Clinical trial results:
A RANDOMIZED, DOUBLE-BLIND, STUDY COMPARING THE PHARMACOKINETICS AND PHARMACODYNAMICS, AND ASSESSING THE SAFETY OF PF-05280586 AND RITUXIMAB IN SUBJECTS WITH ACTIVE RHEUMATOID ARTHRITIS ON A BACKGROUND OF METHOTREXATE WHO HAVE HAD AN INADEQUATE RESPONSE TO ONE OR MORE TNF ANTAGONIST THERAPIES

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2011-002896-40
Trial protocol	GB ES DE PL
Global end of trial date	07 May 2014

Results information

Result version number	v2 (current)
This version publication date	11 May 2016
First version publication date	02 August 2015
Version creation reason	• New data added to full data set reporting periods and duplicate AEs in their data

Trial information

Trial identification

Sponsor protocol code	B3281001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01526057
WHO universal trial number (UTN)	-

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 8007181021,
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021,

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	07 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the pharmacokinetic (PK) similarity of rituximab-Pfizer, the rituximab product MabThera (licensed for use in the European Union [EU], hereafter referred to as rituximab-EU) and the rituximab product Rituxan (licensed for use in the United States [US], hereafter referred to as rituximab-US) in participants with active rheumatoid arthritis (RA) on a background of methotrexate (MTX) who have had an inadequate response to 1 or more tumour necrosis factor (TNF) antagonist therapies.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants. Safety monitoring was performed throughout the study by an independent data monitoring committee (DMC) at approximately 3-month intervals unless safety concerns requiring their attention arose earlier. In addition, early in the study, an internal review committee monitored safety at monthly intervals for approximately the first 10 months of the study.

Background therapy:

Methotrexate (MTX)

Evidence for comparator:

The mechanism of action of rituximab, which results in profound and prolonged B-cell depletion, precludes the conduct of PK studies in healthy volunteer participants. The population studied in this clinical trial included participants with active RA who were receiving background therapy with MTX and had an inadequate response to 1 or more TNF antagonist therapies. Participants might have been exposed to other biologics, with the exception of any B-cell intervention. This study population reflects the approved, labelled indication for MabThera and Rituxan. Therefore, the treatment regimen provided in the rituximab product labelling was used in the study: 1000 mg rituximab-Pfizer, rituximab-EU, or rituximab-US administered as an intravenous (IV) infusion on Days 1 and 15.

Actual start date of recruitment	30 March 2012
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	United Kingdom: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Colombia: 13

Country: Number of subjects enrolled	Swaziland: 8
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	United States: 150
Worldwide total number of subjects	220
EEA total number of subjects	4

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)	178
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multinational, randomised, double-blind, controlled trial in participants with active RA on a background of MTX. The study was conducted at 56 centres in 10 countries. There were a total of 220 participants enrolled in this study: 73 in the rituximab-US arm, 74 in the rituximab-EU arm, and 73 in the rituximab-Pfizer arm.

Pre-assignment

Screening details:

Participants were screened for up to 4 weeks prior to randomisation.

Period 1

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

Blinding implementation details:

Study blinded to participant, investigator/study staff, sponsor's study team conducting trial. The study pharmacists preparing treatment infusions were unblinded. The Independent Review Committee and DMC reviewed partially blinded results (ie, treatment groups identified as Arms A, B, and C). Blinding broken in emergency situations when knowledge of treatment assignment was required for medical management for individual subject safety. The investigator notified the sponsor before breaking blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab-Pfizer

Arm description:

Rituximab-Pfizer group received IV rituximab (PF-05280586) infusion 1000 milligrams (mg) per (/) 500 millilitres (mL) (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

Arm type	Experimental
Investigational medicinal product name	PF-05280586 (Rituximab-Pfizer)
Investigational medicinal product code	
Other name	Rituximab-Pfizer
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab was administered at a dose of 1000 mg/500 mL on study Days 1 and 15. The infusion rate was followed as per the guidance as presented in the protocol. The minimum duration required to deliver rituximab 1000 mg during the first infusion for each subject was 4.25 hours. The minimum duration for the second infusion was 3.25 hours. When the drug product administration was complete, a 3.33 mL/minute flush with diluent for 10 minutes was performed. Infusions could have been longer if infusion interruption or rate reduction was necessary to manage acute infusion reactions.

Arm title	Rituximab-EU

Arm description:

Rituximab-EU group received IV rituximab (MabThera) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

Arm type	Active comparator

Investigational medicinal product name	Rituximab - EU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab was administered at a dose of 1000 mg/500 mL on study Days 1 and 15. The infusion rate was followed as per the guidance as presented in the protocol. The minimum duration required to deliver rituximab 1000 mg during the first infusion for each subject was 4.25 hours. The minimum duration for the second infusion was 3.25 hours. When the drug product administration was complete, a 3.33 mL/minute flush with diluent for 10 minutes was performed. Infusions could have been longer if infusion interruption or rate reduction was necessary to manage acute infusion reactions.

Arm title	Rituximab-US

Arm description:

Rituximab-US group received IV rituximab (Rituxan) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

Arm type	Active comparator
Investigational medicinal product name	Rituximab - US
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab was administered at a dose of 1000 mg/500 mL on study Days 1 and 15. The infusion rate was followed as per the guidance as presented in the protocol. The minimum duration required to deliver rituximab 1000 mg during the first infusion for each subject was 4.25 hours. The minimum duration for the second infusion was 3.25 hours. When the drug product administration was complete, a 3.33 mL/minute flush with diluent for 10 minutes was performed. Infusions could have been longer if infusion interruption or rate reduction was necessary to manage acute infusion reactions.

Number of subjects in period 1	Rituximab-Pfizer	Rituximab-EU	Rituximab-US
Started	73	74	73
Completed	64	71	67
Not completed	9	3	6
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	3	2	2
Adverse event, non-fatal	3	1	1
Other	1	-	1
Lost to follow-up	1	-	1
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab-Pfizer
Reporting group description:	
Rituximab-Pfizer group received IV rituximab (PF-05280586) infusion 1000 milligrams (mg) per (/) 500 millilitres (mL) (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.	
Reporting group title	Rituximab-EU
Reporting group description:	
Rituximab-EU group received IV rituximab (MabThera) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.	
Reporting group title	Rituximab-US
Reporting group description:	
Rituximab-US group received IV rituximab (Rituxan) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.	

Reporting group values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US
Number of subjects	73	74	73
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	54.9	54.9	53.4
standard deviation	± 11.52	± 11.07	± 11.87
Gender categorical			
Units: Subjects			
Female	59	57	54
Male	14	17	19

Reporting group values	Total		
Number of subjects	220		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	170		
Male	50		

End points

End points reporting groups

Reporting group title	Rituximab-Pfizer

Reporting group description:

Rituximab-Pfizer group received IV rituximab (PF-05280586) infusion 1000 milligrams (mg) per (/) 500 millilitres (mL) (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

Reporting group title	Rituximab-EU

Reporting group description:

Rituximab-EU group received IV rituximab (MabThera) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

Reporting group title	Rituximab-US

Reporting group description:

Rituximab-US group received IV rituximab (Rituxan) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

Primary: Maximum Serum Concentration (Cmax) of Rituximab

End point title	Maximum Serum Concentration (Cmax) of Rituximab

End point description:

Cmax is the peak serum concentration of study drug (rituximab) after a dose has been administered. Per protocol (PP) population: all participants who were randomized, received the full doses of the assigned study treatment, and had no major protocol violations that could impact the PK analysis. Exclusions from the PP population were based on a blinded data review by the Medical Monitor and Clinical Pharmacologist.

End point type	Primary

End point timeframe:

Predose (Day 1) and 3, 4.25 (immediately before 1st infusion end), 72, 168, 335 (Day 15 within 1.5 hours before 2nd infusion), 337.5, 339.25 (Day 15 immediately before 2nd infusion end), 408, 504, 672, 1344, and 2016 hours after start of 1st infusion

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	67	63	
Units: ug/mL				
arithmetic mean (standard deviation)	453 (± 153)	422 (± 111)	430 (± 163)	

Statistical analyses

Statistical analysis title	Rituximab-Pfizer, Rituximab-EU

Statistical analysis description:

A 90% confidence interval (CI) on the estimated difference between 2 treatment groups was constructed using a 1-way analysis of variance (ANOVA) model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-EU v Rituximab-Pfizer
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	105.67
Confidence interval	
level	90 %
sides	2-sided
lower limit	96.91
upper limit	115.21

Notes:

[1] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to reference ratios in Cmax and area under the serum concentration-time curve (AUC) from time 0 extrapolated to infinite time (AUC 0-inf) are within the 80.00% to 125.00% range.
Rituximab-Pfizer is the numerator.

Statistical analysis title	Rituximab-Pfizer, Rituximab-US

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-Pfizer v Rituximab-US
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	106.62
Confidence interval	
level	90 %
sides	2-sided
lower limit	97.65
upper limit	116.41

Notes:

[2] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to reference ratios in Cmax and AUC 0-inf are within the 80.00% to 125.00% range.
Rituximab-Pfizer is the numerator.

Statistical analysis title	Rituximab-EU, Rituximab-US

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-EU v Rituximab-US

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	ANOVA
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	100.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	92.38
upper limit	110.2

Notes:

[3] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to reference ratios in Cmax and AUC 0-inf are within the 80.00% to 125.00% range. Rituximab-EU is the numerator.

Primary: AUC 0-inf of Rituximab

End point title	AUC 0-inf of Rituximab

End point description:

The AUC 0-inf refers to the concentration in serum of the drug over time. It represents the total drug exposure over time, from time 0 (the point of drug administration) extrapolated to infinity. PP Population

End point type	Primary

End point timeframe:

Predose (Day 1) and 3, 4.25 (immediately before 1st infusion end), 72, 168, 335 (Day 15 within 1.5 hours before 2nd infusion), 337.5, 339.25 (Day 15 immediately before 2nd infusion end), 408, 504, 672, 1344, and 2016 hours after start of 1st infusion

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	67	62	
Units: ug/mL/hour				
arithmetic mean (standard deviation)	213000 (± 90400)	200000 (± 74600)	214000 (± 95300)	

Statistical analyses

Statistical analysis title	Rituximab-Pfizer, Rituximab-EU

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-Pfizer v Rituximab-EU

Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	104.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	92.75
upper limit	117.06

Notes:

[4] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to reference ratios in Cmax and AUC 0-inf are within the 80.00% to 125.00% range.
Rituximab-Pfizer is the numerator.
For AUC 0-inf calculated after inclusion of additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 104.19 (92.83, 116.93).

Statistical analysis title	Rituximab-Pfizer, Rituximab-US

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-Pfizer v Rituximab-US
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	100.45
Confidence interval	
level	90 %
sides	2-sided
lower limit	89.2
upper limit	113.11

Notes:

[5] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to reference ratios in Cmax and AUC 0-inf are within the 80.00% to 125.00% range.
Rituximab-Pfizer is the numerator.
For AUC 0-inf calculated after inclusion of additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 100.21 (89.12, 112.67).

Statistical analysis title	Rituximab-EU, Rituximab-US

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-EU v Rituximab-US
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	96.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	85.57
upper limit	108.6

Notes:

[6] - PK similarity for a given test-to-reference comparison would be demonstrated if the 90% CI for the test-to reference ratios in Cmax and AUC 0-inf are within the 80.00% to 125.00% range.
Rituximab-EU is the numerator.
For AUC 0-inf calculated after inclusion of additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 96.18 (85.51, 108.19).

Secondary: Rituximab AUC From Time 0 to 2 Weeks (AUC 0-2wk)

End point title	Rituximab AUC From Time 0 to 2 Weeks (AUC 0-2wk)

End point description:

The AUC 0-2wk refers to the concentration in serum of the drug over time. It represents the total drug exposure over time, from time 0 (the point of drug administration) to 2 weeks after drug administration.
PP Population

End point type	Secondary

End point timeframe:

Predose (Day 1) and 3, 4.25 (immediately before 1st infusion end), 72, 168, 335 (Day 15 within 1.5 hours before 2nd infusion), 337.5, 339.25 (Day 15 immediately before 2nd infusion end), 408, 504, 672, 1344, and 2016 hours after start of 1st infusion

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	67	63	
Units: ug/mL/hour				
arithmetic mean (standard deviation)	52100 (± 18000)	49600 (± 14200)	49200 (± 15900)	

Statistical analyses

Statistical analysis title	Rituximab-Pfizer, Rituximab EU

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-Pfizer v Rituximab-EU
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	103.74
Confidence interval	
level	90 %
sides	2-sided
lower limit	95.1
upper limit	113.15

Notes:

[7] - Rituximab-Pfizer is the numerator.

Statistical analysis title	Rituximab-Pfizer, Rituximab-US

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-Pfizer v Rituximab-US
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	105.56
Confidence interval	
level	90 %
sides	2-sided
lower limit	96.64
upper limit	115.3

Notes:

[8] - Rituximab-Pfizer is the numerator.

Statistical analysis title	Rituximab-EU, Rituximab-US

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-EU v Rituximab-US
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	101.76
Confidence interval	
level	90 %
sides	2-sided
lower limit	93.13
upper limit	111.18

Notes:

[9] - Rituximab-EU is the numerator.

Secondary: Rituximab AUC From Time 0 to the Time of the Last Quantifiable Concentration (AUC 0-T)

End point title	Rituximab AUC From Time 0 to the Time of the Last Quantifiable Concentration (AUC 0-T)

End point description:

The AUC 0-T refers to the concentration in serum of the drug over time. It represents the total drug exposure over time, from time 0 (the point of drug administration) to the last measured concentration at time T. PP Population

End point type	Secondary

End point timeframe:

Predose (Day 1) and 3, 4.25 (immediately before 1st infusion end), 72, 168, 335 (Day 15 within 1.5 hours before 2nd infusion), 337.5, 339.25 (Day 15 immediately before 2nd infusion end), 408, 504, 672, 1344, and 2016 hours after start of 1st infusion

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	67	63	
Units: ug/mL/hour				
arithmetic mean (standard deviation)	198000 (± 79600)	188000 (± 64300)	196000 (± 78300)	

Statistical analyses

Statistical analysis title	Rituximab-Pfizer, Rituximab-EU

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-Pfizer v Rituximab-EU
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	103.36
Confidence interval	
level	90 %
sides	2-sided
lower limit	92.81
upper limit	115.12

Notes:

[10] - Rituximab-Pfizer is the numerator.
For AUC 0-T calculated after inclusion of the additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 103.26 (92.13, 115.73).

Statistical analysis title	Rituximab-Pfizer, Rituximab-US

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-Pfizer v Rituximab-US
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	101.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.82
upper limit	113.04

Notes:

[11] - Rituximab-Pfizer is the numerator.
For AUC 0-T calculated after inclusion of the additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 100.45 (89.46, 112.79).

Statistical analysis title	Rituximab-US, Rituximab-EU

Statistical analysis description:

A 90% CI on the estimated difference between 2 treatment groups was constructed using a 1-way ANOVA model based on natural log-transformed data. The estimated differences for the log-transformed PK parameters were then transformed to relative ratios of PK parameters by exponentiation.

Comparison groups	Rituximab-US v Rituximab-EU
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Parameter estimate	Test-to-reference ratio: adjusted means
Point estimate	98.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	87.83
upper limit	109.4

Notes:

[12] - Rituximab-EU is the numerator.
For AUC0- T calculated after inclusion of the additional drug concentration samples collected on Day 169, the ratio (90% CI for ratio) was 97.28 (86.60, 109.27).

Secondary: Cluster of Differentiation 19 (CD19+) B-cell Count AUC From Time 0 to the Last Measurement at Time T (AUC 0-T,B-cell)

End point title	Cluster of Differentiation 19 (CD19+) B-cell Count AUC From Time 0 to the Last Measurement at Time T (AUC 0-T,B-cell)

End point description:

The AUC 0-T,B-cell refers to the concentration in serum of B-cells. It represents the total B-cells over time from time 0 (the point of drug administration) to the last measurement taken at time T. Modified intention-to-treat (mITT) population, defined as all participants who were randomised and received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (end of trial [EOT])

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	69	67	
Units: cells/day/mL				
arithmetic mean (standard deviation)	13312 (± 13309)	14304 (± 13146)	12496 (± 13500)	

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Post-Baseline CD19+ B-cell Count

End point title	Minimum Post-Baseline CD19+ B-cell Count

End point description:

The lowest CD19+ B-cell count measured in a participant's blood post-baseline. mITT population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	69	67	
Units: /uL				
arithmetic mean (standard deviation)	0 (± 0.28)	0 (± 0)	0 (± 0.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Minimum Post-Baseline CD19+ B-cell Count

End point title	Time to Minimum Post-Baseline CD19+ B-cell Count

End point description:

The amount of time in weeks from baseline to the lowest observed CD19+ B-cell count. mITT population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	69	67	
Units: weeks				
arithmetic mean (standard deviation)	1.4 (± 1.41)	1.6 (± 1.68)	1.5 (± 1.31)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of B-cell depletion (τB-cell)

End point title	Duration of B-cell depletion (τB-cell)

End point description:

The τB-cell is defined as the time interval over which the B-cell count was <0.3 cells/microliter (uL) or the detection limit. mITT population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	69	67	
Units: days				
arithmetic mean (standard deviation)	126 (± 41.8)	123 (± 38.6)	120 (± 40.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with CD19+ B-cell Count Recovery

End point title	Percentage of Participants with CD19+ B-cell Count Recovery

End point description:

The percentage of participants with CD19+ B-cell counts which fell to <50% of Baseline value during treatment and which recovered to ≥50% of Baseline value at EOT. mITT population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	69	67	
Units: Percentage of Participants				
number (not applicable)	4.4	8.7	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the CD19+ B-cell count concentration-time profile (AUC 0-T, B-cell)

End point title	Area under the CD19+ B-cell count concentration-time profile (AUC 0-T, B-cell)

End point description:

The AUC 0-T, B-cell refers to the CD19+ B-cell count over time. It represents the total B-cells over time, from time 0 (the point of drug administration) to the last measured count at time T.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 3, 5, 9, 13, 17, 21 and 25 (EOT). mITT population.

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	69	67	
Units: days/cells/uL				
arithmetic mean (standard deviation)	13312.1 (± 13309.15)	14304.2 (± 13145.72)	12495.9 (± 13499.97)	

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline and Change from Baseline in Circulating Immunoglobulin-M (IgM) by Visit

End point title	Baseline and Change from Baseline in Circulating Immunoglobulin-M (IgM) by Visit

End point description:

The level of IgM in serum at Baseline and the change from Baseline at each subsequent visit. mITT population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: g/L				
arithmetic mean (standard deviation)				
Baseline (n=73,74,73)	1.381 (± 0.7617)	1.46 (± 0.8076)	1.394 (± 0.8372)	
Change from Baseline at Week 1 (n=71,69,70)	0 (± 0.15)	0 (± 0.17)	0 (± 0.19)	
Change from Baseline at Week 2 (n=71,72,68)	0 (± 0.17)	0 (± 0.17)	0 (± 0.2)	
Change from Baseline at Week 3 (n=71,74,69)	-0.1 (± 0.18)	-0.1 (± 0.17)	0 (± 0.15)	
Change from Baseline at Week 4 (n=68,69,68)	-0.1 (± 0.27)	-0.1 (± 0.2)	0 (± 0.33)	
Change from Baseline at Week 5 (n=72,71,69)	-0.1 (± 0.3)	-0.1 (± 0.26)	-0.1 (± 0.23)	

Change from Baseline at Week 9 (n=68,73,70)	-0.2 (± 0.32)	-0.3 (± 0.27)	-0.2 (± 0.28)	
Change from Baseline at Week 13 (n=67,72,67)	-0.2 (± 0.52)	-0.3 (± 0.3)	-0.2 (± 0.55)	
Change from Baseline at Week 17 (n=67,71,67)	-0.1 (± 0.92)	-0.3 (± 0.34)	-0.3 (± 0.34)	
Change from Baseline at Week 21 (n=60,65,60)	-0.3 (± 0.42)	-0.4 (± 0.33)	-0.3 (± 0.35)	
Change from Baseline at Week 25 (EOT; n=50,57,55)	-0.4 (± 0.42)	-0.3 (± 0.3)	-0.3 (± 0.48)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent (%) Change from Baseline in Circulating IgM by Visit

End point title	Percent (%) Change from Baseline in Circulating IgM by Visit
End point description:	
The percentage change from Baseline in circulating IgM by visit. mITT population.	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 1, 2, 3, 4, 5, 9, 13, 17, 21 and 25 (EOT)	

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	74	70	
Units: g/L				
arithmetic mean (standard deviation)				
Week 1 (n=71,69,70)	3.3 (± 18.62)	1.4 (± 9.57)	-0.5 (± 9.93)	
Week 2 (n=71,72,68)	0.1 (± 12.45)	-0.3 (± 9.42)	0.7 (± 14.06)	
Week 3 (n=71,74,69)	-3.4 (± 12.98)	-4.9 (± 9.95)	-2.7 (± 9.82)	
Week 4 (n=68,69,68)	-5.5 (± 14.77)	-5 (± 10.59)	-2.2 (± 21.89)	
Week 5 (n=72,71,69)	-8.6 (± 16)	-7.9 (± 15.6)	-5.6 (± 14.39)	
Week 9 (n=68,73,70)	-14.4 (± 13.68)	-16.9 (± 13.69)	-14.1 (± 13.73)	
Week 13 (n=67,72,67)	-11.5 (± 37.17)	-22.2 (± 13.92)	-16.2 (± 30.14)	
Week 17 (n=67,71,67)	5.5 (± 226.39)	-23.7 (± 16.35)	-21.6 (± 14.88)	
Week 21 (n=60,65,60)	-21.6 (± 17.72)	-24.7 (± 21)	-21.3 (± 15.69)	
Week 25 (EOT; n=50,57,55)	-24.2 (± 14.63)	-21 (± 16.95)	-20.5 (± 21.78)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with American College of Rheumatology (ACR) 20% Improvement (ACR20) Response by Visit

End point title	Percentage of Participants with American College of Rheumatology (ACR) 20% Improvement (ACR20) Response by Visit

End point description:

ACR20 response: greater than or equal to (≥)20% improvement in tender joint count; ≥20% improvement in swollen joint count; and ≥20% improvement in at least 3 of 5 remaining ACR core measures: participant assessment of pain; participant global assessment of disease activity; physician global assessment of disease activity; self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ]); and C-Reactive Protein (CRP). Non-responder imputation categorised participants as having a non-response if they did not have data available at a visit due to missing data or study discontinuation. Participants who rolled over to the extension study were not included in the non-responder imputation from that point on. mITT population.

End point type	Secondary

End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: Percentage of Participants				
number (not applicable)				
Week 3 (n=73,74,73)	34.2	33.8	32.9	
Week 5 (n=73,74,73)	54.8	56.8	42.5	
Week 9 (n=73,74,73)	49.3	60.8	58.9	
Week 13 (n=73,74,73)	50.7	70.3	63	
Week 17 (n=73,74,73)	54.8	67.6	67.1	
Week 21 (n=72,74,72)	54.2	62.2	69.4	
Week 25 (EOT; n=62,63,62)	50	60.3	71	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with ACR 70% Improvement (ACR70) Response by Visit

End point title	Percentage of Participants with ACR 70% Improvement (ACR70) Response by Visit

End point description:

ACR70 response: ≥70% improvement in tender joint count; ≥70% improvement in swollen joint count; and ≥70% improvement in at least 3 of 5 remaining ACR core measures: participant assessment of pain; participant global assessment of disease activity; physician global assessment of disease activity; self-assessed disability (disability index of the HAQ); and CRP. Non-responder imputation categorised participants as having a non-response if they did not have data available at a visit due to missing data or study discontinuation. Participants who rolled over to the extension study were not included in the non-responder imputation from that point on. mITT population.

End point type	Secondary

End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: Percentage of Participants				
number (not applicable)				
Week 3 (n=73,74,73)	2.7	2.7	2.7	
Week 5 (n=73,74,73)	6.8	6.8	8.2	
Week 9 (n=73,74,73)	12.3	17.6	16.4	
Week 13 (n=73,74,73)	19.2	28.4	20.5	
Week 17 (n=73,74,73)	15.1	18.9	19.2	
Week 21 (n=72,74,72)	13.9	23	20.8	
Week 25 (EOT; n=62,63,62)	16.1	17.5	19.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with ACR 50% Improvement (ACR50) Response by Visit

End point title	Percentage of Participants with ACR 50% Improvement (ACR50) Response by Visit

End point description:

ACR50 response: ≥50% improvement in tender joint count; ≥50% improvement in swollen joint count; and ≥50% improvement in at least 3 of 5 remaining ACR core measures: participant assessment of pain; participant global assessment of disease activity; physician global assessment of disease activity; self-assessed disability (disability index of the HAQ); and CRP. Non-responder imputation categorized participants as having a non-response if they did not have data available at a visit due to missing data or study discontinuation. Participants who rolled over to the extension study were not included in the non-responder imputation from that point on. mITT population.

End point type	Secondary

End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: Percentage of Participants				
number (not applicable)				
Week 3 (n=73,74,73)	8.2	5.4	9.6	
Week 5 (n=73,74,73)	19.2	16.2	20.5	

Week 9 (n=73,74,73)	21.9	32.4	35.6	
Week 13 (n=73,74,73)	35.6	40.5	31.5	
Week 17 (n=73,74,73)	24.7	36.5	37	
Week 21 (n=72,74,72)	27.8	37.8	38.9	
Week 25 (EOT; n=62,63,62)	21	38.1	33.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Anti-drug Antibody (ADA) Status

End point title	Percentage of Participants by Anti-drug Antibody (ADA) Status

End point description:

Presence of anti-rituximab antibodies in blood. Participants with a positive antibody status at any time during the study were defined as having overall positive antibody status; participants with a negative antibody status throughout the study were defined as having overall negative antibody status. mITT populations.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose), 15 (prior to infusion), 29, 57, 85, and 169.

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: Percentage of Participants				
number (not applicable)	9.6	13.5	12.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Neutralizing Antibody (NAb) in Participants with a Positive ADA by Visit

End point title	Percentage of Participants with Neutralizing Antibody (NAb) in Participants with a Positive ADA by Visit

End point description:

mITT population. Only participants with a positive ADA status were included in the analysis.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose), 15 (prior to infusion), 29, 57, 85, and 169.

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	39	34	
Units: Percentage of participants				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline and Change from Baseline in Disease Activity Score Based on 28-Joint Count and CRP (DAS28-CRP)

End point title	Baseline and Change from Baseline in Disease Activity Score Based on 28-Joint Count and CRP (DAS28-CRP)

End point description:

DAS28-CRP was calculated from the swollen joint count and tender joint count using the 28 joints count and CRP (mg/L). Total score range: 0 to 9.4, higher score indicated more disease activity. DAS28-CRP less than or equal to (≤) 3.2 implied low disease activity, DAS28-CRP greater than (>)3.2 to ≤5.1 implied moderate to high disease activity, and DAS28-CRP less than (<)2.6 implied remission. mITT population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=73,74,73)	5.6862 (± 0.85109)	5.7928 (± 0.9503)	6.2221 (± 0.88162)	
Week 3 (n=69,74,69)	-0.9 (± 1.01)	-0.8 (± 1.13)	-1.1 (± 1.02)	
Week 5 (n=71,71,67)	-1.4 (± 1.17)	-1.4 (± 1.06)	-1.6 (± 1.2)	
Week 9 (n=68,73,70)	-1.7 (± 1.29)	-1.8 (± 1.3)	-2.1 (± 1.37)	
Week 13 (n=67,72,67)	-2 (± 1.43)	-2.1 (± 1.33)	-2.3 (± 1.34)	
Week 17 (n=66,71,67)	-2 (± 1.32)	-2.1 (± 1.39)	-2.4 (± 1.35)	
Week 21 (n=60,65,59)	-2 (± 1.28)	-1.9 (± 1.33)	-2.6 (± 1.35)	
Week 25 (EOT; n=50,58,55)	-1.7 (± 1.25)	-2 (± 1.3)	-2.5 (± 1.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: % Change from Baseline in DAS28-CRP by Visit

End point title	% Change from Baseline in DAS28-CRP by Visit

End point description:

DAS28-CRP was calculated from the swollen joint count and tender joint count using the 28 joints count and CRP (mg/L). Total score range: 0 to 9.4, higher score indicated more disease activity. DAS28-CRP ≤3.2 implied low disease activity, DAS28-CRP >3.2 to ≤5.1 implied moderate to high disease activity, and DAS28-CRP <2.6 implied remission. mITT population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: % change from baseline				
arithmetic mean (standard deviation)				
Week 3 (n= 69, 74, 69)	-16.1 (± 19.08)	-13.6 (± 20.41)	-18.6 (± 17.63)	
Week 5 (n= 71, 71, 67)	-25.4 (± 20.74)	-24 (± 18.22)	-26 (± 21.88)	
Week 9 (n= 68, 73, 70)	-31.2 (± 22.31)	-31 (± 21.92)	-34.2 (± 22.97)	
Week 13 (n= 67, 72, 67)	-34.7 (± 24)	-36.9 (± 22.1)	-37.4 (± 21.42)	
Week 17 (n= 66, 71, 67)	-34.9 (± 22.65)	-35.4 (± 23.28)	-39.1 (± 21.35)	
Week 21 (n= 60, 65, 59)	-35.5 (± 21.99)	-33.4 (± 22.56)	43.2 (± 21.39)	
Week 25 EOT (n= 50, 58, 55)	-31.1 (± 22.72)	-34.6 (± 22.25)	-40 (± 20.55)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Good European League Against Rheumatism (EULAR) Response Based on DAS28 by Visit

End point title	Percentage of Participants with Good European League Against Rheumatism (EULAR) Response Based on DAS28 by Visit

End point description:

The DAS28-based EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline and the level of disease activity reached. Good responders: change from baseline >1.2 with DAS28 ≤3.2; moderate responders: change from baseline >1.2 with DAS28 >3.2 to ≤5.1 or change from baseline >0.6 to ≤1.2 with DAS28 ≤5.1; non-responders: change from baseline ≤0.6, or change from baseline >0.6 and ≤1.2 with DAS28 >5.1. mITT population

End point type	Secondary

End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: Percentage of participants				
number (not applicable)				
Week 3 (n= 69, 74, 69)	14.5	10.8	8.7	
Week 5 (n=71, 71, 67)	22.5	22.5	19.4	
Week 9 (n= 68, 73, 70)	30.9	31.5	25.7	
Week 13 (n= 67, 72, 67)	41.8	44.4	32.8	
Week 17 (n= 66, 71, 67)	36.4	38	32.8	
Week 21 (n= 60, 65, 59)	35	35.4	47.5	
Week 25 EOT (n= 50, 58, 55)	30	36.2	41.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Moderate EULAR Response Based on Disease Activity Score Based on DAS28 by Visit

End point title	Percentage of Participants with Moderate EULAR Response Based on Disease Activity Score Based on DAS28 by Visit

End point description:

The DAS28-based EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline and the level of disease activity reached. Good responders: change from baseline >1.2 with DAS28 ≤3.2; moderate responders: change from baseline >1.2 with DAS28 >3.2 to ≤5.1 or change from baseline >0.6 to ≤1.2 with DAS28 ≤5.1; non-responders: change from baseline ≤0.6, or change from baseline >0.6 and ≤1.2 with DAS28 >5.1. mITT population.

End point type	Secondary

End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: % of participants				
number (not applicable)				
Week 3 (n= 69, 74, 69)	33.3	35.1	42	
Week 5 (n= 71, 71, 67)	47.9	39.4	43.3	
Week 9 (n= 68, 73, 70)	45.6	43.8	54.3	
Week 13 (n= 67, 72, 67)	38.8	37.5	44.8	
Week 17 (n= 66, 71, 67)	45.5	39.4	53.7	
Week 21 (n= 60, 65, 59)	51.7	46.2	39	

Week 25 EOT (n= 50, 58, 55)	50	46.6	43.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with No EULAR Response Based on DAS28 by Visit

End point title	Percentage of Participants with No EULAR Response Based on DAS28 by Visit

End point description:

The DAS28-based EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline and the level of disease activity reached. Good responders: change from baseline >1.2 with DAS28 ≤3.2; moderate responders: change from baseline >1.2 with DAS28 >3.2 to ≤5.1 or change from baseline >0.6 to ≤1.2 with DAS28 ≤5.1; non-responders: change from baseline ≤0.6, or change from baseline >0.6 and ≤1.2 with DAS28 >5.1. mITT population.

End point type	Secondary

End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: % of participants				
number (not applicable)				
Week 3 (n= 69, 74, 69)	52.2	54.1	49.3	
Week 5 (n= 71, 71, 67)	29.6	38	37.3	
Week 9 (n= 68, 73, 70)	23.5	24.7	20	
Week 13 (n= 67, 72, 67)	19.4	18.1	22.4	
Week 17 (n= 66, 71, 67)	18.2	22.5	13.4	
Week 21 (n= 60, 65, 59)	13.3	18.5	13.6	
Week 25 EOT (n= 50, 58, 55)	20	17.2	14.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Low Disease Activity Score (DAS; ≤3.2) by Visit

End point title	Percentage of Participants with Low Disease Activity Score (DAS; ≤3.2) by Visit

End point description:

DAS28-CRP was calculated from the swollen joint count and tender joint count using the 28 joints count and CRP (mg/L). Total score range: 0 to 9.4, higher score indicated more disease activity. DAS28-CRP ≤3.2 implied low disease activity. mITT population.

End point type	Secondary

End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: % of participants				
number (not applicable)				
Week 3 (n=69,74,69)	14.5	10.8	10.1	
Week 5 (n=71,71,67)	23.9	25.4	19.4	
Week 9 (68,73,70)	30.9	32.9	25.7	
Week 13 (n=67,72,67)	41.8	44.4	32.8	
Week 17 (n=66,71,67)	36.4	38	32.8	
Week 21 (n=60,65,59)	35	36.9	47.5	
Week 25 (EOT; n=50,58,55)	32	37.9	41.8	

Statistical analyses

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 3
Comparison groups	Rituximab-Pfizer v Rituximab-EU
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.78

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 3
Comparison groups	Rituximab-US v Rituximab-Pfizer

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.73

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 3
Comparison groups	Rituximab-EU v Rituximab-US
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	2.45

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 5
Comparison groups	Rituximab-Pfizer v Rituximab-EU
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.88

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 5
Comparison groups	Rituximab-US v Rituximab-Pfizer

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.54

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 5
Comparison groups	Rituximab-US v Rituximab-EU
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.44

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 9
Comparison groups	Rituximab-EU v Rituximab-Pfizer
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.73

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 9
Comparison groups	Rituximab-US v Rituximab-Pfizer

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.42

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 9
Comparison groups	Rituximab-US v Rituximab-EU
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.31

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 13
Comparison groups	Rituximab-EU v Rituximab-Pfizer
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.56

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 13
Comparison groups	Rituximab-US v Rituximab-Pfizer

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.22

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 13
Comparison groups	Rituximab-EU v Rituximab-US
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.13

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 17
Comparison groups	Rituximab-EU v Rituximab-Pfizer
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.62

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 17
Comparison groups	Rituximab-US v Rituximab-Pfizer

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.44

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 17
Comparison groups	Rituximab-US v Rituximab-EU
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.36

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 21
Comparison groups	Rituximab-EU v Rituximab-Pfizer
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.69

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 21
Comparison groups	Rituximab-US v Rituximab-Pfizer

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.1

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 21
Comparison groups	Rituximab-US v Rituximab-EU
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.95

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 25
Comparison groups	Rituximab-Pfizer v Rituximab-EU
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 25
Comparison groups	Rituximab-US v Rituximab-Pfizer

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.18

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 25
Comparison groups	Rituximab-US v Rituximab-EU
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.73

Secondary: Percentage of Participants with DAS Remission (DAS <2.6) by Visit

End point title	Percentage of Participants with DAS Remission (DAS <2.6) by Visit

End point description:

DAS28-CRP was calculated from the swollen joint count and tender joint count using the 28 joints count and CRP (mg/L). Total score range: 0 to 9.4, higher score indicated more disease activity. DAS28-CRP <2.6 implied remission. mITT population.

End point type	Secondary

End point timeframe:

Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: Percentage of Participants				
number (not applicable)				
Week 3 (n=69,74,69)	8.7	4.1	7.2	
Week 5 (n=71,71,67)	16.9	8.5	11.9	
Week 9 (n=68,73,70)	26.5	20.5	20	
Week 13 (n=67,72,67)	28.4	29.2	25.4	

Week 17 (n=66,71,67)	25.8	25.4	23.9	
Week 21 (n=60,65,59)	25	16.9	30.5	
Week 25 (EOT; n=50,58,55)	28	24.1	23.6	

Statistical analyses

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 3
Comparison groups	Rituximab-Pfizer v Rituximab-EU
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	1.79

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 3
Comparison groups	Rituximab-US v Rituximab-Pfizer
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	2.6

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 3
Comparison groups	Rituximab-EU v Rituximab-US
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	7.2

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 5
Comparison groups	Rituximab-EU v Rituximab-Pfizer
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.26

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 5
Comparison groups	Rituximab-Pfizer v Rituximab-US
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Log risk ratio
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.62

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 5
Comparison groups	Rituximab-EU v Rituximab-US
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	3.86

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 9

Comparison groups	Rituximab-EU v Rituximab-Pfizer
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.41

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 9
Comparison groups	Rituximab-US v Rituximab-Pfizer
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.4

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 9
Comparison groups	Rituximab-EU v Rituximab-US
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.87

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 13
Comparison groups	Rituximab-EU v Rituximab-Pfizer

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.74

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 13
Comparison groups	Rituximab-US v Rituximab-Pfizer
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.57

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 13
Comparison groups	Rituximab-US v Rituximab-EU
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.5

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 17
Comparison groups	Rituximab-Pfizer v Rituximab-EU

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.74

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 17
Comparison groups	Rituximab-US v Rituximab-Pfizer
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.68

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 17
Comparison groups	Rituximab-US v Rituximab-EU
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.69

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 21
Comparison groups	Rituximab-EU v Rituximab-Pfizer

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.36

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 21
Comparison groups	Rituximab-Pfizer v Rituximab-US
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	2.19

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 21
Comparison groups	Rituximab-EU v Rituximab-US
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	3.5

Statistical analysis title	Rituximab-EU versus rituximab-Pfizer at Week 25
Comparison groups	Rituximab-Pfizer v Rituximab-EU

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.63

Statistical analysis title	Rituximab-US versus rituximab-Pfizer at Week 25
Comparison groups	Rituximab-Pfizer v Rituximab-US
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.62

Statistical analysis title	Rituximab-US versus rituximab-EU at Week 25
Comparison groups	Rituximab-EU v Rituximab-US
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Log risk ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.89

Secondary: Baseline and Change from Baseline in HAQ-DI by Visit

End point title	Baseline and Change from Baseline in HAQ-DI by Visit

End point description:

Health Assessment Questionnaire - Disability Index (HAQ-DI): participant-reported assessment of ability to perform tasks in 8 categories of daily living activities: dress/groom; arise; eat; walk; reach; grip; hygiene; and common activities over past week. Each item scored on 4-point scale from 0 to 3: 0=no difficulty; 1=some difficulty; 2=much difficulty; 3=unable to do. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total

possible score range 0-3 where 0 = least difficulty and 3 = extreme difficulty. mITT population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	74	73	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline (n=73,74,73)	1.6541 (± 0.5734)	1.5929 (± 0.53597)	1.7466 (± 0.62081)	
Week 3 (n=70,74,70)	-0.2 (± 0.39)	-0.2 (± 0.34)	-0.2 (± 0.33)	
Week 5 (n=72,70,68)	-0.3 (± 0.39)	-0.3 (± 0.45)	-0.3 (± 0.43)	
Week 9 (n=68,73,70)	-0.4 (± 0.47)	-0.5 (± 0.5)	-0.5 (± 0.54)	
Week 13 (n=67,72,68)	-0.4 (± 0.55)	-0.6 (± 0.56)	-0.5 (± 0.52)	
Week 17 (n=66,71,67)	-0.3 (± 0.49)	-0.6 (± 0.58)	-0.5 (± 0.55)	
Week 21 (n=63,70,64)	-0.4 (± 0.53)	-0.6 (± 0.58)	-0.6 (± 0.61)	
Week 25 (EOT; n=52,59,55)	-0.4 (± 0.49)	-0.5 (± 0.63)	-0.6 (± 0.57)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in HAQ-DI Score by Visit

End point title	Percent Change from Baseline in HAQ-DI Score by Visit

End point description:

HAQ-DI: participant-reported assessment of ability to perform tasks in 8 categories of daily living activities: dress/groom; arise; eat; walk; reach; grip; hygiene; and common activities over past week. Each item scored on 4-point scale from 0 to 3: 0=no difficulty; 1=some difficulty; 2=much difficulty; 3=unable to do. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0-3 where 0 = least difficulty and 3 = extreme difficulty. mITT population.

End point type	Secondary

End point timeframe:

Baseline and Weeks 3, 5, 9, 13, 17, 21 and 25 (EOT)

End point values	Rituximab-Pfizer	Rituximab-EU	Rituximab-US	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	74	73	
Units: Percentage change				
arithmetic mean (standard deviation)				
Week 3 (n=70,74,70)	-10.4 (± 37.27)	-13.2 (± 26.03)	-9 (± 25.68)	

Week 5 (n=72,70,68)	-15.1 (± 40)	-23.5 (± 30.45)	-14.8 (± 43.82)	
Week 9 (n=68,73,70)	-22.4 (± 35.96)	-31.7 (± 34.64)	-24.5 (± 35.51)	
Week 13 (n=67,72,68)	-14.6 (± 50.35)	-39.5 (± 37.46)	-30.7 (± 31.91)	
Week 17 (n=66,71,67)	-16.9 (± 48.95)	-39.1 (± 38.85)	-28.8 (± 36.43)	
Week 21 (n=63,70,64)	-21 (± 48.04)	-39.2 (± 38.34)	-33.5 (± 35.18)	
Week 25 (EOT; n=52,59,55)	-17.7 (± 54.01)	-37.1 (± 41.18)	-38.4 (± 34.6)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected for 28 days after the last administration of study drug or, in the case of incomplete B-cell count recovery, for up to 1 year after Study Day 1.

Adverse event reporting additional description:

The same event may appear as both an AE and a serious AE (SAE). However, what is presented are distinct events. An event may be categorized as serious in 1 participant and as non-serious in another participant, or 1 participant may have experienced both a serious and non-serious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Rituximab-Pfizer

Reporting group description:

Rituximab-Pfizer group received intravenous (IV) rituximab (PF-05280586) infusion 1000 milligrams (mg) per (/) 500 milliliters (mL) (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

Reporting group title	Rituximab-US

Reporting group description:

Rituximab-US group received IV rituximab (Rituxan) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

Reporting group title	Rituximab-EU

Reporting group description:

Rituximab-EU group received IV rituximab (MabThera) infusion 1000 mg/500 mL (preceded by 100 mg methylprednisolone, an antipyretic such as paracetamol, and an antihistamine such as diphenhydramine) on Study Days 1 and 15 and continued to receive a stable background regimen of MTX 10 to 25 mg/week (7.5 mg/week in the event of prior poor tolerance) for up to 25 weeks. Folate supplementation was encouraged according to local standard of care.

Serious adverse events	Rituximab-Pfizer	Rituximab-US	Rituximab-EU
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 73 (6.85%)	4 / 73 (5.48%)	2 / 74 (2.70%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone neoplasm			

subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenic purpura			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Intentional self-injury			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthropathy			

subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Rituximab-Pfizer	Rituximab-US	Rituximab-EU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 73 (68.49%)	45 / 73 (61.64%)	40 / 74 (54.05%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Benign neoplasm of thyroid gland			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Skin papilloma			

subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	2
Hot flush			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	1 / 74 (1.35%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	4 / 73 (5.48%)	1 / 73 (1.37%)	2 / 74 (2.70%)
occurrences (all)	4	1	2
Hypotension			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Venous insufficiency			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	3 / 73 (4.11%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	3	0	0
Chest discomfort			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	5 / 73 (6.85%)	1 / 73 (1.37%)	1 / 74 (1.35%)
occurrences (all)	7	1	2
Inflammation			

subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Infusion site extravasation			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Local swelling			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Vaginal haemorrhage			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Dry throat			

subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	1 / 73 (1.37%)	3 / 73 (4.11%)	0 / 74 (0.00%)
occurrences (all)	1	3	0
Hypoxia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	1 / 73 (1.37%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	1	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 73 (1.37%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	1	1	0
Productive cough			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Pulmonary congestion			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Rales			
subjects affected / exposed	1 / 73 (1.37%)	2 / 73 (2.74%)	0 / 74 (0.00%)
occurrences (all)	1	2	0
Respiratory disorder			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Respiratory tract congestion			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Sneezing			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Sputum discoloured			

subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Throat irritation			
subjects affected / exposed	1 / 73 (1.37%)	2 / 73 (2.74%)	1 / 74 (1.35%)
occurrences (all)	1	2	1
Wheezing			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 73 (0.00%)	3 / 73 (4.11%)	1 / 74 (1.35%)
occurrences (all)	0	4	1
Depression			
subjects affected / exposed	2 / 73 (2.74%)	3 / 73 (4.11%)	1 / 74 (1.35%)
occurrences (all)	2	3	1
Insomnia			
subjects affected / exposed	1 / 73 (1.37%)	3 / 73 (4.11%)	2 / 74 (2.70%)
occurrences (all)	1	3	2
Mood swings			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Restlessness			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Investigations			
Bilirubin conjugated increased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 73 (1.37%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	1	1	0
Blood bilirubin increased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Blood calcium increased			

subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	1 / 73 (1.37%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	1	1	0
Blood glucose increased			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Blood pressure decreased			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	2 / 74 (2.70%)
occurrences (all)	0	0	2
Blood urea increased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	1 / 74 (1.35%)
occurrences (all)	0	1	1
Haematocrit decreased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Liver function test abnormal			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Weight decreased			

subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 73 (2.74%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	2	1	0
Epicondylitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	1 / 73 (1.37%)	2 / 73 (2.74%)	1 / 74 (1.35%)
occurrences (all)	1	2	1
Foot fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Fractured sacrum			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Hand fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Laceration			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Limb injury			

subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
Lumbar vertebral fracture			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Muscle contusion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Nail avulsion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Tooth fracture			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Underdose			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Vaccination complication			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Wound			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Atrial flutter			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	2	0
Extrasystoles			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Tachycardia paroxysmal			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0

Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 73 (2.74%)	2 / 73 (2.74%)	1 / 74 (1.35%)
occurrences (all)	2	2	1
Headache			
subjects affected / exposed	3 / 73 (4.11%)	4 / 73 (5.48%)	2 / 74 (2.70%)
occurrences (all)	5	4	2
Hypoaesthesia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
Migraine			
subjects affected / exposed	1 / 73 (1.37%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	1	1	0
Neuralgia			
subjects affected / exposed	2 / 73 (2.74%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	2	0	0
Paraesthesia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Sciatica			
subjects affected / exposed	2 / 73 (2.74%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	2	0	0
Sinus headache			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Iron deficiency anaemia			

subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Ear disorder			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Ear pruritus			
subjects affected / exposed	2 / 73 (2.74%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	2	0	0
Tinnitus			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Vertigo positional			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	2
Blepharitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	2	0	0
Conjunctivitis allergic			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Dry eye			

subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Eye haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Eye pruritus			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Eyelid pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 73 (0.00%)	2 / 73 (2.74%)	0 / 74 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	0 / 73 (0.00%)	2 / 73 (2.74%)	0 / 74 (0.00%)
occurrences (all)	0	3	0
Abdominal pain lower			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Abdominal tenderness			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Colitis ulcerative			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 73 (1.37%)	1 / 73 (1.37%)	2 / 74 (2.70%)
occurrences (all)	1	1	2

Diarrhoea			
subjects affected / exposed	1 / 73 (1.37%)	2 / 73 (2.74%)	2 / 74 (2.70%)
occurrences (all)	1	3	2
Diverticulum			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Diverticulum intestinal			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	2 / 73 (2.74%)	0 / 73 (0.00%)	2 / 74 (2.70%)
occurrences (all)	2	0	2
Dyspepsia			
subjects affected / exposed	2 / 73 (2.74%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	2	1	0
Dysphagia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	1 / 74 (1.35%)
occurrences (all)	0	1	1
Haematochezia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Lip swelling			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Lip ulceration			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0

Nausea			
subjects affected / exposed	1 / 73 (1.37%)	4 / 73 (5.48%)	1 / 74 (1.35%)
occurrences (all)	1	5	1
Rectal haemorrhage			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Tongue ulceration			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	2 / 74 (2.70%)
occurrences (all)	0	2	2
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Campbell de Morgan spots			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Erythema			

subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Intertrigo			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Onycholysis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	3 / 73 (4.11%)	2 / 73 (2.74%)	1 / 74 (1.35%)
occurrences (all)	3	2	1
Rash			
subjects affected / exposed	2 / 73 (2.74%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	3	0	1
Rash vesicular			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
Skin mass			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 73 (1.37%)	1 / 73 (1.37%)	1 / 74 (1.35%)
occurrences (all)	1	1	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Hydronephrosis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Nephrolithiasis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0

Renal pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 73 (1.37%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 73 (4.11%)	4 / 73 (5.48%)	4 / 74 (5.41%)
occurrences (all)	3	4	5
Arthritis			
subjects affected / exposed	1 / 73 (1.37%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	1	1	0
Back pain			
subjects affected / exposed	1 / 73 (1.37%)	2 / 73 (2.74%)	1 / 74 (1.35%)
occurrences (all)	1	2	1
Bursitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Costochondritis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Fibromyalgia			
subjects affected / exposed	1 / 73 (1.37%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	1	1	0
Flank pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Joint instability			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	2 / 73 (2.74%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	2	0	0
Muscle atrophy			

subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	4 / 73 (5.48%)	0 / 73 (0.00%)	2 / 74 (2.70%)
occurrences (all)	4	0	2
Musculoskeletal stiffness			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Osteoarthritis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Osteonecrosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 73 (0.00%)	2 / 73 (2.74%)	0 / 74 (0.00%)
occurrences (all)	0	2	0
Periarthritis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Rheumatoid arthritis			

subjects affected / exposed	1 / 73 (1.37%)	5 / 73 (6.85%)	5 / 74 (6.76%)
occurrences (all)	1	6	8
Spinal pain			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Spondylolisthesis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Synovitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Arthritis infective			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	3 / 73 (4.11%)	4 / 73 (5.48%)	2 / 74 (2.70%)
occurrences (all)	3	4	2
Cellulitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
Furuncle			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 73 (0.00%)	2 / 73 (2.74%)	2 / 74 (2.70%)
occurrences (all)	0	2	2
Gastroenteritis viral			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	1 / 74 (1.35%)
occurrences (all)	0	1	1

Gastrointestinal viral infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Herpes simplex			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Infected bites			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	2 / 73 (2.74%)	2 / 73 (2.74%)	1 / 74 (1.35%)
occurrences (all)	2	2	1
Nasopharyngitis			
subjects affected / exposed	3 / 73 (4.11%)	3 / 73 (4.11%)	1 / 74 (1.35%)
occurrences (all)	3	3	1
Oral herpes			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Otitis externa			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0

Rhinitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
Sinusitis			
subjects affected / exposed	3 / 73 (4.11%)	2 / 73 (2.74%)	6 / 74 (8.11%)
occurrences (all)	3	2	8
Tooth abscess			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	2 / 74 (2.70%)
occurrences (all)	1	0	2
Upper respiratory tract infection			
subjects affected / exposed	7 / 73 (9.59%)	4 / 73 (5.48%)	5 / 74 (6.76%)
occurrences (all)	7	4	6
Urinary tract infection			
subjects affected / exposed	1 / 73 (1.37%)	2 / 73 (2.74%)	0 / 74 (0.00%)
occurrences (all)	2	2	0
Viral infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Hyperlipidaemia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Hypokalaemia			

subjects affected / exposed	2 / 73 (2.74%)	0 / 73 (0.00%)	0 / 74 (0.00%)
occurrences (all)	4	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 73 (0.00%)	1 / 73 (1.37%)	1 / 74 (1.35%)
occurrences (all)	0	1	1
Vitamin B12 deficiency			
subjects affected / exposed	0 / 73 (0.00%)	0 / 73 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 January 2012	The original protocol (dated 15 December 2011) was amended on 12 January 2012 with administrative changes. The purpose of this amendment was to correct typographical errors in the Schedule of Activities, References, and Appendices 6 and 7. Appendix 6 (Rescue Therapy) was removed to prevent confusion.
20 January 2012	The protocol was amended on 20 January 2012 with administrative changes. The purpose of this amendment was to adjust terminology referencing biosimilarity and reference products per advice from US Food and Drug Administration (FDA).
02 February 2012	The protocol was amended on 02 February 2012 with administrative changes. The purpose of this amendment was to adjust terminology referencing product licensure per advice from US FDA.
07 September 2012	The protocol was amended on 07 September 2012 with administrative changes, including corrections to typographical errors and updates to section numbering along with clarifications/ corrections to the following sections of the protocol: Primary PK parameters, Schedule of Activities, PK/PD Study Sampling Time Points, Safety of Rituximab (Section 1.1.1.2), Rationale, PK Evaluations, Inclusion and Exclusion Criteria, Preparation and Dosing, Stable Background Pain or Other Arthritis Therapy, Pharmacokinetic Evaluation, Pharmacodynamic Evaluation, Per Protocol (PP) Population, Pharmacokinetic Analysis, Analysis of Clinical Response Endpoints, Interim Look, Concomitant Medications and Procedures.
22 August 2013	The protocol was amended on 22 August 2013 with administrative changes, including corrections to typographical errors and updates to section numbering. Population PK/PD modelling was added as a secondary objective. Visit windows were clarified and inconsistencies within the protocol were corrected. It was clarified that tuberculosis screening should have been conducted per local guidelines and alternative radiological techniques to chest x-ray were acceptable. Updated language regarding interim PK assessment. Corrected dose to 1000 mg, rather than 1000 mg/kg. Updated sections regarding the timeframe for reporting AEs, occupational exposure, exposure during pregnancy, and communication of results to conform to current sponsor standard language.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported