Clinical trial results:
A Randomized, Placebo Controlled, Double-blind, Parallel Group, International Study to Evaluate the Safety and Efficacy of Rituximab in Combination With Methotrexate, Compared to Methotrexate Monotherapy, in Patients With Active Rheumatoid Arthritis

Summary

EudraCT number	2005-002392-32
Trial protocol	IE GB SE DE SI
Global end of trial date	24 July 2013

Results information

Result version number	v1 (current)
This version publication date	19 October 2016
First version publication date	19 October 2016

Trial information

Trial identification

Sponsor protocol code	WA17045

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00299130
WHO universal trial number (UTN)	-
Other trial identifiers	Genentech Protocol Identification: U2973g (SERENE)

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 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, 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	06 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To determine the efficacy and safety at Week 24 of rituximab 500 milligrams (mg) intravenous (IV) times (x) 2 and rituximab 1000 mg IV x 2 when used in combination with methotrexate (MTX) compared to continued MTX monotherapy in participants with active rheumatoid arthritis (RA) that currently have an inadequate clinical response to MTX.
2. To investigate by a population analysis approach the pharmacokinetics (PK) of rituximab in the target RA participant population and the influence of covariates on the PK parameters.
3. To explore a dose separation of rituximab 500 mg IV ×2 from rituximab 1000 mg IV ×2.
4. To explore the long-term efficacy and safety of further courses of rituximab.

Protection of trial subjects:

This study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" International Conference on Harmonization (ICH) Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the individual. The investigator additionally ensured that the basic principles of "Good Clinical Practice" as outlined in the current version of the Federal Regulations (CFR) Title 21, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Patients", and part 56, "Institutional Review Boards", were adhered to. In other countries where "Guideline for Good Clinical Practice" exist, the sponsor and the investigators strictly ensured adherence to the stated provisions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 October 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	48 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovenia: 23
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United Kingdom: 40
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Poland: 56
Country: Number of subjects enrolled	Guatemala: 13
Country: Number of subjects enrolled	Mexico: 69
Country: Number of subjects enrolled	Romania: 35

Country: Number of subjects enrolled	United States: 237
Country: Number of subjects enrolled	Canada: 16
Worldwide total number of subjects	511
EEA total number of subjects	176

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	434
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 511 participants were recruited and randomized between 27 Oct 2005 and 15 Nov 2006. Of these, 2 participants were randomized but received no infusions (one violated inclusion criteria and the other was randomized to rituximab 2 x 1.0 gram [g] + methotrexate [MTX] but failed to return). A total of 509 participants were treated.

Pre-assignment

Screening details:

Of the 509 participants, one participant was randomized first to rituximab 2 x 1.0 g + MTX and then to rituximab 2 x 0.5 g + MTX. No assessments were recorded or medication given after first randomization and all data used in analyses was following the second randomization; hence, participant is included only in rituximab 2 x 0.5 g + MTX arm.

Period 1

Period 1 title	Treatment Period (up to 5 Years)
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 + MTX

Arm description:

Participants received placebo intravenous infusion on Days 1 and 15. From Week 16 onwards, participants could switch to receive rituximab 0.5 g (on Days 1 and 15) every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Placebo and rituximab infusions were preceded with 100 milligrams (mg) intravenous methylprednisolone. Participants also received a stable dose of 10-25 mg/week of MTX and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo to rituximab intravenous infusion.

Arm title	Rituximab 2 x 0.5 g + MTX

Arm description:

Participants received 0.5 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Arm type	Experimental

Investigational medicinal product name	Rituximab
Investigational medicinal product code	Ro 45-2294
Other name	MabThera, Rituxan
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion.

Arm title	Rituximab 2 x 1.0 g + MTX

Arm description:

Participants received 1.0 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	Ro 45-2294
Other name	MabThera, Rituxan
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion.

Number of subjects in period 1	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX
Started	172	168	171
Treated	172	167	170
Completed 24 Weeks	159	162	166
Completed 48 Weeks	155	157	158
Completed 144 Weeks	133	138	132
Completed	119	125	121
Not completed	53	43	50
Consent withdrawn by subject	-	1	1
Adverse Event	13	8	13
Death	1	3	1
Refused Treatment	12	12	19
Reason Not Specified	4	6	4
Protocol Violation	-	1	-
Failure to Return	4	6	6
Insufficient Therapeutic Response	19	6	6

Period 2

Period 2 title	Safety Follow-up (SFU) (48 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + MTX

Arm description:

Participants received placebo intravenous infusion on Days 1 and 15. From Week 16 onwards, participants could switch to receive rituximab 0.5 g (on Days 1 and 15) every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Placebo and rituximab infusions were preceded with 100 milligrams (mg) intravenous methylprednisolone. Participants also received a stable dose of 10-25 mg/week of MTX and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo to rituximab intravenous infusion.

Arm title	Rituximab 2 x 0.5 g + MTX

Arm description:

Participants received 0.5 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	Ro 45-2294
Other name	MabThera, Rituxan
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion.

Arm title	Rituximab 2 x 1.0 g + MTX

Arm description:

Participants received 1.0 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Arm type	Experimental

Investigational medicinal product name	Rituximab
Investigational medicinal product code	Ro 45-2294
Other name	MabThera, Rituxan
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion.

Number of subjects in period 2	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX
Started	119	125	121
Completed	122	120	123
Not completed	45	45	45
Death	4	5	3
Withdrawal by Subject	22	22	21
Administrative/Other	4	9	4
Failure to Return	14	7	15
No SFU Week 48 Date Recorded	-	1	-
Did not Co-operate	1	1	2
Joined	48	40	47
Discontinued Treatment, Entered SFU	48	40	47

Period 3

Period 3 title	Extended SFU (ESFU) (up to 5.1 Years)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab 2 x 0.5 g + MTX

Arm description:

Participants received 0.5 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Arm type	Experimental

Investigational medicinal product name	Rituximab
Investigational medicinal product code	Ro 45-2294
Other name	MabThera, Rituxan
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion.

Arm title	Rituximab 2 x 1.0 g + MTX

Arm description:

Participants received 1.0 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	Ro 45-2294
Other name	MabThera, Rituxan
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion.

Number of subjects in period 3[1]	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX
Started	82	44
Completed	74	38
Not completed	8	6
Death	3	-
'Did not Co-operate/Withdrew Consent '	3	4
Failure to Return	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 whose peripheral CD20+ B cells remained depleted (less than the laboratory lower limit of normal) after the week 48 SFU visit, participated in the ESFU period, with the safety assessments described for SFU week 48 being performed at 12 week intervals until peripheral B cells returned to within normal ranges or baseline levels, whichever was lower.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + MTX

Reporting group description:

Participants received placebo intravenous infusion on Days 1 and 15. From Week 16 onwards, participants could switch to receive rituximab 0.5 g (on Days 1 and 15) every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Placebo and rituximab infusions were preceded with 100 milligrams (mg) intravenous methylprednisolone. Participants also received a stable dose of 10-25 mg/week of MTX and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Rituximab 2 x 0.5 g + MTX

Reporting group description:

Participants received 0.5 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Rituximab 2 x 1.0 g + MTX

Reporting group description:

Participants received 1.0 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX
Number of subjects	172	168	171
Age categorical Units: Subjects			

Age continuous			
Age data was reported for safety population (N = 509).			
Units: years			
arithmetic mean	52.16	51.91	51.3
standard deviation	± 12.39	± 12.93	± 12.64
Gender categorical Units: Subjects			
Male	25	34	32
Female	147	133	138
Not Available	0	1	1

Reporting group values	Total		
Number of subjects	511		
Age categorical Units: Subjects			

Age continuous			
Age data was reported for safety population (N = 509).			
Units: years arithmetic mean standard deviation	--		
Gender categorical Units: Subjects			
Male	91		
Female	418		
Not Available	2		

End points reporting groups

Reporting group title	Placebo + MTX

Reporting group description:

Participants received placebo intravenous infusion on Days 1 and 15. From Week 16 onwards, participants could switch to receive rituximab 0.5 g (on Days 1 and 15) every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Placebo and rituximab infusions were preceded with 100 milligrams (mg) intravenous methylprednisolone. Participants also received a stable dose of 10-25 mg/week of MTX and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Rituximab 2 x 0.5 g + MTX

Reporting group description:

Participants received 0.5 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Rituximab 2 x 1.0 g + MTX

Reporting group description:

Participants received 1.0 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Placebo + MTX

Reporting group description:

Participants received placebo intravenous infusion on Days 1 and 15. From Week 16 onwards, participants could switch to receive rituximab 0.5 g (on Days 1 and 15) every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Placebo and rituximab infusions were preceded with 100 milligrams (mg) intravenous methylprednisolone. Participants also received a stable dose of 10-25 mg/week of MTX and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Rituximab 2 x 0.5 g + MTX

Reporting group description:

Participants received 0.5 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Rituximab 2 x 1.0 g + MTX

Reporting group description:

Participants received 1.0 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Rituximab 2 x 0.5 g + MTX

Reporting group description:

Participants received 0.5 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they

were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Rituximab 2 x 1.0 g + MTX

Reporting group description:

Participants received 1.0 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Subject analysis set title	Rituximab + MTX
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 0.5 g or 1.0 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone.
Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Primary: Percentage of Participants With American College of Rheumatology (ACR) 20 Response at Week 24

End point title	Percentage of Participants With American College of Rheumatology (ACR) 20 Response at Week 24

End point description:

Achieving ACR20 required a ≥20 percent (%) improvement compared with Baseline in tender joint counts (68 joints assessed for tenderness) and swollen joint counts (66 joints assessed for swelling), and a 20% improvement in three of the following five additional measurements:
•Physician's global assessment of disease activity (assessed using a 100 millimeter (mm) Visual Analog Scale [VAS])
•Participant's global assessment of disease activity (assessed using a 100 mm VAS)
•Participant's assessment of pain (assessed using a 100 mm VAS)
•Health Assessment Questionnaire (HAQ; a participant-completed questionnaire consisting of 20 questions, scored from 0-3)
•Acute phase reactant: C-reactive protein (CRP) or, if CRP was missing, erythrocyte sedimentation rate (ESR)
Participants who withdrew prematurely from the study prior to week 24, who received rescue therapy or had insufficient data in order to calculate a clinical response were considered to be non-responders.
ITT Population

End point type	Primary

End point timeframe:

Baseline and Week 24
Each component calculated using the last observation carried forward (LOCF).

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	167	170	
Units: Percentage of Participants				
number (not applicable)	23.3	54.5	50.6	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + MTX v Rituximab 2 x 0.5 g + MTX
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.41

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + MTX v Rituximab 2 x 1.0 g + MTX
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.37

Secondary: Percentage of Participants With an ACR50 Response at Week 24

End point title	Percentage of Participants With an ACR50 Response at Week 24

End point description:

Achieving ACR50 required at least a 50% improvement compared with Baseline in both tender joint counts (68 joints assessed for tenderness) and swollen joint counts (66 joints assessed for swelling), as well as a 50% improvement in three of the following five additional measurements:
•Physician's global assessment of disease activity (assessed using a 100 mm VAS);
•Patient's global assessment of disease activity (assessed using a 100 mm VAS);
•Patient's assessment of pain (assessed using a 100 mm VAS);

•HAQ; a patient completed questionnaire consisting of 20 questions, scored from 0-3;
•Acute phase reactant: CRP or, if CRP was missing, ESR.
Participants who withdrew prematurely from the study prior to week 24, who received rescue therapy or had insufficient data in order to calculate a clinical response were considered to be non-responders.
ITT Population

End point type	Secondary

End point timeframe:

Baseline and Week 24
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	167	170	
Units: Percentage of Participants				
number (not applicable)	9.3	26.3	25.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an ACR70 Response at Week 24

End point title	Percentage of Participants With an ACR70 Response at Week 24

End point description:

To achieve an ACR70 required at least a 70% improvement compared with Baseline in both tender joint counts (68 joints assessed for tenderness) and swollen joint counts (66 joints assessed for swelling), as well as a 70% improvement in three of the following five additional measurements:
•Physician's global assessment of disease activity (assessed using a 100 mm VAS);
•Participant's global assessment of disease activity (assessed using a 100 mm VAS);
•Participant's assessment of pain (assessed using a 100 mm VAS);
•HAQ; a patient completed questionnaire consisting of 20 questions, scored from 0-3;
•Acute phase reactant: CRP or, if CRP was missing, ESR.
Participants who withdrew prematurely from the study prior to week 24, who received rescue therapy or had insufficient data in order to calculate a clinical response were considered to be non-responders.
ITT Population

End point type	Secondary

End point timeframe:

Baseline and Week 24
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	167	170	
Units: Percentage of Participants				
number (not applicable)	5.2	9	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disease Activity Score (DAS28-ESR) at Week 24

End point title	Change From Baseline in Disease Activity Score (DAS28-ESR) at Week 24

End point description:

The DAS28 is a composite score to measure disease activity in patients with rheumatoid arthritis, derived from the following variables:
•The number of swollen and tender joints assessed using the 28-joint count;
•ESR;
•Participant's global assessment of disease activity measured on a 100 mm visual analog scale.
The DAS28 score ranges from zero to ten. A DAS28 score above 5.1 means high disease activity whereas a DAS28 less than or equal to 3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6.
ITT population.

End point type	Secondary

End point timeframe:

Baseline and Week 24
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	166	168	
Units: DAS28-ESR				
arithmetic mean (standard deviation)	-0.76 (± 1.304)	-1.71 (± 1.334)	-1.68 (± 1.342)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With European League Against Rheumatism (EULAR) Response at Week 24

End point title	Percentage of Participants With European League Against Rheumatism (EULAR) Response at Week 24

End point description:

A EULAR response reflects an improvement in disease activity and an attainment of a lower degree of disease activity based on the DAS28 score. The DAS28 score ranges from 0-10, with higher scores indicating more disease activity.

A Good Response is defined as an improvement (decrease) in the DAS28 of more than 1.2 compared

with Baseline and attainment of a DAS28 score of less than or equal to (≤)3.2.

A Moderate Response is defined as either:
•an improvement (decrease) in the DAS28 of greater than (>)0.6 and ≤1.2 from Baseline and attainment of a DAS28 score of ≤5.1 or,
•an improvement (decrease) in the DAS28 of >1.2 from Baseline and attainment of a DAS28 score of >3.2.

No Response is defined as either an improvement (decrease) in the DAS28 of ≤0.6, or an improvement (decrease) in the DAS28 of >0.6 and ≤1.2 and attainment of a DAS28 of >5.1.
ITT Population

End point type	Secondary

End point timeframe:

Baseline and Week 24
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	167	170	
Units: Percentage of Participants				
number (not applicable)				
No Response	66.3	33.5	37.1	
Moderate Response	29.1	49.1	51.2	
Good Response	4.7	17.4	11.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Swollen Joint Count at Week 24 and Week 48

End point title	Percent Change From Baseline in Swollen Joint Count at Week 24 and Week 48

End point description:

Sixty-six joints were assessed and classified as swollen/not swollen by pressure and joint manipulation on physical examination. The percentage change from baseline at each post-baseline visit was calculated as: [(post-baseline value minus baseline value) divided by Baseline value] times (*)100. A negative percentage change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population

End point type	Secondary

End point timeframe:

Baseline, Week 24, and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	166	170	
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 24 [n=172, 166, 170]	-21.6 (± 65.82)	-47.4 (± 43.49)	-49.1 (± 38.59)	
Week 48 [n=172, 166, 170]	-38.9 (± 66.83)	-54 (± 38.66)	-59.3 (± 37.04)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Tender Joint Count at Week 24 and Week 48

End point title	Percent Change From Baseline in Tender Joint Count at Week 24 and Week 48

End point description:

Sixty-eight joints were assessed and classified as tender/not tender by pressure and joint manipulation on physical examination. The percentage change from baseline at each post-baseline visit was calculated as: [(post-baseline value minus baseline value) divided by Baseline value]*100. A negative percentage change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	166	170	
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 24 [n=172, 166, 170]	-14.2 (± 69.2)	-42.5 (± 64.41)	-31.5 (± 66.52)	
Week 48 [n=172, 166, 170]	-37.1 (± 55.08)	-50.2 (± 62.74)	-45.1 (± 62.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Participant's Global Assessment of Disease Activity

End point title	Percent Change From Baseline in Participant's Global Assessment of Disease Activity

End point description:

The participant's overall assessment of their current disease activity measured on a 100 mm horizontal VAS. The left-hand extreme of the line (0 mm) was described as "no disease activity" (symptom-free and no arthritis symptoms) and the right-hand extreme (100 mm) as "maximum disease activity" (maximum arthritis disease activity). The percentage change from baseline at each post-baseline visit was calculated as: [(post-baseline value minus baseline value) divided by Baseline value]*100. A negative percentage change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	166	169	
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 24 [n=171, 166, 169]	-14 (± 48.94)	-31.5 (± 46.4)	-29.1 (± 54.43)	
Week 48 [n=171, 166, 169]	-28 (± 50.78)	-39.7 (± 40.53)	-36.6 (± 47.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Participant’s Pain Assessment

End point title	Percent Change From Baseline in Participant’s Pain Assessment

End point description:

The participant’s assessment of their current level of pain on a 100 mm horizontal VAS, where the left-hand extreme of the line (0 mm) was described as "no pain" and the right-hand extreme (100 mm) as "unbearable pain". The percentage change from baseline at each post-baseline visit was calculated as: [(post-baseline value minus baseline value) divided by Baseline value]*100. A negative percentage change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	166	169	
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 24 [n=171, 166, 169]	-9.7 (± 52.58)	-25.7 (± 58.52)	-29.1 (± 53.11)	
Week 48 [n=171, 166, 169]	-24.4 (± 60.22)	-35.5 (± 50.45)	-36.3 (± 47.87)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Physician’s Global Assessment of Disease Activity

End point title	Percent Change From Baseline in Physician’s Global Assessment of Disease Activity

End point description:

The physician’s assessment of the participant's current disease activity on a 100 mm horizontal VAS, where the left-hand extreme of the line (0 mm) was described as "no disease activity" (symptom-free and no arthritis symptoms) and the right-hand extreme (100 mm) as "maximum disease activity". The percentage change from baseline at each post-baseline visit was calculated as: [(post-baseline value minus baseline value) divided by Baseline value]*100. A negative percentage change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	166	170	
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 24 [n=172, 166, 170]	-25.3 (± 38.52)	-36.9 (± 61.26)	-35.4 (± 46.99)	
Week 48 [n=172, 166, 170]	-39.4 (± 39.95)	-40.5 (± 74.54)	-49 (± 40.01)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The Stanford Health Assessment Questionnaire disability index is a patient-reported questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and daily activities. Participants choose from four response categories, ranging from 'without any difficulty' (Score=0) to 'unable to do' (Score=3). The overall score is the average of each of the 8 category scores and ranges from 0 to 3, where zero represents no disability and three very severe, high-dependency disability. The percentage change from baseline at each post-baseline visit was calculated as: [(post-baseline value minus baseline value) divided by Baseline value]*100. A negative percentage change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	165	170	
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 24 [n=172, 165, 170]	-14.7 (± 38.41)	-26.9 (± 40.89)	-23.4 (± 49.52)	
Week 48 [n=172, 165, 170]	-22.6 (± 39.63)	-30.2 (± 41.64)	-30.6 (± 39.95)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in C-Reactive Protein

End point title	Percent Change From Baseline in C-Reactive Protein

End point description:

CRP was measured from blood samples by a central laboratory as a marker for inflammation. The percentage change from baseline at each post-baseline visit was calculated as: [(post-baseline value minus baseline value) divided by Baseline value]*100. A negative percentage change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	166	170	
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 24 [n=172, 166, 170]	58.1 (± 385.23)	-27.5 (± 84.36)	-23.1 (± 119.75)	
Week 48 [n=172, 166, 170]	40.1 (± 402.67)	-37.3 (± 94.65)	-34.9 (± 82.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Erythrocyte Sedimentation Rate

End point title	Percent Change From Baseline in Erythrocyte Sedimentation Rate

End point description:

ESR indirectly measures how much inflammation is in the body. A higher ESR is indicative of increased inflammation. The percentage change from baseline at each post-baseline visit was calculated as: [(post-baseline value minus baseline value) divided by Baseline value]*100. A negative percentage change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	166	169	
Units: Percent Change				
arithmetic mean (standard deviation)				
Week 24 [n=172, 166, 169]	8 (± 130.71)	-28 (± 42.2)	-29.2 (± 52.32)	
Week 48 [n=172, 166, 169]	-14.5 (± 68.55)	-31.3 (± 49.72)	-36.7 (± 51.49)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Short Form 36 Health Survey (SF-36) Summary Scores (Physical and Mental Components)

End point title	Percent Change From Baseline in Short Form 36 Health Survey (SF-36) Summary Scores (Physical and Mental Components)

End point description:

SF-36 measured impact of disease on overall quality of life and consists of 36 questions split into 2 major components: physical health and mental health. Physical health includes four domains: physical health, bodily pain, physical functioning and physical role limitations. Under the mental health domain there are four domains; mental health, vitality, social functioning, and emotional role limitation. Individual domain scores are aggregated to derive a physical-component summary score and a mental-component summary score which range from 0 to 100, with higher scores indicating a better level of functioning. Percentage change from baseline at each post-baseline visit was calculated as: [(post-baseline value minus baseline value) divided by Baseline value]*100. A positive percentage change from baseline score indicates an improvement. For each parameter/ treatment group, n equals the number of analyzed participants. ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154	154	162	
Units: Percent Change				
arithmetic mean (standard deviation)				
Physical Component: Week 24 [n=147, 152, 155]	11.1 (± 27.63)	23.7 (± 31.63)	22.8 (± 33.09)	
Physical Component: Week 48 [n=154, 154, 162]	21.3 (± 30.99)	26.4 (± 35.81)	27.4 (± 31.93)	
Mental Component: Week 24 [n=147, 152, 155]	8.4 (± 29.43)	12.6 (± 29.13)	19.6 (± 56.64)	
Mental Component: Week 48 [n=154, 154, 162]	12.7 (± 30.52)	18.4 (± 38.87)	18.7 (± 57.34)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 Health Survey (SF-36) General Health Domain Score

End point title	Change From Baseline in Short Form 36 Health Survey (SF-36) General Health Domain Score

End point description:

The SF-36 measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). The individual domain scores are calculated and transformed to range from 0 to 100, with higher scores indicating a better level of functioning. A positive change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	154	155	
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 24 [n=138, 154, 155]	2.078 (± 7.3032)	3.532 (± 8.2747)	3.866 (± 9.2154)	
Week 48 [n=137, 148, 147]	4.214 (± 8.2352)	4.165 (± 9.5894)	4.362 (± 8.1242)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 Health Survey (SF-36) Bodily Pain Domain Score

End point title	Change From Baseline in Short Form 36 Health Survey (SF-36) Bodily Pain Domain Score

End point description:

The SF-36 measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). The individual domain scores are calculated and transformed to range from 0 to 100, with higher scores indicating a better level of functioning. A positive change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	152	156	
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 24 [n=138, 152, 156]	3.304 (± 8.5631)	6.931 (± 8.2254)	7.604 (± 8.5238)	
Week 48 [n=137, 147, 147]	8.449 (± 9.3543)	8.079 (± 9.5435)	8.964 (± 8.989)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 Health Survey (SF-36) Physical Functioning Domain Score

End point title	Change From Baseline in Short Form 36 Health Survey (SF-36) Physical Functioning Domain Score

End point description:

The SF-36 measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). The individual domain scores are calculated and transformed to range from 0 to 100, with higher scores indicating a better level of functioning. A positive change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	154	154	
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 24 [n=138, 154, 154]	3.553 (± 8.4181)	5.46 (± 8.3099)	5.653 (± 9.6817)	
Week 48 [n=137, 148, 146]	6.212 (± 9.6882)	6.778 (± 8.7117)	6.854 (± 9.3833)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 Health Survey (SF-36) Physical Role Limitations Domain Score

End point title	Change From Baseline in Short Form 36 Health Survey (SF-36) Physical Role Limitations Domain Score

End point description:

The SF-36 measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). The individual domain scores are calculated and transformed to range from 0 to 100, with higher scores indicating a better level of functioning. A positive change from baseline score

indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	153	156	
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 24 [n=136, 153, 156]	2.713 (± 8.7263)	5.618 (± 9.0459)	5.175 (± 8.8018)	
Week 48 [n=137, 148, 147]	6.423 (± 9.6752)	6.812 (± 9.8633)	6.497 (± 8.482)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 Health Survey (SF-36) Mental Health Domain Score

End point title	Change From Baseline in Short Form 36 Health Survey (SF-36) Mental Health Domain Score

End point description:

The SF-36 measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). The individual domain scores are calculated and transformed to range from 0 to 100, with higher scores indicating a better level of functioning. A positive change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	153	156	
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 24 [n=137, 153, 156]	3.278 (± 8.685)	2.77 (± 9.9943)	4.486 (± 9.493)	
Week 48 [n=135, 147, 147]	3.89 (± 8.7493)	4.583 (± 10.5625)	4.224 (± 9.9831)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 Health Survey (SF-36) Vitality Domain Score

End point title	Change From Baseline in Short Form 36 Health Survey (SF-36) Vitality Domain Score

End point description:

The SF-36 measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). The individual domain scores are calculated and transformed to range from 0 to 100, with higher scores indicating a better level of functioning. A positive change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	154	156	
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 24 [n=137, 154, 156]	3.631 (± 8.7662)	4.23 (± 9.3631)	5.91 (± 9.5802)	
Week 48 [n=135, 147, 147]	6.853 (± 9.8221)	5.925 (± 10.1495)	5.869 (± 9.6168)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 Health Survey (SF-36) Social Functioning Domain Score

End point title	Change From Baseline in Short Form 36 Health Survey (SF-36) Social Functioning Domain Score

End point description:

The SF-36 measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). The individual domain scores are calculated and transformed to range from 0 to 100, with higher scores indicating a better level of functioning. A positive change from baseline score

indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	154	156	
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 24 [n=138, 154, 156]	2.529 (± 9.6435)	5.985 (± 10.2986)	6.468 (± 10.8868)	
Week 48 [n=137, 148, 147]	6.569 (± 10.6674)	7.112 (± 11.5329)	6.159 (± 11.0244)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 Health Survey (SF-36) Emotional Role Limitations Domain Score

End point title	Change From Baseline in Short Form 36 Health Survey (SF-36) Emotional Role Limitations Domain Score

End point description:

The SF-36 measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). The individual domain scores are calculated and transformed to range from 0 to 100, with higher scores indicating a better level of functioning. A positive change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	151	155	
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 24 [n=136, 151, 155]	1.829 (± 11.5405)	4.634 (± 11.6419)	4.464 (± 13.6883)	
Week 48 [n=137, 146, 146]	4.724 (± 12.2649)	6.257 (± 12.964)	4.446 (± 13.4036)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Scores

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Scores

End point description:

The FACIT questionnaire is a self-administered patient questionnaire that consists of 13 questions designed to measure the degree of fatigue experienced by participants in the previous 7 days. Participants respond to the questions using a value in the range of 0 (not at all) to 4 (very much). The scale score is computed by summing the item scores, after reversing those items that are worded in the negative direction. The FACIT subscale score ranges from 0 to 52, where higher scores represent less fatigue. A positive change from baseline score indicates an improvement. For each parameter and treatment group, n equals the number of analyzed participants.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Week 24 and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	165	169	
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Week 24 [n=170, 165, 168]	2.661 (± 9.5093)	5.564 (± 9.7438)	6.398 (± 10.2143)	
Week 48 [170, 165, 169]	5.506 (± 10.9651)	6.269 (± 9.7495)	6.203 (± 9.7833)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With DAS28-ESR Low Disease Activity Score and Clinical Remission at Week 24

End point title	Percentage of Participants With DAS28-ESR Low Disease Activity Score and Clinical Remission at Week 24

End point description:

The DAS28 is a composite score to measure disease activity in participants with rheumatoid arthritis, derived from the following variables:
•The number of swollen and tender joints assessed using the 28-joint count;

•ESR;
•Patient's global assessment of disease activity measured on a 100 mm VAS.

The DAS28 score ranges from zero to ten. DAS28 above 5.1 indicates high disease activity.

Low disease activity is defined by a DAS28 score less than or equal to 3.2. Remission is defined by a DAS28 score less than 2.6.

ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Week 24
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	166	170	
Units: Percentage of Participants				
number (not applicable)				
Low Disease Activity	4.7	17.5	12.4	
Clinical Remission	2.3	9.6	9.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HAQ-DI Improved, Unchanged or Worsened at Week 24

End point title	Percentage of Participants With HAQ-DI Improved, Unchanged or Worsened at Week 24

End point description:

The Stanford Health Assessment Questionnaire disability index is a patient-reported questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and daily activities. Participants choose from four response categories, ranging from 'without any difficulty' (Score=0) to 'unable to do' (Score=3). The overall score is the average of each of the 8 category scores and ranges from 0 to 3, where zero represents no disability and three very severe, high-dependency disability. A negative change from baseline score indicates an improvement.

Improved HAQ-DI is defined as a change from Baseline score ≤-0.22.

An Unchanged HAQ-DI is defined as a change from Baseline score >-0.22 and <0.22.

A worsened HAQ-DI score is defined as a change from Baseline score of ≥0.22.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline and Week 24
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	165	170	
Units: Percentage of Participants				
number (not applicable)				
Improved	47.7	66.1	58.2	
No Change	32.6	23.6	32.4	
Worsened	19.8	10.3	9.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HAQ-DI Improved, Unchanged or Worsened at Week 48

End point title	Percentage of Participants With HAQ-DI Improved, Unchanged or Worsened at Week 48

End point description:

The Stanford Health Assessment Questionnaire disability index is a patient-reported questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and daily activities. Participants choose from four response categories, ranging from 'without any difficulty' (Score=0) to 'unable to do' (Score=3). The overall score is the average of each of the 8 category scores and ranges from 0 to 3, where zero represents no disability and three very severe, high-dependency disability. A negative change from baseline score indicates an improvement.

Improved HAQ-DI is defined as a change from Baseline score ≤-0.22.

An Unchanged HAQ-DI is defined as a change from Baseline score >-0.22 and <0.22.

A worsened HAQ-DI score is defined as a change from Baseline score of ≥0.22.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	165	170	
Units: Percentage of Participants				
number (not applicable)				
Improved	54.7	73.3	68.8	
No Change	29.1	17	25.3	
Worsened	16.3	9.7	5.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With European League Against Rheumatism (EULAR) Response at Week 48

End point title	Percentage of Participants With European League Against Rheumatism (EULAR) Response at Week 48

End point description:

A EULAR response reflects an improvement in disease activity and an attainment of a lower degree of disease activity based on the DAS28 score.

A Good Response is defined as an improvement (decrease) in the DAS28 of >1.2 compared with Baseline and attainment of a DAS28 score ≤3.2.

A Moderate Response is defined as either:
•an improvement (decrease) in the DAS28 >0.6 and ≤1.2 and attainment of a DAS28 score of ≤5.1 or,
•an improvement (decrease) in the DAS28 of >1.2 and attainment of a DAS28 score of >3.2.

No Response is defined as either an improvement (decrease) in the DAS28 of ≤0.6, or an improvement (decrease) in the DAS28 of >0.6 and ≤1.2 and attainment of a DAS28 score of 5.1 or higher.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Baseline and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	167	170	
Units: Percentage of Participants				
number (not applicable)				
No Response	41.3	26.9	31.8	
Moderate Response	41.9	53.3	47.6	
Good Response	16.9	19.8	20.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With DAS28-ESR Low Disease Activity Score and Clinical Remission at Week 48

End point title	Percentage of Participants With DAS28-ESR Low Disease Activity Score and Clinical Remission at Week 48

End point description:

The DAS28 is a composite score to measure disease activity in participants with rheumatoid arthritis, derived from the following variables:
•The number of swollen and tender joints assessed using the 28-joint count;
•ESR;
•Patient's global assessment of disease activity measured on a 100 mm VAS.

The DAS28 score ranges from zero to ten. DAS28 above 5.1 indicates high disease activity.

Low disease activity is defined by a DAS28 score ≤3.2. Remission is defined by a DAS28 score <2.6.
ITT Population: included participants with available data.

End point type	Secondary

End point timeframe:

Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	165	169	
Units: Percentage of Participants				
number (not applicable)				
Low Disease Activity	18.1	20	24.3	
Clinical Remission	7	9.1	11.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an ACR50 Response at Week 48

End point title	Percentage of Participants With an ACR50 Response at Week 48

End point description:

To achieve an ACR50 required at least a 50% improvement compared with Baseline in both tender joint counts (68 joints assessed for tenderness) and swollen joint counts (66 joints assessed for swelling), as well as a 50% improvement in three of the following five additional measurements:
•Physician's global assessment of disease activity (assessed using a 100 mm VAS);
•Patient's global assessment of disease activity (assessed using a 100 mm VAS);
•Patient's assessment of pain (assessed using a 100 mm VAS);
•HAQ; a patient completed questionnaire consisting of 20 questions, scored from 0-3;
•Acute phase reactant: CRP or, if CRP was missing, ESR.

Participants who withdrew prematurely from the study prior to week 48, who received rescue therapy or had insufficient data in order to calculate a clinical response were considered to be non-responders.
ITT Population

End point type	Secondary

End point timeframe:

Baseline and Week 48
Each component calculated using the LOCF.

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	167	170	
Units: Percentage of Participants				
number (not applicable)	18.6	32.9	34.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an ACR70 Response at Week 48

End point title	Percentage of Participants With an ACR70 Response at Week 48

End point description:

To achieve an ACR70 required at least a 70% improvement compared with baseline in both tender joint counts (68 joints assessed for tenderness) and swollen joint counts (66 joints assessed for swelling), as well as a 70% improvement in three of the following five additional measurements:
•Physician's global assessment of disease activity (assessed using a 100 mm VAS);
•Patient's global assessment of disease activity (assessed using a 100 mm VAS);
•Patient's assessment of pain (assessed using a 100 mm VAS);
•HAQ; a patient completed questionnaire consisting of 20 questions, scored from 0-3;
•Acute phase reactant: CRP or, if CRP was missing, ESR.

Participants who withdrew prematurely from the study prior to Week 48, who received rescue therapy or had insufficient data in order to calculate a clinical response were considered to be non-responders.
ITT Population

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	167	170	
Units: Percentage of Participants				
number (not applicable)	9.3	12.6	13.5	

Statistical analyses

No statistical analyses for this end point

Post-hoc: Time to Repletion of Peripheral CD19+ B-cells

End point title	Time to Repletion of Peripheral CD19+ B-cells

End point description:

Peripheral CD19+ B-cell repletion was defined as a CD19+ B-cell count that returned to the Baseline value or returned to ≥ the LLN, whichever was lower.
ESFU Population

End point type	Post-hoc

End point timeframe:

Beginning of the first infusion (Day 1) in the last treatment cycle until repletion or the end of the study

End point values	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	43		
Units: Weeks				
median (confidence interval 95%)	110.3 (89.6 to 148.3)	109.6 (94.1 to 134.9)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Percentage of Participants With Low Immunoglobulin Concentrations Pre- and Post-Rituximab Treatment

End point title	Percentage of Participants With Low Immunoglobulin Concentrations Pre- and Post-Rituximab Treatment

End point description:

A low immunoglobulin concentration was defined as a concentration below the lower level of normal. Safety follow-up population.

End point type	Post-hoc

End point timeframe:

Baseline (pre-rituximab), Beginning of the safety follow-up period to the end of the study (approximately 6 years) (post-rituximab)

End point values	Rituximab + MTX			
Subject group type	Subject analysis set			
Number of subjects analysed	491			
Units: Percentage of Participants				
number (not applicable)				
Pre-Rituximab (N=490)	0.2			
Post-Rituximab (N=491)	5.1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 5.1 years after last dose in treatment period (treatment period = up to 5 years)

Adverse event reporting additional description:

During the 5-year treatment period, all adverse events (AEs) regardless of seriousness were reported. During the standard 48-week safety follow-up (SFU) and extended safety follow-up (ESFU), all serious adverse events (SAEs) and all non-serious infections were reported.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Placebo + MTX

Reporting group description:

Includes all data for participants who remained on placebo, and data up to the point of switch if the participant switched to treatment with rituximab.
Participants received placebo intravenous infusion on Days 1 and 15. From Week 16 onwards, participants could switch to receive rituximab 0.5 g (on Days 1 and 15) every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Placebo and rituximab infusions were preceded with 100 mg intravenous methylprednisolone. Participants also received a stable dose of 10-25 mg/week of MTX and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Rituximab 2 x 0.5 g + MTX

Reporting group description:

Participants received 0.5 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone. Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Rituximab 2 x 1.0 g + MTX

Reporting group description:

Participants received 1.0 g rituximab administered by intravenous infusion on Days 1 and 15. After Week 24, participants received further courses of rituximab every 24 weeks for up to 5 years if they were not in clinical remission and safety criteria were met. Rituximab infusions were preceded with 100 mg intravenous methylprednisolone. Participants also received a stable dose of 10-25 mg/week of methotrexate and ≥ 5 mg/week folic acid for the duration of their participation in the study.
All participants entered a 48-week safety follow-up (SFU) period following the treatment period.

Reporting group title	Switch Population: Placebo + MTX

Reporting group description:

Includes all data up to the point of switch for participants in the Placebo + Methotrexate treatment group who switched to treatment with rituximab after Week 24.

Reporting group title	Switch Population: Rituximab

Reporting group description:

Includes all data from the point of switch for participants who switched from Placebo + Methotrexate to treatment with rituximab.

Reporting group title	Rituximab 2 x 0.5 g + MTX - Extended Safety Follow-up Period

Reporting group description:

Participants received no treatment during the extended safety follow-up period.

Reporting group title	Rituximab 2 x 1.0 g + MTX - Extended Safety Follow-up Period

Reporting group description:

Participants received no treatment during the extended safety follow-up period.

Serious adverse events	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 172 (9.30%)	52 / 167 (31.14%)	46 / 170 (27.06%)
number of deaths (all causes)	2	6	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 172 (0.58%)	0 / 167 (0.00%)	0 / 170 (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
Lung squamous cell carcinoma stage unspecified			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer metastatic			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pancreatic carcinoma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
T-cell prolymphocytic leukaemia			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haematoma			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Thrombosis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	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 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion threatened			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 172 (0.00%)	2 / 167 (1.20%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Device failure			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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

Fibrosis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia obstructive			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal prolapse			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystocele			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
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 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Testicular necrosis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 172 (0.00%)	2 / 167 (1.20%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
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	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung disorder			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Investigations			
Hepatitis B DNA increased			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 172 (0.58%)	4 / 167 (2.40%)	3 / 170 (1.76%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Road traffic accident			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Ankle fracture			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Foot fracture			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
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 limb fracture			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 172 (0.58%)	0 / 167 (0.00%)	0 / 170 (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
Stress fracture			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Subdural haematoma			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial rupture			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic coma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	2 / 172 (1.16%)	3 / 167 (1.80%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 3	1 / 8	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 172 (0.00%)	4 / 167 (2.40%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	1 / 170 (0.59%)
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 pectoris			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
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 myocardial infarction			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Atrial flutter			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Pleuropericarditis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 172 (0.58%)	0 / 167 (0.00%)	0 / 170 (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
Demyelination			
subjects affected / exposed	1 / 172 (0.58%)	0 / 167 (0.00%)	0 / 170 (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
Benign intracranial hypertension			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic hyperosmolar coma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dizziness			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
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 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Pancytopenia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	2 / 170 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	2 / 170 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	1 / 172 (0.58%)	0 / 167 (0.00%)	0 / 170 (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
Diverticulum intestinal			
subjects affected / exposed	1 / 172 (0.58%)	0 / 167 (0.00%)	0 / 170 (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
Gastritis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	2 / 170 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	2 / 170 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	2 / 170 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 172 (0.00%)	2 / 167 (1.20%)	0 / 170 (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
Abdominal pain			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral hernia, obstructive			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal ulcer			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia, obstructive			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
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 obstruction			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Volvulus			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Abdominal wall haematoma			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 172 (1.16%)	0 / 167 (0.00%)	0 / 170 (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
Cholecystitis			
subjects affected / exposed	0 / 172 (0.00%)	2 / 167 (1.20%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Skin and subcutaneous tissue disorders			
Lichen planus			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 172 (0.58%)	1 / 167 (0.60%)	0 / 170 (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
Endocrine disorders			
Vertigo			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Goitre			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 172 (0.58%)	4 / 167 (2.40%)	5 / 170 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	1 / 172 (0.58%)	2 / 167 (1.20%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Osteonecrosis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			

subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Muscular weakness			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Spinal column stenosis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondyloarthropathy			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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	1 / 172 (0.58%)	3 / 167 (1.80%)	4 / 170 (2.35%)
occurrences causally related to treatment / all	1 / 1	2 / 3	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 172 (1.16%)	1 / 167 (0.60%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 172 (0.00%)	3 / 167 (1.80%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 172 (0.00%)	3 / 167 (1.80%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 172 (0.00%)	2 / 167 (1.20%)	0 / 170 (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
Bronchitis			
subjects affected / exposed	0 / 172 (0.00%)	2 / 167 (1.20%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 172 (0.00%)	2 / 167 (1.20%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 172 (0.58%)	1 / 167 (0.60%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 172 (0.58%)	0 / 167 (0.00%)	0 / 170 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 172 (0.00%)	2 / 167 (1.20%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			

subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal sepsis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Abscess soft tissue			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Pulmonary sepsis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Pulmonary tuberculosis			

subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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 tract infection			
subjects affected / exposed	1 / 172 (0.58%)	0 / 167 (0.00%)	0 / 170 (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
Sepsis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Septic shock			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinusitis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Skin infection			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubo-ovarian abscess			
subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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
Urosepsis			

subjects affected / exposed	0 / 172 (0.00%)	1 / 167 (0.60%)	0 / 170 (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 / 172 (0.00%)	0 / 167 (0.00%)	2 / 170 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 172 (0.00%)	0 / 167 (0.00%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Switch Population: Placebo + MTX	Switch Population: Rituximab	Rituximab 2 x 0.5 g + MTX - Extended Safety Follow-up Period
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 155 (7.74%)	45 / 155 (29.03%)	8 / 82 (9.76%)
number of deaths (all causes)	0	3	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 155 (0.65%)	0 / 155 (0.00%)	0 / 82 (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
Lung squamous cell carcinoma stage unspecified			

subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Bladder cancer			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Meningioma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Non-small cell lung cancer			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Non-small cell lung cancer metastatic			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			

subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
T-cell prolymphocytic leukaemia			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	1 / 82 (1.22%)
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			
Aortic stenosis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haematoma			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion threatened			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device failure			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrosis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia obstructive			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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			
Vaginal prolapse			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Cystocele			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Testicular necrosis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	0 / 155 (0.00%)	2 / 155 (1.29%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Asthma			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Dyspnoea			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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 disorder			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Hepatitis B DNA increased			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 155 (0.00%)	3 / 155 (1.94%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Road traffic accident			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Ankle fracture			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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

Limb injury			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress fracture			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial rupture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Tendon rupture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic coma			

subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	2 / 155 (1.29%)	3 / 155 (1.94%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Angina pectoris			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pleuropericarditis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Tachycardia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Cardiac arrest			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Palpitations			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	1 / 82 (1.22%)
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	1 / 155 (0.65%)	3 / 155 (1.94%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Demyelination			

subjects affected / exposed	1 / 155 (0.65%)	1 / 155 (0.65%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign intracranial hypertension			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Diabetic hyperosmolar coma			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	1 / 82 (1.22%)
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 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Cataract			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Diverticular perforation			
subjects affected / exposed	1 / 155 (0.65%)	0 / 155 (0.00%)	0 / 82 (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
Diverticulum intestinal			
subjects affected / exposed	1 / 155 (0.65%)	0 / 155 (0.00%)	0 / 82 (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
Gastritis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	2 / 155 (1.29%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			

subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Diarrhoea			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Duodenal ulcer			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Femoral hernia, obstructive			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal ulcer			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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, obstructive			

subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haematoma			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Rectal haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 155 (0.65%)	1 / 155 (0.65%)	0 / 82 (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
Cholecystitis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			

subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Lichen planus			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 155 (0.00%)	0 / 82 (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
Endocrine disorders			
Vertigo			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Goitre			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 155 (0.00%)	0 / 82 (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
Rheumatoid arthritis			

subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Osteonecrosis			
subjects affected / exposed	0 / 155 (0.00%)	2 / 155 (1.29%)	0 / 82 (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
Arthritis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			

subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Spinal osteoarthritis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Spondyloarthropathy			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 155 (0.65%)	3 / 155 (1.94%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 155 (1.29%)	1 / 155 (0.65%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Cellulitis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Bronchitis			

subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Diverticulitis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 155 (0.65%)	0 / 155 (0.00%)	0 / 82 (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
Bronchopneumonia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal sepsis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess soft tissue			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Arthritis infective			

subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Soft tissue infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Tubo-ovarian abscess			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Dehydration			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			

subjects affected / exposed	0 / 155 (0.00%)	1 / 155 (0.65%)	0 / 82 (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
Hypoglycaemia			
subjects affected / exposed	0 / 155 (0.00%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Rituximab 2 x 1.0 g + MTX - Extended Safety Follow-up Period		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 44 (4.55%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung squamous cell carcinoma stage unspecified			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningioma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-small cell lung cancer				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-small cell lung cancer metastatic				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal adenocarcinoma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal carcinoma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of the cervix				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
T-cell prolymphocytic leukaemia				

subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intra-abdominal haematoma			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abortion threatened			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device failure				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fibrosis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hernia obstructive				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Drug hypersensitivity				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Vaginal prolapse				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystocele				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Menorrhagia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postmenopausal haemorrhage				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Testicular necrosis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uterine haemorrhage				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Asthma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Major depression				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Hepatitis B DNA increased				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incisional hernia				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ankle fracture				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stress fracture				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Synovial rupture				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic coma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Coronary artery disease				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic valve incompetence				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleuropericarditis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Demyelination				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Benign intracranial hypertension				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetic hyperosmolar coma				

subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radiculopathy			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Diverticular perforation				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral hernia, obstructive				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileal ulcer				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia, obstructive				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Retroperitoneal haemorrhage				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Volvulus				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal wall haematoma				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholelithiasis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				

Lichen planus			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Vertigo			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Goitre			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rheumatoid arthritis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical spinal stenosis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar spinal stenosis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal column stenosis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal osteoarthritis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spondyloarthropathy				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal abscess				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal sepsis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abscess soft tissue				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis infective				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculosis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				

subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tubo-ovarian abscess				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Diabetes mellitus				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Placebo + MTX	Rituximab 2 x 0.5 g + MTX	Rituximab 2 x 1.0 g + MTX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 172 (65.12%)	149 / 167 (89.22%)	151 / 170 (88.82%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 172 (1.74%)	28 / 167 (16.77%)	18 / 170 (10.59%)
occurrences (all)	3	30	21
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 172 (0.58%)	13 / 167 (7.78%)	11 / 170 (6.47%)
occurrences (all)	1	16	13
Oedema peripheral			
subjects affected / exposed	2 / 172 (1.16%)	9 / 167 (5.39%)	12 / 170 (7.06%)
occurrences (all)	2	11	13
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 172 (4.07%)	13 / 167 (7.78%)	22 / 170 (12.94%)
occurrences (all)	7	13	25
Rhinitis allergic			
subjects affected / exposed	0 / 172 (0.00%)	6 / 167 (3.59%)	10 / 170 (5.88%)
occurrences (all)	0	6	11
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 172 (4.07%)	9 / 167 (5.39%)	8 / 170 (4.71%)
occurrences (all)	7	10	8
Depression			
subjects affected / exposed	0 / 172 (0.00%)	15 / 167 (8.98%)	7 / 170 (4.12%)
occurrences (all)	0	16	7
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	33 / 172 (19.19%)	59 / 167 (35.33%)	59 / 170 (34.71%)
occurrences (all)	44	160	148
Fall			

subjects affected / exposed	5 / 172 (2.91%)	14 / 167 (8.38%)	5 / 170 (2.94%)
occurrences (all)	5	22	6
Laceration			
subjects affected / exposed	1 / 172 (0.58%)	2 / 167 (1.20%)	10 / 170 (5.88%)
occurrences (all)	1	2	10
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 172 (3.49%)	18 / 167 (10.78%)	15 / 170 (8.82%)
occurrences (all)	6	28	21
Dizziness			
subjects affected / exposed	4 / 172 (2.33%)	11 / 167 (6.59%)	10 / 170 (5.88%)
occurrences (all)	4	11	11
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 172 (2.91%)	9 / 167 (5.39%)	12 / 170 (7.06%)
occurrences (all)	5	9	13
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 172 (1.16%)	8 / 167 (4.79%)	6 / 170 (3.53%)
occurrences (all)	2	9	7
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 172 (4.07%)	27 / 167 (16.17%)	20 / 170 (11.76%)
occurrences (all)	8	33	30
Nausea			
subjects affected / exposed	4 / 172 (2.33%)	21 / 167 (12.57%)	17 / 170 (10.00%)
occurrences (all)	4	22	21
Dyspepsia			
subjects affected / exposed	3 / 172 (1.74%)	4 / 167 (2.40%)	4 / 170 (2.35%)
occurrences (all)	3	4	6
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 172 (1.16%)	7 / 167 (4.19%)	10 / 170 (5.88%)
occurrences (all)	2	8	10
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	2 / 172 (1.16%)	8 / 167 (4.79%)	7 / 170 (4.12%)
occurrences (all)	2	12	9

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 172 (0.58%)	9 / 167 (5.39%)	7 / 170 (4.12%)
occurrences (all)	1	12	8
Alopecia			
subjects affected / exposed	1 / 172 (0.58%)	9 / 167 (5.39%)	6 / 170 (3.53%)
occurrences (all)	1	10	6
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	30 / 172 (17.44%)	49 / 167 (29.34%)	36 / 170 (21.18%)
occurrences (all)	42	71	49
Back pain			
subjects affected / exposed	3 / 172 (1.74%)	22 / 167 (13.17%)	14 / 170 (8.24%)
occurrences (all)	3	28	18
Arthralgia			
subjects affected / exposed	3 / 172 (1.74%)	9 / 167 (5.39%)	15 / 170 (8.82%)
occurrences (all)	3	16	22
Muscle spasms			
subjects affected / exposed	4 / 172 (2.33%)	7 / 167 (4.19%)	7 / 170 (4.12%)
occurrences (all)	4	9	7
Osteoarthritis			
subjects affected / exposed	1 / 172 (0.58%)	8 / 167 (4.79%)	10 / 170 (5.88%)
occurrences (all)	1	12	10
Pain in extremity			
subjects affected / exposed	1 / 172 (0.58%)	9 / 167 (5.39%)	9 / 170 (5.29%)
occurrences (all)	1	11	10
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	13 / 172 (7.56%)	59 / 167 (35.33%)	50 / 170 (29.41%)
occurrences (all)	14	100	84
Nasopharyngitis			
subjects affected / exposed	17 / 172 (9.88%)	43 / 167 (25.75%)	42 / 170 (24.71%)
occurrences (all)	22	82	77
Urinary tract infection			
subjects affected / exposed	12 / 172 (6.98%)	41 / 167 (24.55%)	25 / 170 (14.71%)
occurrences (all)	23	72	45

Sinusitis			
subjects affected / exposed	6 / 172 (3.49%)	24 / 167 (14.37%)	21 / 170 (12.35%)
occurrences (all)	6	39	36
Bronchitis			
subjects affected / exposed	3 / 172 (1.74%)	27 / 167 (16.17%)	25 / 170 (14.71%)
occurrences (all)	3	39	30
Gastroenteritis			
subjects affected / exposed	8 / 172 (4.65%)	15 / 167 (8.98%)	14 / 170 (8.24%)
occurrences (all)	8	16	17
Pharyngitis			
subjects affected / exposed	10 / 172 (5.81%)	15 / 167 (8.98%)	11 / 170 (6.47%)
occurrences (all)	10	17	13
Influenza			
subjects affected / exposed	1 / 172 (0.58%)	17 / 167 (10.18%)	20 / 170 (11.76%)
occurrences (all)	1	26	30
Tooth abscess			
subjects affected / exposed	0 / 172 (0.00%)	9 / 167 (5.39%)	8 / 170 (4.71%)
occurrences (all)	0	12	9
Herpes zoster			
subjects affected / exposed	2 / 172 (1.16%)	10 / 167 (5.99%)	4 / 170 (2.35%)
occurrences (all)	2	10	4
Lower respiratory tract infection			
subjects affected / exposed	1 / 172 (0.58%)	2 / 167 (1.20%)	8 / 170 (4.71%)
occurrences (all)	1	3	17
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	4 / 172 (2.33%)	13 / 167 (7.78%)	6 / 170 (3.53%)
occurrences (all)	4	14	6
Hypercholesterolaemia			
subjects affected / exposed	1 / 172 (0.58%)	7 / 167 (4.19%)	9 / 170 (5.29%)
occurrences (all)	1	7	9

Non-serious adverse events	Switch Population: Placebo + MTX	Switch Population: Rituximab	Rituximab 2 x 0.5 g + MTX - Extended Safety Follow-up Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 155 (63.87%)	131 / 155 (84.52%)	5 / 82 (6.10%)

Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 155 (1.29%)	15 / 155 (9.68%)	0 / 82 (0.00%)
occurrences (all)	2	19	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 155 (0.00%)	8 / 155 (5.16%)	0 / 82 (0.00%)
occurrences (all)	0	8	0
Oedema peripheral			
subjects affected / exposed	2 / 155 (1.29%)	5 / 155 (3.23%)	0 / 82 (0.00%)
occurrences (all)	2	6	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 155 (4.52%)	11 / 155 (7.10%)	0 / 82 (0.00%)
occurrences (all)	7	15	0
Rhinitis allergic			
subjects affected / exposed	0 / 155 (0.00%)	6 / 155 (3.87%)	0 / 82 (0.00%)
occurrences (all)	0	6	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 155 (3.87%)	5 / 155 (3.23%)	0 / 82 (0.00%)
occurrences (all)	6	7	0
Depression			
subjects affected / exposed	0 / 155 (0.00%)	7 / 155 (4.52%)	0 / 82 (0.00%)
occurrences (all)	0	7	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	28 / 155 (18.06%)	39 / 155 (25.16%)	0 / 82 (0.00%)
occurrences (all)	38	105	0
Fall			
subjects affected / exposed	4 / 155 (2.58%)	18 / 155 (11.61%)	0 / 82 (0.00%)
occurrences (all)	4	23	0
Laceration			
subjects affected / exposed	1 / 155 (0.65%)	6 / 155 (3.87%)	0 / 82 (0.00%)
occurrences (all)	1	6	0
Nervous system disorders			

Headache			
subjects affected / exposed	5 / 155 (3.23%)	16 / 155 (10.32%)	0 / 82 (0.00%)
occurrences (all)	5	24	0
Dizziness			
subjects affected / exposed	3 / 155 (1.94%)	0 / 155 (0.00%)	0 / 82 (0.00%)
occurrences (all)	3	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 155 (2.58%)	7 / 155 (4.52%)	0 / 82 (0.00%)
occurrences (all)	4	7	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 155 (1.29%)	9 / 155 (5.81%)	0 / 82 (0.00%)
occurrences (all)	2	9	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 155 (4.52%)	20 / 155 (12.90%)	0 / 82 (0.00%)
occurrences (all)	8	26	0
Nausea			
subjects affected / exposed	4 / 155 (2.58%)	12 / 155 (7.74%)	0 / 82 (0.00%)
occurrences (all)	4	12	0
Dyspepsia			
subjects affected / exposed	3 / 155 (1.94%)	11 / 155 (7.10%)	0 / 82 (0.00%)
occurrences (all)	3	12	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 155 (1.29%)	4 / 155 (2.58%)	0 / 82 (0.00%)
occurrences (all)	2	4	0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	2 / 155 (1.29%)	8 / 155 (5.16%)	0 / 82 (0.00%)
occurrences (all)	2	9	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 155 (0.65%)	6 / 155 (3.87%)	0 / 82 (0.00%)
occurrences (all)	1	6	0
Alopecia			

subjects affected / exposed	0 / 155 (0.00%)	3 / 155 (1.94%)	0 / 82 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	26 / 155 (16.77%)	31 / 155 (20.00%)	0 / 82 (0.00%)
occurrences (all)	38	49	0
Back pain			
subjects affected / exposed	3 / 155 (1.94%)	10 / 155 (6.45%)	0 / 82 (0.00%)
occurrences (all)	3	10	0
Arthralgia			
subjects affected / exposed	2 / 155 (1.29%)	7 / 155 (4.52%)	0 / 82 (0.00%)
occurrences (all)	2	8	0
Muscle spasms			
subjects affected / exposed	4 / 155 (2.58%)	10 / 155 (6.45%)	0 / 82 (0.00%)
occurrences (all)	4	14	0
Osteoarthritis			
subjects affected / exposed	1 / 155 (0.65%)	8 / 155 (5.16%)	0 / 82 (0.00%)
occurrences (all)	1	8	0
Pain in extremity			
subjects affected / exposed	1 / 155 (0.65%)	7 / 155 (4.52%)	0 / 82 (0.00%)
occurrences (all)	1	8	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	13 / 155 (8.39%)	39 / 155 (25.16%)	0 / 82 (0.00%)
occurrences (all)	14	74	0
Nasopharyngitis			
subjects affected / exposed	16 / 155 (10.32%)	34 / 155 (21.94%)	0 / 82 (0.00%)
occurrences (all)	20	61	0
Urinary tract infection			
subjects affected / exposed	9 / 155 (5.81%)	34 / 155 (21.94%)	5 / 82 (6.10%)
occurrences (all)	10	50	7
Sinusitis			
subjects affected / exposed	6 / 155 (3.87%)	29 / 155 (18.71%)	0 / 82 (0.00%)
occurrences (all)	6	46	0
Bronchitis			

subjects affected / exposed	2 / 155 (1.29%)	24 / 155 (15.48%)	0 / 82 (0.00%)
occurrences (all)	2	37	0
Gastroenteritis			
subjects affected / exposed	7 / 155 (4.52%)	17 / 155 (10.97%)	0 / 82 (0.00%)
occurrences (all)	7	23	0
Pharyngitis			
subjects affected / exposed	10 / 155 (6.45%)	9 / 155 (5.81%)	0 / 82 (0.00%)
occurrences (all)	10	10	0
Influenza			
subjects affected / exposed	1 / 155 (0.65%)	13 / 155 (8.39%)	0 / 82 (0.00%)
occurrences (all)	1	15	0
Tooth abscess			
subjects affected / exposed	0 / 155 (0.00%)	7 / 155 (4.52%)	0 / 82 (0.00%)
occurrences (all)	0	7	0
Herpes zoster			
subjects affected / exposed	2 / 155 (1.29%)	5 / 155 (3.23%)	0 / 82 (0.00%)
occurrences (all)	2	5	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 155 (0.65%)	9 / 155 (5.81%)	0 / 82 (0.00%)
occurrences (all)	1	19	0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	3 / 155 (1.94%)	7 / 155 (4.52%)	0 / 82 (0.00%)
occurrences (all)	3	8	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 155 (0.65%)	5 / 155 (3.23%)	0 / 82 (0.00%)
occurrences (all)	1	6	0

Non-serious adverse events	Rituximab 2 x 1.0 g + MTX - Extended Safety Follow-up Period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 44 (4.55%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Laceration			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Dizziness			

subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 0 / 44 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 0 / 44 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	 0 / 44 (0.00%) 0 0 / 44 (0.00%) 0 0 / 44 (0.00%) 0 0 / 44 (0.00%) 0		
Hepatobiliary disorders Hepatotoxicity subjects affected / exposed occurrences (all)	 0 / 44 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all)	 0 / 44 (0.00%) 0 0 / 44 (0.00%) 0		
Musculoskeletal and connective tissue disorders			

Rheumatoid arthritis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Back pain				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Arthralgia				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Muscle spasms				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Osteoarthritis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Pain in extremity				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Infections and infestations				
Upper respiratory tract infection				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Urinary tract infection				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	3			
Sinusitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Bronchitis				
subjects affected / exposed	0 / 44 (0.00%)			
occurrences (all)	0			
Gastroenteritis				

subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Tooth abscess			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Herpes zoster			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Hypercholesterolaemia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2006	The first amendment, B, made three main changes: 1. Correction of the dose of pre-infusion antihistamine from diphenhydramine 100 mg to diphenhydramine 50 mg (or equivalent), in accordance with clinical practice. 2. Removal of immunoglobulin concentrations from the eligibility criteria for retreatment. 3. Extended the screening period to 42 days for participants requiring vaccination. The other items were minor changes, clarifications and corrections that did not affect the study conduct.
22 March 2007	The second amendment, C, made the following changes: 1. The addition of a comparison of the efficacy of two courses of 2 x 0.5 g rituximab with two courses of 2 x 1.0 g rituximab. This required the addition of study objective No. 3: "to explore a dose separation of rituximab 0.5 g IV x 2 from rituximab 1.0 g IV x 2 at Week 48", and additions to the assessments and statistical analysis sections. Blinding was extended from Week 24 to Week 48; i.e., although after Week 24 all retreatment infusions were of rituximab, investigators, participants, and study team remained blinded to the dose, and also to the previous first course of treatment. 2. Hepatitis monitoring was added for Hepatitis B core antigen (HBcAg)-positive participants who might have been admitted to the study if they were Hepatitis surface antigen (HBsAb)-negative (HBsAb-positive participants were excluded from the study). Further courses of rituximab for these participants would only be allowed if their hepatitis B viral load was negative and their aspartate aminotransferase (AST) or alanine aminotransferase (ALT) were ≤2.5 x the upper limit of normal (ULN). 3. The rituximab warnings and precautions were updated in line with the latest Investigator's Brochure. 4. The assessment of eligibility for retreatment was clarified, especially the timing of assessment and the maximum time from assessment to initiation of retreatment. 5. Addition of the proportion of participants with a minimal clinically important difference (MCID) in the health assessment questionnaire (HAQ) as a secondary endpoint. The other changes including corrections, updates and clarifications did not affect the study conduct.
19 November 2008	The third amendment, D, made the following changes: 1. Extension of study to provide additional information on the safety of long-term treatment with rituximab in RA participants. 2. Update to safety information (including PML update). 3. Update of study procedures.
31 August 2012	The fourth amendment, E, made the following changes: 1. Discontinuation of extended B-cell follow up following the safety follow-up period. 2. Administrative updates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/20488885