Clinical trial results:
A Randomized, Phase 3, Controlled, Double-Blind, Parallel-Group, Multicenter Study to Evaluate the Safety and Efficacy of Rituximab in Combination With Methotrexate (MTX) Compared to MTX Alone, in Methotrexate-Naive Patients With Active Rheumatoid Arthritis

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

Summary

EudraCT number	2005-002395-15
Trial protocol	FI ES DE BE SE CZ IT GB DK
Global end of trial date	22 July 2013

Results information

Result version number	v2 (current)
This version publication date	15 July 2016
First version publication date	07 August 2015
Version creation reason	• Correction of full data set Due to EMA system issues, the record results need correction by the MAH.

Trial information

Trial identification

Sponsor protocol code	WA17047

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00299104
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 July 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of rituximab in the prevention of progression in structural joint damage and to evaluate the safety of rituximab in participants with active rheumatoid arthritis initiating treatment with MTX.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 January 2006
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 States: 181
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 42
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Brazil: 43
Country: Number of subjects enrolled	Canada: 29
Country: Number of subjects enrolled	China: 36
Country: Number of subjects enrolled	Guatemala: 22
Country: Number of subjects enrolled	India: 35

Country: Number of subjects enrolled	Mexico: 65
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Panama: 10
Country: Number of subjects enrolled	Peru: 34
Country: Number of subjects enrolled	Philippines: 17
Country: Number of subjects enrolled	Poland: 54
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Korea, Republic of: 18
Worldwide total number of subjects	748
EEA total number of subjects	241

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)	668
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening was from Day -28 to Day 1 which could be extended to accommodate washout of prohibited medications. Participants randomized to the study were 251, 252 and 252 in placebo+methotrexate arm, rituximab(0.5 g x 2) + methotrexate and rituximab(1.0 g x 2) + methotrexate, respectively, out of which 748 received study drug.

Period 1

Period 1 title	Treatment Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Plus (+) Methotrexate

Arm description:

Placebo intravenously on Days 1 and 15 + methotrexate orally at a dose of 7.5 milligrams (mg) escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. From Week 104 participants were eligible to receive Rituximab 2 X 0.5 grams (g) or Rituximab 2 X 1.0 g every 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8.

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

Dosage and administration details:

Participants received placebo intravenously on Days 1 and 15.

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

Dosage and administration details:

Participants received either 0.5 mg or 1.0 mg rituximab intravenously on Days 1 and 15.

Arm title	Rituximab (0.5 g X 2) + Methotrexate

Arm description:

Rituximab intravenously at a dose of 0.5 g on Days 1 and 15 + a background of methotrexate orally at a

dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS-ESR) result was greater than or equal to (≥)2.6.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8.

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

Dosage and administration details:

Participants received rituximab intravenously at a dose of 0.5 g on Days 1 and 15. Subsequent rituximab courses were given every 24 weeks for up to 5 years, as indicated.

Arm title	Rituximab (1.0 g x 2) + Methotrexate

Arm description:

Rituximab intravenously at a dose of 1.0 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the DAS-ESR result was ≥2.6.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 1.0 mg intravenously on Days 1 and 15. Subsequent treatment courses were given every 24 weeks up to 5 years, as indicated.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

7.5 mg escalating by 2.5 mg a week ever 1-2 weeks to achieve 15 mg per week by week 4 and 20 mg per week by Week 8.

Number of subjects in period 1	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate
Started	249	249	250
Safety/ITT: Received Study Drug	249	249	250
Completed Week 24	227	240	241
Completed Week 52	213	227	232
Completed Week 104	178	213	216
Completed	62	77	80
Not completed	187	172	170
Insufficient therapeutic response	34	13	8
Consent withdrawn by subject	14	19	9
Death	1	1	1
Administrative reasons	104	117	135
Refused treatment	9	2	2
Adverse event	14	9	7
Violation of selection criteria	1	2	-
Lost to follow-up	9	8	8
Protocol deviation	1	1	-

Period 2

Period 2 title	Safety Follow-Up (SFU)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	SFU: Placebo + Methotrexate

Arm description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	SFU: Rituximab (0.5 g x 2) + Methotrexate

Arm description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	SFU: Rituximab (1.0 g x 2) + Methotrexate

Arm description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	SFU: Placebo + Methotrexate	SFU: Rituximab (0.5 g x 2) + Methotrexate	SFU: Rituximab (1.0 g x 2) + Methotrexate
Started	62	77	80
Entered Extended Safety Follow-Up	129	40	51
Completed	129	171	176
Not completed	55	41	37
Consent withdrawn by subject	16	21	11
Failure to return	-	11	20
Death	3	2	1
Administrative reasons	27	7	5
Lost to follow-up	9	-	-
Joined	122	135	133
Completed Week 104 of Treatment Phase	-	135	133
Entered Safety Follow-Up	122	-	-

Period 3

Period 3 title	Extended Safety Follow-Up (ESFU) Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ESFU: Placebo + Methotrexate

Arm description:

At the end of 48-Week SFU participants entered ESFU. Participants who did not receive any study drug were not required to enter ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	ESFU: Rituximab (0.5 g x 2) + Methotrexate

Arm description:

At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	ESFU: Rituximab (1.0 g x 2) + Methotrexate

Arm description:

At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3[1]	ESFU: Placebo + Methotrexate	ESFU: Rituximab (0.5 g x 2) + Methotrexate	ESFU: Rituximab (1.0 g x 2) + Methotrexate
Started	34	40	51
Completed	29	31	39
Not completed	5	9	12
Consent withdrawn by subject	2	4	8
Administrative reasons	1	2	2
Death	-	1	-
Lost to follow-up	2	2	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only participants with CD19+ B-cell counts below baseline level or less than 80 cells/microliter entered the ESFU period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Plus (+) Methotrexate

Reporting group description:

Placebo intravenously on Days 1 and 15 + methotrexate orally at a dose of 7.5 milligrams (mg) escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. From Week 104 participants were eligible to receive Rituximab 2 X 0.5 grams (g) or Rituximab 2 X 1.0 g every 24 weeks.

Reporting group title	Rituximab (0.5 g X 2) + Methotrexate

Reporting group description:

Rituximab intravenously at a dose of 0.5 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS-ESR) result was greater than or equal to (≥)2.6.

Reporting group title	Rituximab (1.0 g x 2) + Methotrexate

Reporting group description:

Rituximab intravenously at a dose of 1.0 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the DAS-ESR result was ≥2.6.

Reporting group values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate
Number of subjects	249	249	250
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 48.06 ± 12.692	 47.87 ± 13.391	 47.89 ± 13.324
Gender categorical Units: Subjects			
Female	192	203	212
Male	57	46	38

Reporting group values	Total		
Number of subjects	748		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -	 	
Gender categorical Units: Subjects			
Female	607		

Male	141		

End points

End points reporting groups

Reporting group title	Placebo Plus (+) Methotrexate

Reporting group description:

Placebo intravenously on Days 1 and 15 + methotrexate orally at a dose of 7.5 milligrams (mg) escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. From Week 104 participants were eligible to receive Rituximab 2 X 0.5 grams (g) or Rituximab 2 X 1.0 g every 24 weeks.

Reporting group title	Rituximab (0.5 g X 2) + Methotrexate

Reporting group description:

Rituximab intravenously at a dose of 0.5 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS-ESR) result was greater than or equal to (≥)2.6.

Reporting group title	Rituximab (1.0 g x 2) + Methotrexate

Reporting group description:

Rituximab intravenously at a dose of 1.0 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the DAS-ESR result was ≥2.6.

Reporting group title	SFU: Placebo + Methotrexate

Reporting group description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

Reporting group title	SFU: Rituximab (0.5 g x 2) + Methotrexate

Reporting group description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

Reporting group title	SFU: Rituximab (1.0 g x 2) + Methotrexate

Reporting group description:

At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered.

Reporting group title	ESFU: Placebo + Methotrexate

Reporting group description:

At the end of 48-Week SFU participants entered ESFU. Participants who did not receive any study drug were not required to enter ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

Reporting group title	ESFU: Rituximab (0.5 g x 2) + Methotrexate

Reporting group description:

At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

Reporting group title	ESFU: Rituximab (1.0 g x 2) + Methotrexate

Reporting group description:

At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

Primary: Change From Baseline in Modified Total Sharp Score (mTSS) From Screening at Week 52

End point title	Change From Baseline in Modified Total Sharp Score (mTSS) From Screening at Week 52

End point description:

Rate of progression in structural joint damage (PJD) by change in Total Modified Sharp Score (TMSS) from screening to Week 52 in the modified intent-to-treat (MITT) population. MITT population included all randomized participants who received at least one infusion and had both screening and post-baseline radiographic assessments at the given time-point for analysis. TMSS is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change and higher scores represent a worsening of joint erosions and joint space narrowing. Modified intent-to-treat (MITT) population includes patients with a screening and at least one post-baseline radiographic evaluation, grouped as randomized. Linear interpolation/extrapolation used for missing data.

End point type	Primary

End point timeframe:

Baseline and Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232[1]	239[2]	244[3]	
Units: score on a scale				
arithmetic mean (standard deviation)	1.079 (± 4.0934)	0.646 (± 1.9196)	0.359 (± 1.0095)	

Notes:

[1] - MITT population

[2] - MITT population

[3] - MITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Comparing all three treatment groups. The Closure Principle was used to adjust for multiple comparisons.

Comparison groups	Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate v Rituximab (1.0 g x 2) + Methotrexate
Number of subjects included in analysis	715
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0016
Method	Kruskal-wallis

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Rituximab 2 x 0.5 g + Methotrexate arm versus (vs) Placebo + Methotrexate, stratified for region and baseline rheumatoid factor (RF) status. The Closure Principle was used to adjust for multiple comparisons.

Comparison groups	Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1824
Method	Van-Elteren

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Rituximab 2 x 1.0 g + Methotrexate arm vs Placebo + Methotrexate, stratified for region and baseline RF status. The Closure Principle was used to adjust for multiple comparisons.

Comparison groups	Placebo Plus (+) Methotrexate v Rituximab (1.0 g x 2) + Methotrexate
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0004
Method	Van-Elteren

Secondary: Change From Baseline in Modified Sharp Erosion Score at Week 52

End point title	Change From Baseline in Modified Sharp Erosion Score at Week 52

End point description:

Rate of PJD by change in modified Sharp erosion score from screening to Week 52. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. A score of 0 would indicate no change and higher scores represent a worsening of joint erosions.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232[4]	239[5]	244[6]	
Units: score on a scale				
arithmetic mean (standard deviation)	0.738 (± 2.048)	0.453 (± 1.2065)	0.233 (± 0.6252)	

Notes:

[4] - MITT population

[5] - MITT population

[6] - MITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Comparing all three treatment groups; The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

Comparison groups	Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate v Rituximab (1.0 g x 2) + Methotrexate
Number of subjects included in analysis	715
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0004
Method	Kruskal-wallis

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Rituximab 2 x 0.5 g + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status. The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

Comparison groups	Rituximab (0.5 g X 2) + Methotrexate v Placebo Plus (+) Methotrexate
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1194
Method	Van-Elteren

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Rituximab 2 x 1.0 g + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status. The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

Comparison groups	Placebo Plus (+) Methotrexate v Rituximab (1.0 g x 2) + Methotrexate
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	Van-Elteren

Secondary: Percentage of Participants Without Radiographic Progression at Week 52

End point title	Percentage of Participants Without Radiographic Progression at Week 52

End point description:

Percentage of participants without radiographic progression at Week 52, defined as change in total modified Sharp Score (TMSS) ≤ 0. TMSS is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a

range of 0 to 168. A score of 0 would indicate no change.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232[7]	239[8]	244[9]	
Units: Percentage				
number (not applicable)	53.4	57.7	63.5	

Notes:

[7] - MITT population

[8] - MITT population

[9] - MITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Rituximab 2 x 0.5 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline RF status

Comparison groups	Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3803 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.13

Notes:

[10] - This was a secondary endpoint in a hierarchical testing structure.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+) Methotrexate
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0309 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.18

Notes:

[11] - This was a secondary endpoint in a hierarchical testing structure.

Secondary: Percentage of Participants Without Radiographic Progression in Total Erosion Score at Week 52

End point title	Percentage of Participants Without Radiographic Progression in Total Erosion Score at Week 52

End point description:

No radiographic progression is defined as a change in the total erosion score at Week 52 of less than or equal to zero.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232[12]	239[13]	244[14]	
Units: Percentage of participants				
number (not applicable)	54.7	59	66.8	

Notes:

[12] - MITT population

[13] - MITT population

[14] - MITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rituximab (0.5 g X 2) + Methotrexate v Placebo Plus (+) Methotrexate
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.3752 [16]
Method	Cochran-Mantel-Haenszel

Notes:

[15] - Rituximab (0.5 g x 2) + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status.

[16] - This was a secondary endpoint in a hierarchical testing structure.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Rituximab (1.0 g x 2) + Methotrexate versus Placebo + Methotrexate, stratified for region and Baseline RF status.

Comparison groups	Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+)

	Methotrexate
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0081 [17]
Method	Cochran-Mantel-Haenszel

Notes:

[17] - This was a secondary endpoint in a hierarchical testing structure.

Secondary: Change From Baseline in Modified Joint Space Narrowing (JSN) Score at Week 52

End point title	Change From Baseline in Modified Joint Space Narrowing (JSN) Score at Week 52

End point description:

Rate of progression in structural joint damage (PJD) by change in modified joint space narrowing (JSN) from screening to Week 52. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change and higher scores represent a worsening of joint space narrowing.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232[18]	239[19]	244[20]	
Units: Units on a scale				
arithmetic mean (standard deviation)	0.341 (± 2.2408)	0.193 (± 0.9422)	0.126 (± 0.6363)	

Notes:

[18] - MITT population

[19] - MITT population

[20] - MITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Comparing all three treatment groups

Comparison groups	Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate v Rituximab (1.0 g x 2) + Methotrexate
Number of subjects included in analysis	715
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5939 [21]
Method	Kruskal-wallis

Notes:

[21] - The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

	Statistical Analysis 2

Statistical analysis title	

Statistical analysis description:

Rituximab 2 x 0.5 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline RF status

Comparison groups	Rituximab (0.5 g X 2) + Methotrexate v Placebo Plus (+) Methotrexate
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5478 [22]
Method	Van-Elteren

Notes:

[22] - The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Rituximab 2 x 1.0 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline RF status

Comparison groups	Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+) Methotrexate
Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3096 [23]
Method	Van-Elteren

Notes:

[23] - The Closure Principle was used to adjust for multiple comparisons. This was a secondary endpoint in a hierarchical testing structure.

Secondary: Change From Baseline in the Modified Total Sharp Score at Week 24

End point title	Change From Baseline in the Modified Total Sharp Score at Week 24

End point description:

The modified Total Sharp Score is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change and higher scores represent a worsening of joint erosions and joint space narrowing.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	226[24]	238[25]	242[26]	
Units: Score on a scale				
arithmetic mean (standard deviation)	0.701 (± 2.9116)	0.508 (± 1.7349)	0.328 (± 0.9443)	

Notes:

[24] - MITT population

[25] - MITT population

[26] - MITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Total Erosion Score at Week 24

End point title	Change From Baseline in the Total Erosion Score at Week 24

End point description:

Total Erosion Score is determined by evaluation of fourteen sites in each wrist and hand and six joints in each foot using an eight-point scale from 0 (normal: no erosions) to 3.5 (Very severe; erosions of 100% of the articular surfaces. The Total Erosion Score at Week 24 - Total Erosion Score at baseline is calculated.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	226	238	242	
Units: Score on a scale				
arithmetic mean (standard deviation)	0.491 (± 1.3789)	0.404 (± 1.039)	0.22 (± 0.5802)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Modified Joint Space Narrowing (JSN) Score at Week 24

End point title	Change From Baseline in Modified Joint Space Narrowing (JSN) Score at Week 24

End point description:

Joint Space Narrowing is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change and higher scores represent a worsening of joint space narrowing.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	226[27]	238[28]	242[29]	
Units: Score on a scale				
arithmetic mean (standard deviation)	0.21 (± 1.7403)	0.176 (± 0.8949)	0.108 (± 0.6118)	

Notes:

[27] - MITT population

[28] - MITT population

[29] - MITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Without Radiographic Progression at Week 24

End point title	Percentage of Participants Without Radiographic Progression at Week 24

End point description:

Percentage of participants without radiographic progression at Week 24 defined as change in total modified Sharp score (TMSS) ≤ 0. TMSS is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233	239	244	
Units: Percentage of participants				
number (not applicable)	59.7	65.3	71.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With American College of Rheumatology (ACR) ACR50 Response at Week 52

End point title	Percentage of Participants With American College of Rheumatology (ACR) ACR50 Response at Week 52

End point description:

To achieve an ACR50 response requires at least a 50% improvement compared with baseline in both Total Joint Count and Swollen Joint Count, as well as a 50% improvement in three of five additional measurements from:

The physician's global assessment of disease activity;
Patient's global assessment of disease activity;
Patient's assessment of pain;
HAQ-DI (Health Assessment Questionnaire disability index);
Intent to treat (ITT) population includes all randomized participants who received at least one infusion. Patients are considered non-responders if data are missing or from the point of withdrawal, rescue use or receipt of non-permitted Disease-modifying anti-rheumatic drugs (DMARDs).

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249[30]	249[31]	250[32]	
Units: Percentage of participants				
number (not applicable)	41.8	59.4	64.8	

Notes:

[30] - ITT population

[31] - ITT population

[32] - ITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Rituximab 2 x 0.5 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline RF status

Comparison groups	Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [33]
Method	Cochran-Mantel-Haenszel

Notes:

[33] - This was a secondary endpoint in a hierarchical testing structure.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Rituximab 2 x 1.0 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline RF status

Comparison groups	Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+) Methotrexate
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [34]
Method	Cochran-Mantel-Haenszel

Notes:

[34] - This was a secondary endpoint in a hierarchical testing structure.

Secondary: Change From Baseline in the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 52

End point title	Change From Baseline in the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS28-ESR) at Week 52

End point description:

DAS28-ESR is calculated from the following formula:
(0.56 * TJC) + (0.28 * SJC) + (0.70 * ln ESR) + (0.014 * GH) TJC = tender joint count, based on 28 joints SJC = swollen joint count, based on 28 joints ESR = erythrocyte sedimentation rate in millimeters per hour (mm/h)
GH = patient's global assessment of disease activity A DAS28-ESR score of 5.1 or above is considered to indicate high disease activity. Participants can also be defined as having low disease activity (DAS28-ESR ≤ 3.2) or remission (DAS28-ESR < 2.6).

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	244[35]	247[36]	248[37]	
Units: Score on a scale				
arithmetic mean (standard deviation)	-2.33 (± 1.691)	-3.35 (± 1.663)	-3.46 (± 1.64)	

Notes:

[35] - ITT population

[36] - ITT population

[37] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With American College of Rheumatology (ACR) ACR70 Response at Week 52

End point title	Percentage of Participants With American College of Rheumatology (ACR) ACR70 Response at Week 52

End point description:

To achieve an ACR70 response requires at least a 70% improvement compared with baseline in both Total Joint Count and Swollen Joint Count, as well as a 70% improvement in three of five additional measurements from:
The physician's global assessment of disease activity;
Patient's global assessment of disease activity;
Patient's assessment of pain;
HAQ-DI (Health Assessment Questionnaire disability index);
An acute phase reactant C-Reactive Protein (CRP). (If CRP was missing then Erythrocyte Sedimentation Rate (ESR) was used if available.);

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249[38]	249[39]	250[40]	
Units: Percentage of participants				
number (not applicable)	24.9	42.2	46.8	

Notes:

[38] - ITT population

[39] - ITT population

[40] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With DAS28-ESR Remission at Week 52

End point title	Percentage of Participants With DAS28-ESR Remission at Week 52

End point description:

The DAS28-4(ESR) score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity (mm), and ESR. DAS28-4(ESR) scores range from 0 - 10.
Remission is defined as achieving a DAS28-ESR score of less than 2.6

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247[41]	248[42]	249[43]	
Units: Percentage of participants				
number (not applicable)	12.6	25.4	30.5	

Notes:

[41] - ITT population

[42] - ITT population

[43] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With European League Against Rheumatism (EULAR) Good Response at Week 52

End point title	Percentage of Participants With European League Against Rheumatism (EULAR) Good Response at Week 52

End point description:

European League Against Rheumatism (EULAR) criteria reflects an improvement in disease activity and an attainment of a lower degree of disease activity. A good response is defined as an improvement in the DAS28-ESR of >1.2 compared with baseline, and attainment of a DAS28-ESR of <3.2.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249[44]	249[45]	250[46]	
Units: Percentage of participants				
number (not applicable)	18.1	39	41.6	

Notes:

[44] - ITT population

[45] - ITT population

[46] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Major Clinical Response at Week 52

End point title	Percentage of Participants With Major Clinical Response at Week 52

End point description:

Major clinical response is defined as a continuous six-month period of success by the ACR70.
ACR70= 70% improvement compared with baseline in both Total Joint Count and Swollen Joint Count, as well as a 70% improvement in 3 of five additional measurements from:
The physician's global assessment of disease activity;
Patient's global assessment of disease activity;
Patient's assessment of pain
HAQ-DI (Health Assessment Questionnaire disability index)
An acute phase reactant C-Reactive Protein (CRP). (If CRP was missing then Erythrocyte Sedimentation Rate (ESR) was used if available.)

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249[47]	249[48]	250[49]	
Units: Percentage of participants				
number (not applicable)	8.4	18.1	21.2	

Notes:

[47] - ITT population

[48] - ITT population

[49] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With DAS28-ESR Low Disease Activity at Week 52

End point title	Percentage of Participants With DAS28-ESR Low Disease Activity at Week 52

End point description:

The DAS28-4(ESR) score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity (mm), and ESR. DAS28-4(ESR) scores range from 0 - 10.
Low disease activity is defined as achieving a DAS28-ESR score of less than or equal to 3.2

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247[50]	248[51]	249[52]	
Units: Percentage of participants				
number (not applicable)	19.8	40.3	43	

Notes:

[50] - ITT population

[51] - ITT population

[52] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With American College of Rheumatology (ACR) ACR20 Response at Week 52

End point title	Percentage of Participants With American College of Rheumatology (ACR) ACR20 Response at Week 52

End point description:

To achieve an ACR20 response requires at least a 20% improvement compared with baseline in both Total Joint Count and Swollen Joint Count, as well as a 20% improvement in three of five additional measurements from:
The physician's global assessment of disease activity;
Patient's global assessment of disease activity;
Patient's assessment of pain;
HAQ-DI (Health Assessment Questionnaire disability index);
An acute phase reactant C-Reactive Protein (CRP). (If CRP was missing then Erythrocyte Sedimentation Rate (ESR) was used if available.)

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249[53]	249[54]	250[55]	
Units: Percentage of participants				
number (not applicable)	64.3	76.7	80	

Notes:

[53] - ITT population

[54] - ITT population

[55] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With American College of Rheumatology (ACR) ACR90 Response at Week 52

End point title	Percentage of Participants With American College of Rheumatology (ACR) ACR90 Response at Week 52

End point description:

To achieve an ACR90 response requires at least a 90% improvement compared with baseline in both Total Joint Count and Swollen Joint Count, as well as a 90% improvement in three of five additional measurements from:
The physician's global assessment of disease activity patient's global assessment of disease activity;
Patient's assessment of pain;
HAQ-DI (Health Assessment Questionnaire disability index);
An acute phase reactant C-Reactive Protein (CRP). (If CRP was missing then Erythrocyte Sedimentation Rate (ESR) was used if available.)

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249[56]	249[57]	250[58]	
Units: Percentage of participants				
number (not applicable)	9.2	17.3	16.4	

Notes:

[56] - ITT population

[57] - ITT population

[58] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) Score From Baseline at Week 52

End point title	Change in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) Score From Baseline at Week 52

End point description:

FACIT-F is a 13-item questionnaire. Participants scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the participant's response to the questions (with the exception of 2 negatively stated), the greater the participant's fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the Participant's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score). A higher score reflects an improvement in the participant's health status.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	198[59]	206[60]	218[61]	
Units: Score on a scale				
arithmetic mean (standard deviation)	10.154 (± 11.1344)	11.833 (± 11.5807)	12.426 (± 12.2535)	

Notes:

[59] - ITT population

[60] - ITT population

[61] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Week 52

End point title	Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Week 52

End point description:

The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a participant completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip,and common daily activities. Each domain has at least two component questions. There are four possible responses for each component ranging from 0(without any difficulty) to 4 (unable to do).HAQ-DI=sum of worst scores in each domain divided by the number of domains answered. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	248[62]	247[63]	249[64]	
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.8 (± 0.7764)	-1.038 (± 0.7625)	-1.023 (± 0.7634)	

Notes:

[62] - ITT population

[63] - ITT population

[64] - ITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Rituximab (0.5 g x 2) + Methotrexate versus Placebo + Methotrexate stratified for region and RF status.

Comparison groups	Placebo Plus (+) Methotrexate v Rituximab (0.5 g X 2) + Methotrexate
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [65]
Method	ANOVA

Notes:

[65] - Secondary endpoint in hierarchical testing structure.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Rituximab (1.0 g x 2) + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status.

Comparison groups	Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+) Methotrexate
Number of subjects included in analysis	497
Analysis specification	Pre-specified
Analysis type	other[66]
P-value	< 0.0001 [67]
Method	ANOVA

Notes:

[66] - Rituximab (1.0 g x 2) + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status.

[67] - Secondary endpoint in hierarchical testing structure.

Secondary: Change From Baseline in the SF-36 Physical Health Component Summary Score at Week 52 and Week 104

End point title	Change From Baseline in the SF-36 Physical Health Component Summary Score at Week 52 and Week 104

End point description:

The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement.
Means are adjusted for baseline value, Rheumatoid Factor status and region.

End point type	Secondary

End point timeframe:

Baseline, Week 52, Week 104

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	240[68]	236[69]	242[70]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 52 (n=239,236,241)	8.953 (± 9.3986)	11.022 (± 9.6246)	12.205 (± 9.4986)	
Week 104 (n=240,236,242)	8.617 (± 9.85)	11.032 (± 9.9631)	12.649 (± 10.4331)	

Notes:

[68] - ITT population

[69] - ITT population

[70] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the SF-36 Mental Health Component Summary Score at Week 52 and Week 104

End point title	Change From Baseline in the SF-36 Mental Health Component Summary Score at Week 52 and Week 104

End point description:

The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement.
Means are adjusted for baseline value, Rheumatoid Factor status and region.

End point type	Secondary

End point timeframe:

Baseline, Week 52, Week 104

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	240[71]	236[72]	242[73]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 52 (n=239,236,241)	6.689 (± 13.116)	7.718 (± 11.8903)	8.167 (± 12.1709)	
Week 104 (n= 240,236,242)	6.295 (± 13.9813)	7.617 (± 12.0793)	9.066 (± 12.5325)	

Notes:

[71] - ITT population

[72] - ITT population

[73] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Categorical Change in Health Assessment Questionnaire- Disability Index (HAQ-DI) From Baseline at Week 52

End point title	Percentage of Participants With Categorical Change in Health Assessment Questionnaire- Disability Index (HAQ-DI) From Baseline at Week 52

End point description:

The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a patient completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Each domain has at least two component questions. There are four possible responses for each component on a scale of 0 (without difficulty) to 3 (unable to do). Higher scores = greater dysfunction. Improved:HAQ-DI score change ≤-0.22 Unchanged:HAQ-DI score change -0.22 to 0.22 Worsened:HAQ score ≥0.22

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	249[74]	249[75]	250[76]	
Units: Percentage of participants				
number (not applicable)				
Improved	77.1	86.7	86.8	
Unchanged	14.1	8.8	8	
Worsened	8.4	3.6	4.4	
Not Assessable	0.4	0.8	0.8	

Notes:

[74] - ITT population

[75] - ITT population

[76] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Minimally Clinically Important Difference (MCID) in the SF-36 Physical Health Component Score at Week 52

End point title	Percentage of Participants With Minimally Clinically Important Difference (MCID) in the SF-36 Physical Health Component Score at Week 52

End point description:

MCID is defined as a change from baseline in SF-36 Physical Health Component Score of >5.42.
SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	239[77]	236[78]	242[79]	
Units: percentage of participants				
number (not applicable)	63.2	69.9	76.4	

Notes:

[77] - ITT population

[78] - ITT population

[79] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Minimally Clinically Important Difference (MCID) in the Short-Form 36 (SF-36) Mental Health Component Score at Week 52

End point title	Percentage of Participants With Minimally Clinically Important Difference (MCID) in the Short-Form 36 (SF-36) Mental Health Component Score at Week 52

End point description:

MCID is defined as a change from baseline in SF-36 Mental Health Component Score of >6.33.
SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical (PCS) and Mental (MCS) Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	239[80]	236[81]	242[82]	
Units: Percentage of participants				
number (not applicable)	49	50.8	57	

Notes:

[80] - ITT population

[81] - ITT population

[82] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Modified Total Sharp Score at Week 104

End point title	Change From Baseline in the Modified Total Sharp Score at Week 104

End point description:

The modified Total Sharp Score is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change and higher scores represent a worsening of joint erosions and joint space narrowing.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	229	238	243	
Units: Score on a scale				
arithmetic mean (standard deviation)	1.948 (± 5.5782)	0.761 (± 2.6181)	0.406 (± 1.4312)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 104: Rituximab 2 x 0.5 g + Methotrexate arm versus Placebo + Methotrexate, stratified for region and baseline rheumatoid factor (RF) status

Comparison groups	Rituximab (0.5 g X 2) + Methotrexate v Placebo Plus (+) Methotrexate
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [83]
Method	Van-Elteren

Notes:

[83] - This was a secondary endpoint in a hierarchical testing structure.

Secondary: Change From Baseline in the Total Erosion Score at Week 104

End point title	Change From Baseline in the Total Erosion Score at Week 104

End point description:

Total Erosion Score is determined by evaluation of 14 sites in each wrist and hand and six joints in each foot using an eight-point scale from 0 (normal: no erosions) to 3.5 (Very severe; erosions of 100% of the articular surfaces). The change from the score at baseline to Week 104 is calculated.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	229[84]	238[85]	243[86]	
Units: Score on a scale				
arithmetic mean (standard deviation)	1.315 (± 3.2466)	0.499 (± 1.7221)	0.227 (± 0.7939)	

Notes:

[84] - MITT population

[85] - MITT population

[86] - MITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Without Radiographic Progression at Week 104

End point title	Percentage of Participants Without Radiographic Progression at Week 104

End point description:

Percentage of participants without radiographic progression at Week 104, defined as change in total modified Sharp Score (TMSS) ≤0. TMSS is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233[87]	239[88]	244[89]	
Units: Percentage of participants				
number (not applicable)	37.3	49.4	56.6	

Notes:

[87] - MITT population

[88] - MITT population

[89] - MITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Without Radiographic Progression in the Total Erosion Score at Week 104

End point title	Percentage of Participants Without Radiographic Progression in the Total Erosion Score at Week 104

End point description:

Total Erosion Score is determined by evaluation of fourteen sites in each wrist and hand and six joints in each foot using an eight-point scale from 0 (normal: no erosions) to 3.5 (Very severe; erosions of 100% of the articular surfaces). The score at baseline is compared to the score at Week 104. No progression is defined as a change from score at screening to Week 104 ≤0.

End point type	Secondary

End point timeframe:

Week 104

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	233[90]	239[91]	244[92]	
Units: Percentage of participants				
number (not applicable)	38.2	52.7	58.6	

Notes:

[90] - MITT population

[91] - MITT population

[92] - MITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Week 104

End point title	Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Week 104

End point description:

The Stanford Health Assessment Questionnaire disability index (HAQ-DI) is a participant completed questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Each domain has at least two component questions. There are four possible responses for each component ranging from 0 (without any difficulty) to 4 (unable to do). HAQ-DI=sum of worst scores in each domain divided by the number of domains answered. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 104

End point values	Placebo Plus (+) Methotrexate	Rituximab (0.5 g X 2) + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	248[93]	247[94]	248[95]	
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.806 (± 0.7968)	-1038 (± 0.8142)	-1.055 (± 0.7901)	

Notes:

[93] - ITT population

[94] - ITT population

[95] - ITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Rituximab (0.5 g x 2) + Methotrexate versus Placebo + Methotrexate, stratified for region and baseline RF status.

Comparison groups	Rituximab (0.5 g X 2) + Methotrexate v Placebo Plus (+) Methotrexate
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	other[96]
P-value	< 0.0001
Method	ANOVA

Notes:

[96] - Secondary endpoint in hierarchical testing structure.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Rituximab (1.0 g x 2) + Methotrexate versus Placeb

Comparison groups	Rituximab (1.0 g x 2) + Methotrexate v Placebo Plus (+) Methotrexate
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [97]
Method	ANOVA

Notes:

[97] - Secondary endpoint in hierarchical testing structure.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline to End of ESFU, a total of 96 weeks after the end of 3 year Treatment Period.

Adverse event reporting additional description:

Safety Population includes all participants who received at least one dose of study drug, grouped as treated. After Week 104 participants in the placebo group were eligible to receive either Rituximab 2 X 0.5 g + MTX or Rituximab 2 X 1.0g + MTX. Adverse events reported for placebo patients after switching to Rituximab are not included below.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo + Methotrexate

Reporting group description:

Treatment period : Placebo intravenously on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. From Week 104 participants were eligible to receive Rituximab 2 X 0.5 g or Rituximab 2 X 1.0 g every 24 weeks. At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered. At the end of 48-Week SFU participants entered ESFU. Participants who did not receive any study drug were not required to enter ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

Reporting group title	Rituximab (1.0 g x 2) + Methotrexate

Reporting group description:

Treatment period: Rituximab intravenously at a dose of 1.0 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS-ESR) result was ≥2.6. At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered. At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

Reporting group title	Rituximab (0.5 g x 2) + Methotrexate

Reporting group description:

Treatment period: Rituximab intravenously at a dose of 0.5 g on Days 1 and 15 + a background of methotrexate orally at a dose of 7.5 mg escalating by 2.5 mg a week every 1-2 weeks to achieve: 15 mg per week by Week 4 and 20 mg per week by Week 8. Subsequent Rituximab treatment courses were given at 24 week intervals for 5 years provided the Disease Activity Score 28 Joint Count- Erythrocyte Sedimentation Rate (DAS-ESR) result was ≥2.6. At the end of 3 year treatment period participants were followed for a 48-Week Safety Follow-Up. During the SFU period no further study drug was administered. At the end of 48-Week SFU participants entered ESFU. Only participants who received the study drug entered ESFU for a period of additional 48 weeks. During the ESFU period no further study drug was administered.

Serious adverse events	Placebo + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	Rituximab (0.5 g x 2) + Methotrexate
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 249 (19.28%)	58 / 263 (22.05%)	54 / 348 (15.52%)
number of deaths (all causes)	4	2	4
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 249 (0.40%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Anaplastic large-cell lymphoma			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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

Lung neoplasm malignant			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Lymphoma			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Metastatic Neoplasm			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Monoclonal gammopathy			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Myelodysplastic syndrome			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Paget's disease of nipple			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Primary mediastinal large B-cell lymphoma			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Prostate cancer stage II			

subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Carcinoma in situ of skin			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Venous insufficiency			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angiopathy			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Hypertensive crisis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Pelvic venous thrombosis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Peripheral ischaemia			

subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 249 (0.40%)	2 / 263 (0.76%)	2 / 348 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 249 (0.40%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical failure			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Ulcer haemorrhage			

subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	2 / 249 (0.80%)	0 / 263 (0.00%)	0 / 348 (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
Cystocele			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Ovarian cyst ruptured			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 249 (0.40%)	2 / 263 (0.76%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pulmonary embolism			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Asthma			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Laryngeal hypertrophy			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Nasal polyps			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Respiratory failure			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status asthmaticus			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 249 (0.00%)	2 / 263 (0.76%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			

subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug dependence			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 249 (1.20%)	1 / 263 (0.38%)	2 / 348 (0.57%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	2 / 249 (0.80%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accident			
subjects affected / exposed	1 / 249 (0.40%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Infusion related reaction			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Intentional overdose			

subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Ligament sprain			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Multiple fractures			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Rib fracture			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 249 (0.00%)	2 / 263 (0.76%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	2 / 348 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 249 (0.40%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Angina pectoris			

subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Mitral valve sclerosis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Pericardial effusion			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid arteriosclerosis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Cerebral infarction			

subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Convulsion			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Embolic stroke			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive encephalopathy			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Vertigo positional			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 249 (0.40%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 249 (0.40%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Inguinal hernia obstructive			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Colitis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Colitis Ulcerative			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Duodenal ulcer			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastritis			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal dysplasia			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal hypomotility			

subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Inguinal hernia			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Large intestinal stenosis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Rectal polyp			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Umbilical hernia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	2 / 348 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 249 (0.40%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 249 (0.40%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Liver disorder			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Skin and subcutaneous tissue disorders			
Diabetic ulcer			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Nephrolithiasis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Endocrine disorders			

Goitre			
subjects affected / exposed	1 / 249 (0.40%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	1 / 249 (0.40%)	2 / 263 (0.76%)	3 / 348 (0.86%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 249 (0.40%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Pathological fracture			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal pain			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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			
Pneumonia			
subjects affected / exposed	6 / 249 (2.41%)	4 / 263 (1.52%)	7 / 348 (2.01%)
occurrences causally related to treatment / all	4 / 6	2 / 4	1 / 7
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	4 / 249 (1.61%)	0 / 263 (0.00%)	2 / 348 (0.57%)
occurrences causally related to treatment / all	1 / 4	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 249 (0.00%)	3 / 263 (1.14%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	2 / 348 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	2 / 348 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			

subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 249 (0.40%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute tonsillitis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Arthritis bacterial			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Atypical pneumonia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Bronchitis			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic abscess			

subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Gangrene			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
H1N1 influenza			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung infection			

subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Sepsis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Septic shock			

subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Tonsillitis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 263 (0.00%)	0 / 348 (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
Tracheobronchitis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 249 (0.00%)	0 / 263 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 263 (0.38%)	0 / 348 (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

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

Non-serious adverse events	Placebo + Methotrexate	Rituximab (1.0 g x 2) + Methotrexate	Rituximab (0.5 g x 2) + Methotrexate
Total subjects affected by non-serious adverse events			
subjects affected / exposed	193 / 249 (77.51%)	208 / 263 (79.09%)	232 / 348 (66.67%)
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	53 / 249 (21.29%)	67 / 263 (25.48%)	69 / 348 (19.83%)
occurrences (all)	100	121	150

Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 249 (7.23%)	24 / 263 (9.13%)	22 / 348 (6.32%)
occurrences (all)	20	25	27
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 249 (7.23%)	31 / 263 (11.79%)	17 / 348 (4.89%)
occurrences (all)	23	40	19
Dizziness			
subjects affected / exposed	13 / 249 (5.22%)	20 / 263 (7.60%)	12 / 348 (3.45%)
occurrences (all)	15	21	14
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	25 / 249 (10.04%)	19 / 263 (7.22%)	14 / 348 (4.02%)
occurrences (all)	25	23	15
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	42 / 249 (16.87%)	46 / 263 (17.49%)	45 / 348 (12.93%)
occurrences (all)	51	60	54
Diarrhoea			
subjects affected / exposed	15 / 249 (6.02%)	18 / 263 (6.84%)	24 / 348 (6.90%)
occurrences (all)	23	29	25
Dyspepsia			
subjects affected / exposed	13 / 249 (5.22%)	14 / 263 (5.32%)	15 / 348 (4.31%)
occurrences (all)	14	14	16
Gastritis			
subjects affected / exposed	13 / 249 (5.22%)	10 / 263 (3.80%)	11 / 348 (3.16%)
occurrences (all)	13	13	12
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	35 / 249 (14.06%)	38 / 263 (14.45%)	37 / 348 (10.63%)
occurrences (all)	47	51	50
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 249 (4.42%)	24 / 263 (9.13%)	19 / 348 (5.46%)
occurrences (all)	13	27	24
Musculoskeletal and connective tissue disorders			

Rheumatoid arthritis			
subjects affected / exposed	42 / 249 (16.87%)	29 / 263 (11.03%)	30 / 348 (8.62%)
occurrences (all)	69	47	45
Back pain			
subjects affected / exposed	14 / 249 (5.62%)	9 / 263 (3.42%)	19 / 348 (5.46%)
occurrences (all)	16	11	20
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	44 / 249 (17.67%)	58 / 263 (22.05%)	59 / 348 (16.95%)
occurrences (all)	70	126	103
Nasopharyngitis			
subjects affected / exposed	43 / 249 (17.27%)	52 / 263 (19.77%)	53 / 348 (15.23%)
occurrences (all)	71	76	81
Urinary tract infection			
subjects affected / exposed	26 / 249 (10.44%)	43 / 263 (16.35%)	36 / 348 (10.34%)
occurrences (all)	40	76	51
Bronchitis			
subjects affected / exposed	15 / 249 (6.02%)	20 / 263 (7.60%)	32 / 348 (9.20%)
occurrences (all)	23	35	39
Sinusitis			
subjects affected / exposed	11 / 249 (4.42%)	20 / 263 (7.60%)	23 / 348 (6.61%)
occurrences (all)	18	28	30
Pharyngitis			
subjects affected / exposed	16 / 249 (6.43%)	14 / 263 (5.32%)	14 / 348 (4.02%)
occurrences (all)	22	20	22
Influenza			
subjects affected / exposed	11 / 249 (4.42%)	16 / 263 (6.08%)	9 / 348 (2.59%)
occurrences (all)	15	19	13
Gastroenteritis			
subjects affected / exposed	7 / 249 (2.81%)	16 / 263 (6.08%)	9 / 348 (2.59%)
occurrences (all)	8	17	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2006	Safety information was updated and eligibility criteria and other study procedures were clarified.
09 March 2007	Enrollment criteria was updated in line with protocol to allow patients who are Hepatitis B core antibody (HbcAb) positive / DNA negative to be enrolled; Safety information (infections including reports of progressive multifocal leukoencephalopathy, PML) was updated. Eligibility criteria and other study procedures were clarified.
24 July 2007	Sample size and safety information were updated. Study procedures were clarified.
06 March 2009	Placebo switch dose was amended and safety information updated. Extension of study was specified. Safety information (including PML Update) was updated and study procedures were clarified.
26 November 2009	This Amendment was to implement dosing discontinuation due to progressive multifocal leukoencephalopathy (PML) reports in Rheumatoid Arthritis (RA) patients. All patients exposed to MabThera (Rituximab) went into safety follow up SFU.
06 September 2012	This amendment was for termination of extended B cell Safety Follow-UP (SFU).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported