will be performed centrally and which will be 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