Clinical trial results:
A randomized, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab compared to placebo in patients with active rheumatoid arthritis continuing methotrexate treatment

Summary

EudraCT number	2006-005147-28
Trial protocol	DE BE ES FR AT GR GB
Global end of trial date	22 April 2015

Results information

Result version number	v2 (current)
This version publication date	06 January 2018
First version publication date	04 August 2017
Version creation reason	
Summary attachment (see zip file)	WA20494_CSR synopsis (CSR Synopsis_WA20494.pdf)

Trial information

Trial identification

Sponsor protocol code	WA20494

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00406419
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy and safety of ocrelizumab versus placebo in reducing the signs and symptoms of rheumatoid arthritis (RA), when used in combination with methotrexate (MTX) in subjects with active RA who have an inadequate response to MTX therapy.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

Every patient had to take methotrexate.

Evidence for comparator:

Comparator was placebo.

Actual start date of recruitment	30 November 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 44
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Brazil: 95
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	China: 22
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Guatemala: 8
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Mexico: 79
Country: Number of subjects enrolled	New Zealand: 9
Country: Number of subjects enrolled	Panama: 9
Country: Number of subjects enrolled	Peru: 32
Country: Number of subjects enrolled	Korea, Republic of: 23

Country: Number of subjects enrolled	Russian Federation: 103
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Taiwan: 27
Country: Number of subjects enrolled	Thailand: 25
Country: Number of subjects enrolled	Ukraine: 26
Country: Number of subjects enrolled	United States: 360
Country: Number of subjects enrolled	United Kingdom: 20
Worldwide total number of subjects	1015
EEA total number of subjects	95

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)	878
From 65 to 84 years	135
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1015 subjects were enrolled in the study. The study consisted of 3 parts: double-blind treatment period (Day 1 - Week 48); study extension period (during which eligible subjects could receive open-label treatment with ocrelizumab, at the discretion of the investigator); safety follow-up period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo × 2 IV + MTX

Arm description:

Subjects received two intravenous (IV) infusion matching placebo to ocrelizumab on Day 1 and Day 15. A repeat course was
administered at Weeks 24 and 26. Methotrexate 7.5-25 milligram (mg) was administered weekly.

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:

Matching placebo to ocrelizumab two IV infusions on Day 1 and Day 15.

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

Dosage and administration details:

Methotrexate 7.5-25 mg tablet was administered weekly.

Arm title	Ocrelizumab 200 mg × 2 IV + MTX

Arm description:

Subjects received two IV infusion of ocrelizumab 200 mg on Day 1 and Day 15. A repeat course was administered at Weeks 24 and 26. Methotrexate 7.5-25 mg was administered weekly.

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

Dosage and administration details:

Two IV infusions Ocrelizumab 200 mg on Day 1 and Day 15.

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

Dosage and administration details:

Methotrexate 7.5-25 mg tablet was administered weekly.

Arm title	Ocrelizumab 500 mg × 2 IV + MTX

Arm description:

Subjects received two IV infusion of ocrelizumab 500 mg on Day 1 and Day 15. A repeat course was administered at Weeks 24 and 26. Methotrexate 7.5-25 mg was administered weekly.

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

Dosage and administration details:

Methotrexate 7.5-25mg tablet was administered weekly.

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

Dosage and administration details:

Two IV infusions Ocrelizumab 500 mg on Day 1 and Day 15.

Number of subjects in period 1	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX
Started	324	344	347
Completed	0	0	0
Not completed	324	344	347
Adverse Event	10	12	16
Other	260	288	282
Death	3	1	4
NOn-Compliance with Study Drug	5	6	3
Withdrawal by Subject	17	24	26
Lost to follow-up	11	10	5
Protocol deviation	6	2	5
Lack of efficacy	12	1	6

Baseline characteristics

Reporting groups	
Reporting group title	Placebo × 2 IV + MTX
Reporting group description:	
Subjects received two intravenous (IV) infusion matching placebo to ocrelizumab on Day 1 and Day 15. A repeat course was administered at Weeks 24 and 26. Methotrexate 7.5-25 milligram (mg) was administered weekly.	
Reporting group title	Ocrelizumab 200 mg × 2 IV + MTX
Reporting group description:	
Subjects received two IV infusion of ocrelizumab 200 mg on Day 1 and Day 15. A repeat course was administered at Weeks 24 and 26. Methotrexate 7.5-25 mg was administered weekly.	
Reporting group title	Ocrelizumab 500 mg × 2 IV + MTX
Reporting group description:	
Subjects received two IV infusion of ocrelizumab 500 mg on Day 1 and Day 15. A repeat course was administered at Weeks 24 and 26. Methotrexate 7.5-25 mg was administered weekly.	

Reporting group values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects	324	344	347
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	50.5	51.8	50.8
standard deviation	± 11.6	± 12.0	± 12.3
Gender Categorical Units: Subjects			
Female	251	284	285
Male	73	60	62

Reporting group values	Total		
Number of subjects	1015		
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	820		
Male	195		

End points

End points reporting groups

Reporting group title	Placebo × 2 IV + MTX
Reporting group description:	
Subjects received two intravenous (IV) infusion matching placebo to ocrelizumab on Day 1 and Day 15. A repeat course was administered at Weeks 24 and 26. Methotrexate 7.5-25 milligram (mg) was administered weekly.	
Reporting group title	Ocrelizumab 200 mg × 2 IV + MTX
Reporting group description:	
Subjects received two IV infusion of ocrelizumab 200 mg on Day 1 and Day 15. A repeat course was administered at Weeks 24 and 26. Methotrexate 7.5-25 mg was administered weekly.	
Reporting group title	Ocrelizumab 500 mg × 2 IV + MTX
Reporting group description:	
Subjects received two IV infusion of ocrelizumab 500 mg on Day 1 and Day 15. A repeat course was administered at Weeks 24 and 26. Methotrexate 7.5-25 mg was administered weekly.	

Primary: Percentage of Subjects with American College of Rheumatology (ACR) 20 Response at Week 24

End point title	Percentage of Subjects with American College of Rheumatology (ACR) 20 Response at Week 24
End point description:	
ACR20 is defined as 20 percent improvement respectively in: a) swollen joint count (SJC) and tender joint count (TJC) and b) Three of the following 5 assessments: Subject's global assessment of pain by VAS Subject's global assessment of disease activity (VAS) Investigator/Physician's global assessment of disease activity (VAS) Subject's assessment of disability measured by HAQ-DI Acute phase reactant (ESR or CRP). Intent-to-treat (ITT) population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint.	
End point type	Primary
End point timeframe:	
Week 24	

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	319	343	343	
Units: Percentage of Subjects				
number (confidence interval 95%)	35.7 (30.5 to 41.0)	56.9 (51.6 to 62.1)	54.5 (49.2 to 59.8)	

Statistical analyses

Statistical analysis title	Ocrelizumab 500 mg vs Placebo
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	662
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	11
upper limit	25.9

Statistical analysis title	Ocrelizumab 200 mg vs Placebo
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	662
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	21.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.1
upper limit	28.8

Primary: Percentage of Subjects with ACR20 Response at Week 48

End point title	Percentage of Subjects with ACR20 Response at Week 48

End point description:

ACR20 is defined as 20 percent improvement respectively in: a) swollen joint count (SJC) and tender joint count (TJC) and b) Three of the following 5 assessments:

Subject's global assessment of pain by VAS
Subject's global assessment of disease activity (VAS)
Investigator/Physician's global assessment of disease activity (VAS)
Subject's assessment of disability measured by HAQ-DI
Acute phase reactant (ESR or CRP). ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint.

End point type	Primary

End point timeframe:

Week 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	319	343	343	
Units: Percentage of Subjects				
number (confidence interval 95%)	27.6 (22.7 to 32.5)	58.3 (53.1 to 63.5)	62.1 (57.0 to 67.2)	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	662
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	30.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.7
upper limit	37.9

Statistical analysis title	Ocrelizumab 500 mg vs Placebo
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	662
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	34.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.4
upper limit	41.5

Primary: Percentage of Subjects With Adverse Events (AEs)

End point title	Percentage of Subjects With Adverse Events (AEs)[1]

End point description:

An AE was defined as any untoward medical occurrence in a subject administered a pharmaceutical product which does not necessarily have a causal relationship with the treatment. Pre-existing conditions which worsened during the study were also reported as AEs. The safety population included all subjects who were randomized and received any part of an infusion of study drug and provided at least one assessment of safety.

End point type	Primary

End point timeframe:

Up to 8.5 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was planned to be reported for this endpoint.

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Percentage of Subjects				
number (not applicable)	79.4	82.2	83.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Major Clinical Response (ACR70 for ≥ 6 months) at Week 48

End point title	Percentage of Subjects With a Major Clinical Response (ACR70 for ≥ 6 months) at Week 48

End point description:

ACR70 is defined as 70 percent improvement respectively in: a) swollen joint count (SJC) and tender joint count (TJC) and b) Three of the following 5 assessments:

Subject's global assessment of pain by VAS
Subject's global assessment of disease activity (VAS)
Investigator/Physician's global assessment of disease activity (VAS)
Subject's assessment of disability measured by HAQ-DI
Acute phase reactant (ESR or CRP). ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Week 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Percentage of Subjects				
number (confidence interval 95%)	0.9 (0.0 to 2.0)	6.1 (3.6 to 8.7)	7.3 (4.5 to 10.0)	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	8.1

Statistical analysis title	Ocrelizumab 500 mg vs Placebo
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.1
upper limit	9.4

Secondary: Percentage of Subjects Achieving Disease Activity Score 28 (DAS28) Remission (DAS28 < 2.6) at Weeks 24 and 48

End point title	Percentage of Subjects Achieving Disease Activity Score 28 (DAS28) Remission (DAS28 < 2.6) at Weeks 24 and 48

End point description:

The Disease Activity Score (DAS28) score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity and Erythrocyte Sedimentation Rate (ESR). DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A negative change from Baseline indicated improvement. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint. 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Week 24 (n= 319, 343, 343)	5.3 (2.9 to 7.8)	7.9 (5.0 to 10.7)	10.8 (7.5 to 14.1)	
Week 48 (n= 319, 343, 343)	5.3 (2.9 to 7.8)	16.0 (12.2 to 19.9)	17.5 (13.5 to 21.5)	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1472
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	6.7

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX

Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0082
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	9.9

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	15.4

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.3
upper limit	17

Secondary: Change From Baseline in DAS28 at Weeks 24 and 48

End point title	Change From Baseline in DAS28 at Weeks 24 and 48

End point description:

The Disease Activity Score (DAS28) score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity and Erythrocyte Sedimentation Rate (ESR). DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A negative change from Baseline indicated improvement. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint. 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Baseline (n= 316, 340, 336)	6.42 (± 1.103)	6.40 (± 1.143)	6.40 (± 1.077)	
Change at Week 24 (n= 227, 299, 300)	-1.33 (± 1.329)	-2.00 (± 1.248)	-2.02 (± 1.310)	
Change at Week 48 (n= 187, 271, 278)	-1.38 (± 1.290)	-2.42 (± 1.504)	-2.68 (± 1.475)	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.4

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX

Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.5

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.8

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	-1

Secondary: European League Against Rheumatism (EULAR) Response Rates

(Categorical DAS Responders) at Weeks 24 and 48	
End point title	European League Against Rheumatism (EULAR) Response Rates (Categorical DAS Responders) at Weeks 24 and 48

End point description:

DAS 28 score is a measure of the subject's disease activity. It is based on the tender joint count (28 joints), swollen joint count (28 joints), patient's global assessment of disease activity and ESR. DAS28 total scores range from 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A negative change from Baseline indicated improvement. EULAR Good response: DAS28 ≤ 3.2 and a change from Baseline < -1.2. EULAR Moderate response: DAS28 >3.2 to ≤ 5.1 or a change from Baseline < -0.6 to ≥ -1.2. ITT population included all randomised subjects who had received any part of an infusion of study medication. Data for good /moderate response are grouped. Here, the number of subjects analysed signifies subjects evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Percentage of Subjects				
number (not applicable)				
Week 24	41.6	68.8	70.0	
Week 48	35.3	65.9	72.0	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Odds ratio (OR)
Point estimate	2.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.09
upper limit	3.82

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX

Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Odds ratio (OR)
Point estimate	3.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.24
upper limit	4.11

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Odds ratio (OR)
Point estimate	3.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.77
upper limit	5.1

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Odds ratio (OR)
Point estimate	4.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.36
upper limit	6.23

Secondary: Percentage of Subjects Achieving an ACR50 Response at Weeks 24 and

48

End point title	Percentage of Subjects Achieving an ACR50 Response at Weeks 24 and 48

End point description:

ACR50 is defined as 50 percent improvement respectively in: a) swollen joint count (SJC) and tender joint count (TJC) and b) Three of the following 5 assessments:

Subject's global assessment of pain by VAS
Subject's global assessment of disease activity (VAS)
Investigator/Physician's global assessment of disease activity (VAS)
Subject's assessment of disability measured by HAQ-DI
Acute phase reactant (ESR or CRP).
ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: percentage of subjects				
number (confidence interval 95%)				
Week 24 (n= 319, 343, 343)	16.3 (12.2 to 20.4)	31.8 (26.9 to 36.7)	31.2 (26.3 to 36.1)	
Week 48 (n= 319, 343, 343)	12.9 (9.2 to 16.5)	39.9 (34.8 to 45.1)	36.7 (31.6 to 41.8)	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	15.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.5
upper limit	22.2

	Ocrelizumab 500 mg vs Placebo at Week 24

Statistical analysis title	
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	15
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.6
upper limit	21.4

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	27.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.1
upper limit	33.6

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	23.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.4
upper limit	29.9

Secondary: Percentage of Subjects Achieving an ACR70 Response at Weeks 24 and 48

End point title	Percentage of Subjects Achieving an ACR70 Response at Weeks 24 and 48

End point description:

ACR70 is defined as 70 percent improvement respectively in: a) swollen joint count (SJC) and tender joint count (TJC) and b) Three of the following 5 assessments:

Subject's global assessment of pain by VAS
Subject's global assessment of disease activity (VAS)
Investigator/Physician's global assessment of disease activity (VAS)
Subject's assessment of disability measured by HAQ-DI
Acute phase reactant (ESR or CRP).
ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint. 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: percentage of subjects				
number (confidence interval 95%)				
Week 24 (n= 319, 343, 343)	5.6 (3.1 to 8.2)	14.3 (10.6 to 18.0)	12.2 (8.8 to 15.7)	
Week 48 (n= 319, 343, 343)	6.6 (3.9 to 9.3)	20.7 (16.4 to 25.0)	22.4 (18.0 to 26.9)	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	8.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.2
upper limit	13.3

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.4
upper limit	11.2

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	14.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.2
upper limit	19.4

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX

Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted difference
Point estimate	15.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.5
upper limit	20.9

Secondary: Percent Change From Baseline in Swollen Joint Count (SJC) at Weeks 24 and 48

End point title	Percent Change From Baseline in Swollen Joint Count (SJC) at Weeks 24 and 48

End point description:

66 joints were assessed for swelling and joints are classified as swollen/not swollen giving a total possible swollen joint count score of 0 to 66. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Swollen joints				
arithmetic mean (standard deviation)				
Change at Week 24 (n= 235, 311, 308)	-38.20 (± 66.127)	-51.82 (± 80.805)	-54.76 (± 39.896)	
Change at Week 48 (n= 211, 296, 299)	-39.39 (± 59.184)	-61.36 (± 44.414)	-64.22 (± 65.234)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Tender Joint Count (TJC) at Weeks 24 and 48

End point title	Percent Change From Baseline in Tender Joint Count (TJC) at Weeks 24 and 48

End point description:

68 joints were assessed for tenderness and joints were classified as tender/not tender giving a total possible tender joint count score of 0 to 68. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	243	243	
Units: Tendor joints				
arithmetic mean (standard deviation)				
Change at Week 24 (n= 235, 311, 308)	-36.97 (± 58.675)	-55.11 (± 37.962)	-51.07 (± 49.700)	
Change at Week 48 (n= 211, 296, 299)	-35.91 (± 64.358)	-61.51 (± 37.229)	-59.55 (± 48.474)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Patient's Pain Visual Analogue Scale (VAS) at Weeks 24 and 48

End point title	Percent Change From Baseline in Patient's Pain Visual Analogue Scale (VAS) at Weeks 24 and 48

End point description:

The patient assessed their pain on a 0 to 100 millimeters (mm) horizontal visual analogue scale (VAS). The left-hand extreme of the line equals 0 mm, and is described as "no pain" and the right-hand extreme equals 100 mm as "unbearable pain". A negative change indicated improvement. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Week 24 (n =230, 307, 304)	-9.10 (± 109.646)	-32.02 (± 88.637)	-27.73 (± 139.732)	

Change at Week 48 (n =206, 293, 295)	-2.28 (± 148.933)	-38.86 (± 104.267)	-32.47 (± 197.692)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Physician's Global VAS at Weeks 24 and 48

End point title	Percent Change From Baseline in Physician's Global VAS at Weeks 24 and 48

End point description:

The physician's global assessment of disease activity is assessed on a 0 to 100 millimetres (mm) horizontal visual analogue scale (VAS) by the physician. The left-hand extreme of the line equals 0 mm, and is described as "no disease activity" (symptom-free and no arthritis symptoms) and the right-hand extreme equals 100 mm as "maximum disease activity" (maximum arthritis disease activity). ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Week 24 (n= 234, 311, 307)	-40.23 (± 39.655)	-51.44 (± 34.669)	-53.02 (± 34.479)	
Change at Week 48 (n= 210, 296, 298)	-41.60 (± 43.285)	-61.29 (± 31.543)	-62.10 (± 30.866)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Patient's Global VAS at Weeks 24 and 48

End point title	Percent Change From Baseline in Patient's Global VAS at Weeks 24 and 48

End point description:

The patient's global assessment of disease activity is assessed on a 0 to 100 millimeters (mm) horizontal visual analogue scale (VAS) by the patient. The left-hand extreme of the line equals 0 mm, and is described as "no disease activity" (symptom-free and no arthritis symptoms) and the right-hand extreme equals 100 mm, as "maximum disease activity" (maximum arthritis disease activity). A

negative change from Baseline indicated improvement. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Week 24 (n= 231, 308, 303)	-20.73 (± 74.480)	-37.96 (± 83.908)	-36.99 (± 79.130)	
Change at Week 48 (n= 207, 294, 294)	-17.13 (± 100.706)	-42.02 (± 103.526)	-55.26 (± 37.873)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in C-Reactive Protein (CRP) at Weeks 24 and 48

End point title	Percent Change From Baseline in C-Reactive Protein (CRP) at Weeks 24 and 48

End point description:

The serum concentration of C-Reactive Protein (CRP) is measured in milligrams per deciliter (mg/dL). A reduction in the level is considered an improvement. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Milligrams per deciliter (mg/dL)				
arithmetic mean (standard deviation)				
Change at Week 24 (n= 235, 311, 308)	11.64 (± 116.697)	-30.41 (± 109.193)	-23.07 (± 109.193)	
Change at Week 48 (n= 211, 296, 299)	22.01 (± 190.346)	-40.89 (± 90.139)	15.14 (± 820.007)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) at Weeks 24 and 48

End point title	Percent Change From Baseline in the Health Assessment Questionnaire Disability Index (HAQ-DI) at Weeks 24 and 48

End point description:

HAQ-DI is a self-completed patient questionnaire specific for Rheumatoid Arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component 0=without any difficulty 1=with some difficulty 2=with much difficulty 3=unable to do. Calculate HAQ-DI the patient must have a domain score for at least 6 of 8 domains. The HAQ-DI is the sum of the scores, divided by the number of domains that have a score (in range 6-8) for a total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from baseline indicated improvement. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Week 24 (n= 231, 301, 305)	-20.11 (± 48.921)	-30.12 (± 86.217)	-40.83 (± 38.243)	
Change at Week 48 (n= 207, 286, 296)	-22.67 (± 57.893)	-35.47 (± 78.670)	-45.63 (± 39.241)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in the Erythrocyte Sedimentation Rate (ESR) at Weeks 24 and 48

End point title	Percent Change From Baseline in the Erythrocyte Sedimentation Rate (ESR) at Weeks 24 and 48

End point description:

The Erythrocyte Sedimentation Rate (ESR) was measured in millimeters per hour (mm/hr). A reduction in the level is considered an improvement. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Millimeters per hour (mm/hr)				
arithmetic mean (standard deviation)				
Change at Week 24 (n= 234, 311, 308)	-2.51 (± 66.453)	-20.10 (± 90.059)	-29.98 (± 57.195)	
Change at Week 48 (n= 211, 296, 299)	-2.72 (± 90.088)	-27.24 (± 147.973)	-41.19 (± 55.485)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Modified Total Sharp Score (mTSS) at Weeks 24 and 48

End point title	Change From Baseline in the Modified Total Sharp Score (mTSS) at Weeks 24 and 48

End point description:

mTSS: measure of joint damage that combines scores for bone erosion and joint space narrowing (JNS). Erosion score: total of 14 locations in each hand and wrist and 6 joints in the foot were evaluated for erosion using an 8-point scale where 0=normal to 3.5=very severe erosion. JNS score: total of 13 locations in each hand and wrist and 6 joints in the foot were evaluated for joint narrowing score using a 9-point scale where 0=normal to 4.0=definite ankylosis (stiffness or fixation of a joint). mTSS scores ranged from 0 (normal) to 292 (worst possible total score). Change= mTSS score at Week 24 minus score at baseline. An increase in mTSS from baseline represents disease progression and/or joint worsening, no change represents halting of disease progression, and a decrease represents improvement. mITT population. Number of subjects analysed signifies subjects who were evaluated for the endpoint. 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	305	322	329	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 305, 322, 329)	33.58 (± 51.106)	31.45 (± 51.323)	31.99 (± 49.602)	
Change at Week 24 (n= 268, 308, 313)	1.04 (± 2.842)	0.34 (± 2.424)	-0.03 (± 2.534)	
Change at Week 48 (n= 268, 308, 313)	1.74 (± 5.293)	0.26 (± 2.791)	-0.03 (± 2.911)	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024
Method	Van Elteren's test

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Van Elteren's test

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Van Elteren's test

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX

Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Van Elteren's test

Secondary: Change From Baseline in Modified Erosion Score at Weeks 24 and 48

End point title	Change From Baseline in Modified Erosion Score at Weeks 24 and 48

End point description:

Erosion score was defined as a total of 14 locations in each hand and wrist and 6 joints in the foot using an 8-point scale where 0=normal to 3.5=very severe erosion. mITT population included all subjects who were in the ITT analysis set and had both baseline radiograph and at least one post-baseline radiograph for campaign 1. Here, the number of subjects analysed signifies subjects who were evaluated for the endpoint. 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	305	322	329	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 305, 322, 329)	17.10 (± 27.256)	16.22 (± 27.875)	16.24 (± 26.103)	
Change at Week 24 (n= 268, 308, 313)	0.61 (± 1.778)	0.18 (± 1.487)	0.04 (± 1.511)	
Change at week 48 (n= 268, 308, 313)	1.06 (± 3.238)	0.08 (± 1.690)	-0.08 (± 1.588)	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	Van Elteren’s test

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX

Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Van Elteren’s test

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Van Elteren’s test

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Van Elteren’s test

Secondary: Change From Baseline in Modified Joint Space Narrowing Score at Weeks 24 and 48

End point title	Change From Baseline in Modified Joint Space Narrowing Score at Weeks 24 and 48

End point description:

Joint Space Narrowing score was defined as a total of 13 locations in each hand and wrist and 6 joints in the foot using a 9-point scale where 0=normal to 4.0=definite ankylosis (stiffness or fixation of a joint). mITT population included all subjects who were in the ITT analysis set and had both baseline radiograph and at least one post-baseline radiograph for campaign 1. Here, the number of subjects analysed signifies subjects who were evaluated for the endpoint. 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	305	322	329	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 305, 322, 329)	16.47 (± 25.990)	15.22 (± 25.012)	15.75 (± 25.118)	
Change at Week 24 (n= 268, 308, 313)	0.43 (± 1.654)	0.16 (± 1.655)	-0.07 (± 1.504)	
Change at Week 48 (n= 268, 308, 313)	0.68 (± 2.777)	0.18 (± 1.471)	0.05 (± 1.859)	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0923
Method	Van Elteren’s test

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Van Elteren’s test

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1171
Method	Van Elteren’s test

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX

Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Van Elteren’s test

Secondary: Percentage of Subjects Without Radiographic Progression Defined as Change in mTSS ≤ 0 at Weeks 24 and 48

End point title	Percentage of Subjects Without Radiographic Progression Defined as Change in mTSS ≤ 0 at Weeks 24 and 48

End point description:

Radiographic progression was defined as a change from baseline in the modified total sharp scale greater than zero. The modified Intent-to-Treat (mITT) population included all subjects who were in the ITT analysis set and had both baseline radiograph and at least one post-baseline radiograph for campaign 1. Here, the number of subjects analysed signifies subjects who were evaluated for the endpoint. 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Weeks 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	305	322	329	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Week 24 (n= 305, 322, 329)	47.5 (41.9 to 53.1)	58.7 (53.3 to 64.1)	65.3 (60.2 to 70.5)	
Week 48 (n= 305, 322, 329)	37.7 (32.3 to 43.1)	58.7 (53.3 to 64.1)	60.8 (55.5 to 66.1)	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0036
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	11.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.8
upper limit	19.2

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	18.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.6
upper limit	25.8

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	21.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.7
upper limit	28.9

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX

Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	23.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.1
upper limit	31.2

Secondary: Percentage of Subjects With a Reduction in Modified Total Sharp Score (mTSS) From Baseline at Week 48

End point title	Percentage of Subjects With a Reduction in Modified Total Sharp Score (mTSS) From Baseline at Week 48

End point description:

mTSS: measure of joint damage that combines scores for bone erosion and joint space narrowing (JNS). Erosion score: total of 14 locations in each hand and wrist and 6 joints in the foot were evaluated for erosion using an 8-point scale where 0=normal to 3.5=very severe erosion. JNS score: total of 13 locations in each hand and wrist and 6 joints in the foot were evaluated for joint narrowing score using a 9-point scale where 0=normal to 4.0=definite ankylosis (stiffness or fixation of a joint). mTSS scores ranged from 0 (normal) to 292 (worst possible total score). Change= mTSS score at Week 24 minus score at baseline. An increase in mTSS from baseline represents disease progression and/or joint worsening, no change represents halting of disease progression, and a decrease represents improvement. mITT population. Number of subjects analysed signifies subjects who were evaluated for the endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	305	322	329	
Units: Percentage of Subjects				
number (confidence interval 95%)	11.8 (8.2 to 15.4)	22.7 (18.1 to 27.2)	29.8 (24.8 to 34.7)	

Statistical analyses

Statistical analysis title	Ocrelizumab 500 mg vs Placebo
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX

Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	18.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.1
upper limit	24.4

Statistical analysis title	Ocrelizumab 200 mg vs Placebo
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	10.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	16.8

Secondary: Percentage of Subjects With a Reduction of Greater Than or Equal to 0.25 Units in the HAQ-DI Score at Weeks 24 and 48

End point title	Percentage of Subjects With a Reduction of Greater Than or Equal to 0.25 Units in the HAQ-DI Score at Weeks 24 and 48

End point description:

HAQ-DI is a self-completed patient questionnaire specific for Rheumatoid Arthritis. It consists of 20 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip; common daily activities. Each domain has at least 2 component questions. There are 4 possible responses for each component 0=without any difficulty 1=with some difficulty 2=with much difficulty 3=unable to do. Calculate HAQ-DI the patient must have a domain score for at least 6 of 8 domains. The HAQ-DI is the sum of the scores, divided by the number of domains that have a score (in range 6-8) for a total possible score minimum/maximum 0 (best) to 3 (worst). A negative change from baseline indicated improvement. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint. 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Week 24 (n= 319, 343, 343)	42.3 (36.9 to 47.7)	59.8 (54.6 to 65.0)	66.5 (61.5 to 71.5)	
Week 48 (n= 319, 343, 343)	34.8 (29.6 to 40.0)	58.9 (53.7 to 64.1)	65.9 (60.9 to 70.9)	

Statistical analyses

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	17.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	10
upper limit	24.9

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	23.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.4
upper limit	31.1

Statistical analysis title	Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	24.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.9
upper limit	31.4

Statistical analysis title	Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted Difference
Point estimate	30.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.7
upper limit	38.1

Secondary: Change From Baseline in Short Form Health Survey (SF-36) Subscale and Summary Scores at Weeks 24 and 48

End point title	Change From Baseline in Short Form Health Survey (SF-36) Subscale and Summary Scores at Weeks 24 and 48

End point description:

The SF-36 is a questionnaire used to assess physical functioning and is made up of eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. Transforming and standardizing these domains leads to the calculation of the Physical and Mental Component Summary measures. Scores ranging from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint. 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:
Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline:MCS (n= 312, 334, 334)	40.54 (± 12.282)	39.99 (± 11.863)	40.48 (± 12.822)	
Change at Week 24:MCS (n= 229, 303, 302)	4.38 (± 10.886)	6.11 (± 10.082)	5.80 (± 11.224)	
Change at Week 48:MCS (n= 206, 290, 292)	4.15 (± 10.326)	6.36 (± 10.212)	6.43 (± 11.795)	
Baseline:PCS (n= 312, 334, 334)	31.86 (± 7.387)	32.24 (± 7.401)	31.58 (± 8.039)	
Change at Week 24:PCS (n= 229, 303, 302)	5.29 (± 8.421)	6.73 (± 8.385)	7.71 (± 7.328)	
Change at Week 48:PCS (n= 206, 290, 292)	5.28 (± 8.373)	8.38 (± 8.347)	9.15 (± 8.389)	

Statistical analyses

Statistical analysis title	MCS: Ocrelizumab 200 mg vs Placebo Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1103
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	2.8

Statistical analysis title	MCS: Ocrelizumab 500 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX

Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2011
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	2.5

Statistical analysis title	MCS: Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0186
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	3.6

Statistical analysis title	MCS: Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0127
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	3.7

Statistical analysis title	PCS: Ocrelizumab 200 mg vs Placebo at Week 24

Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0232
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2.8

Statistical analysis title	PCS: Ocrelizumab 500 mg vs Placebo at Week 24
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	3.6

Statistical analysis title	PCS: Ocrelizumab 200 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 200 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	4.5

Statistical analysis title	PCS: Ocrelizumab 500 mg vs Placebo at Week 48
Comparison groups	Placebo × 2 IV + MTX v Ocrelizumab 500 mg × 2 IV + MTX
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	5

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) Fatigue Assessment at Weeks 24 and 48

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) Fatigue Assessment at Weeks 24 and 48

End point description:

The FACIT-Fatigue score was calculated according to a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. Participants scored each item on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the participant's response to the questions (with the exception of 2 negatively stated), the greater the participant's fatigue. For all questions, except for the 2 negatively stated ones, the code was reversed and a new score was calculated as (4 minus the participant's response). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worst score) to 52 (best score). ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint. 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 317, 340, 340)	27.25 (± 10.821)	26.87 (± 10.920)	26.57 (± 11.194)	
Change at Week 24 (n= 235, 309, 308)	5.14 (± 9.864)	7.18 (± 9.755)	7.07 (± 10.269)	
Change at Week 48 (n= 211, 296, 298)	5.39 (± 10.054)	8.01 (± 10.132)	8.41 (± 10.682)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pain Quality and Impact of Pain on Daily Function Measured by the Brief Pain Inventory (BPI) Short Form at Weeks 24 and 48

End point title	Change From Baseline in Pain Quality and Impact of Pain on Daily Function Measured by the Brief Pain Inventory (BPI) Short Form at Weeks 24 and 48

End point description:

The modified BPI (short-form) is a short questionnaire to assess the severity of pain and the impact of pain on daily functions. The first two questions relate to average and current pain respectively and are assessed on a scale from 0 to 10, where 0 represents no pain, and 10 represents pain as bad as one can imagine. The degree to which pain has interfered with 7 different aspects is also rated on a scale from 0 to 10, where 0 represents that pain does not interfere and 10 that pain completely interferes. ITT population included all randomised subjects who had received any part of an infusion of study medication. Here, the number of subjects analysed signifies subjects evaluated for this endpoint. 'n' signifies the number of subjects evaluated at a specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 24, 48

End point values	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	320	343	343	
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Baseline: average pain (n=316,340,335)	6.39 (± 2.011)	6.28 (± 2.077)	6.42 (± 2.194)	
Baseline: pain right now (n=317,340,337)	5.57 (± 2.398)	5.75 (± 2.495)	5.82 (± 2.533)	
Change at Week 24: average pain (n=234,304,298)	-1.82 (± 2.441)	-2.45 (± 2.299)	-2.48 (± 2.424)	
Change at Week 24: pain right now (n=235,303,299)	-1.57 (± 2.775)	-2.32 (± 2.659)	-2.24 (± 2.671)	
Change at Week 48: average pain (n=188,273,280)	-1.78 (± 2.619)	-2.92 (± 2.442)	-3.06 (± 2.422)	
Change at Week 48: pain right now (n=188,272,282)	-1.53 (± 2.795)	-2.66 (± 2.676)	-2.92 (± 2.681)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 8.5 years	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Placebo × 2 IV + MTX
Reporting group description:	
Subjects received two intravenous (IV) infusion matching placebo to ocrelizumab on Day 1 and Day 15. A repeat course was administered at Weeks 24 and 26. Methotrexate 7.5-25 milligram (mg) was administered weekly.	
Reporting group title	Ocrelizumab 200 mg × 2 IV + MTX
Reporting group description:	
Subjects received two IV infusion of ocrelizumab 200 mg on Day 1 and Day 15. A repeat course was administered at Weeks 24 and 26. Methotrexate 7.5-25 mg was administered weekly.	
Reporting group title	Ocrelizumab 500 mg × 2 IV + MTX
Reporting group description:	
Subjects received two IV infusion of ocrelizumab 500 mg on Day 1 and Day 15. A repeat course was administered at Weeks 24 and 26. Methotrexate 7.5-25 mg was administered weekly.	

Serious adverse events	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX
Total subjects affected by serious adverse events			
subjects affected / exposed	73 / 318 (22.96%)	61 / 343 (17.78%)	78 / 345 (22.61%)
number of deaths (all causes)	5	2	8
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 318 (0.31%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Basal cell carcinoma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	3 / 345 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 318 (0.31%)	1 / 343 (0.29%)	0 / 345 (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
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Bronchial carcinoma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma stage 0			

subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Gastric cancer			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammatory carcinoma of the breast			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Malignant melanoma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic renal cell carcinoma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myxoid liposarcoma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer metastatic			

subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian epithelial cancer			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Renal cell carcinoma			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
T-cell lymphoma			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Thyroid neoplasm			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	2 / 318 (0.63%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Aortic dissection			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Hypertension			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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 vasculitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitis necrotising			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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 missed			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion spontaneous			

subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical dysplasia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Endometrial hyperplasia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Endometriosis			

subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst ruptured			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Uterine polyp			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 318 (0.63%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	2 / 345 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 318 (0.00%)	2 / 343 (0.58%)	0 / 345 (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
Alveolitis			

subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Bronchiectasis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Interstitial lung disease			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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 oedema			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinus disorder			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	2 / 345 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug dependence			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomania			

subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Mental status changes			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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			
Haemoglobin abnormal			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 318 (0.00%)	3 / 343 (0.87%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 318 (0.00%)	2 / 343 (0.58%)	2 / 345 (0.58%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	2 / 345 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	2 / 318 (0.63%)	1 / 343 (0.29%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 318 (0.31%)	1 / 343 (0.29%)	0 / 345 (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

Multiple fractures			
subjects affected / exposed	0 / 318 (0.00%)	2 / 343 (0.58%)	0 / 345 (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
Multiple injuries			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	2 / 345 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 318 (0.31%)	1 / 343 (0.29%)	0 / 345 (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
Accidental overdose			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Ankle fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Carbon monoxide poisoning			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Clavicle fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Comminuted fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Fall			

subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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 neck fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Joint dislocation			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Laceration			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Lower limb fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Overdose			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Tendon rupture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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			
Myocardial infarction			

subjects affected / exposed	3 / 318 (0.94%)	1 / 343 (0.29%)	2 / 345 (0.58%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 318 (0.63%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Coronary artery disease			
subjects affected / exposed	2 / 318 (0.63%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	2 / 318 (0.63%)	0 / 343 (0.00%)	0 / 345 (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
Pericarditis			
subjects affected / exposed	2 / 318 (0.63%)	0 / 343 (0.00%)	0 / 345 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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 fibrillation			

subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Atrial flutter			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Diastolic dysfunction			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Palpitations			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 318 (0.00%)	2 / 343 (0.58%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 318 (0.00%)	2 / 343 (0.58%)	0 / 345 (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
Brain oedema			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral ischaemia			

subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Convulsion			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Grand mal convulsion			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Headache			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Ischaemic stroke			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Lacunar infarction			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Nerve compression			

subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Anaemia of chronic disease			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Febrile neutropenia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Neutropenia			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Inner ear disorder			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Otosalpingitis			

subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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	1 / 318 (0.31%)	0 / 343 (0.00%)	2 / 345 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 318 (0.31%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 318 (0.31%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Diverticular perforation			

subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Pancreatitis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Vomiting			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	2 / 318 (0.63%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	0 / 318 (0.00%)	2 / 343 (0.58%)	0 / 345 (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
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	2 / 318 (0.63%)	3 / 343 (0.87%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	2 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus ureteric			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Hydronephrosis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Nephrolithiasis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stag horn calculus			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Urogenital fistula			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Endocrine disorders			

Basedow's disease			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	4 / 318 (1.26%)	1 / 343 (0.29%)	2 / 345 (0.58%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 318 (0.31%)	1 / 343 (0.29%)	0 / 345 (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
Foot deformity			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Osteochondrosis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Osteonecrosis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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	3 / 318 (0.94%)	4 / 343 (1.17%)	10 / 345 (2.90%)
occurrences causally related to treatment / all	4 / 4	3 / 4	6 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 3
Urinary tract infection			
subjects affected / exposed	4 / 318 (1.26%)	1 / 343 (0.29%)	3 / 345 (0.87%)
occurrences causally related to treatment / all	0 / 4	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	3 / 318 (0.94%)	1 / 343 (0.29%)	3 / 345 (0.87%)
occurrences causally related to treatment / all	1 / 3	1 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	4 / 318 (1.26%)	1 / 343 (0.29%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	3 / 318 (0.94%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	2 / 318 (0.63%)	1 / 343 (0.29%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	2 / 318 (0.63%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			

subjects affected / exposed	1 / 318 (0.31%)	1 / 343 (0.29%)	0 / 345 (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
Abscess soft tissue			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Acute hepatitis B			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Acute sinusitis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Borrelia infection			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Bronchopneumonia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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 gangrenous			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Clostridium difficile colitis			

subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Dengue fever			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Extradural abscess			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Fungal oesophagitis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 318 (0.31%)	2 / 343 (0.58%)	3 / 345 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Histoplasmosis			

subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Mycobacterium kansasii infection			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Osteomyelitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Paronychia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Pharyngitis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Pneumonia viral			

subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Purulent synovitis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Soft tissue infection			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			

subjects affected / exposed	0 / 318 (0.00%)	1 / 343 (0.29%)	0 / 345 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 318 (0.00%)	0 / 343 (0.00%)	1 / 345 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Electrolyte imbalance			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 318 (0.31%)	0 / 343 (0.00%)	0 / 345 (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

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

Non-serious adverse events	Placebo × 2 IV + MTX	Ocrelizumab 200 mg × 2 IV + MTX	Ocrelizumab 500 mg × 2 IV + MTX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	228 / 318 (71.70%)	272 / 343 (79.30%)	273 / 345 (79.13%)
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	62 / 318 (19.50%)	89 / 343 (25.95%)	96 / 345 (27.83%)
occurrences (all)	136	164	168
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 318 (8.18%)	42 / 343 (12.24%)	37 / 345 (10.72%)
occurrences (all)	28	43	45

Nervous system disorders			
Headache			
subjects affected / exposed	24 / 318 (7.55%)	29 / 343 (8.45%)	32 / 345 (9.28%)
occurrences (all)	29	33	38
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 318 (5.35%)	13 / 343 (3.79%)	13 / 345 (3.77%)
occurrences (all)	19	14	15
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	17 / 318 (5.35%)	16 / 343 (4.66%)	14 / 345 (4.06%)
occurrences (all)	21	18	15
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	23 / 318 (7.23%)	21 / 343 (6.12%)	23 / 345 (6.67%)
occurrences (all)	28	22	29
Dyspepsia			
subjects affected / exposed	14 / 318 (4.40%)	17 / 343 (4.96%)	22 / 345 (6.38%)
occurrences (all)	15	18	24
Gastritis			
subjects affected / exposed	8 / 318 (2.52%)	14 / 343 (4.08%)	18 / 345 (5.22%)
occurrences (all)	9	16	18
Nausea			
subjects affected / exposed	17 / 318 (5.35%)	15 / 343 (4.37%)	22 / 345 (6.38%)
occurrences (all)	21	17	26
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 318 (2.52%)	13 / 343 (3.79%)	20 / 345 (5.80%)
occurrences (all)	8	15	23
Psychiatric disorders			
Depression			
subjects affected / exposed	19 / 318 (5.97%)	18 / 343 (5.25%)	21 / 345 (6.09%)
occurrences (all)	19	20	23
Insomnia			
subjects affected / exposed	19 / 318 (5.97%)	19 / 343 (5.54%)	15 / 345 (4.35%)
occurrences (all)	19	19	16
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	16 / 318 (5.03%)	19 / 343 (5.54%)	26 / 345 (7.54%)
occurrences (all)	17	20	27
Infections and infestations			
Bronchitis			
subjects affected / exposed	39 / 318 (12.26%)	43 / 343 (12.54%)	40 / 345 (11.59%)
occurrences (all)	57	59	47
Gastroenteritis			
subjects affected / exposed	16 / 318 (5.03%)	11 / 343 (3.21%)	15 / 345 (4.35%)
occurrences (all)	22	12	20
Herpes zoster			
subjects affected / exposed	16 / 318 (5.03%)	14 / 343 (4.08%)	12 / 345 (3.48%)
occurrences (all)	17	16	13
Influenza			
subjects affected / exposed	20 / 318 (6.29%)	31 / 343 (9.04%)	29 / 345 (8.41%)
occurrences (all)	26	37	35
Nasopharyngitis			
subjects affected / exposed	45 / 318 (14.15%)	43 / 343 (12.54%)	51 / 345 (14.78%)
occurrences (all)	60	56	77
Pharyngitis			
subjects affected / exposed	18 / 318 (5.66%)	9 / 343 (2.62%)	9 / 345 (2.61%)
occurrences (all)	22	14	13
Sinusitis			
subjects affected / exposed	18 / 318 (5.66%)	33 / 343 (9.62%)	28 / 345 (8.12%)
occurrences (all)	27	48	35
Upper respiratory tract infection			
subjects affected / exposed	64 / 318 (20.13%)	79 / 343 (23.03%)	85 / 345 (24.64%)
occurrences (all)	130	130	157
Urinary tract infection			
subjects affected / exposed	40 / 318 (12.58%)	38 / 343 (11.08%)	48 / 345 (13.91%)
occurrences (all)	67	49	69

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2006	1. Provided more information on the definition and incidence of infusion-related reactions (IRRs) as applied to previous studies with ocrelizumab (2004-002132-26 and NCT00077870) 2. Included a statement mandating the signing of informed consent forms by subjects prior to the performance of any screening procedures 3. Defined the period during which subjects who withdrew from the study should continue in safety follow-up and clarified the end of study for individual subjects 4. Included some additional text cautioning the investigator to review safety criteria, which were also added to the text, prior to the administration of subsequent infusions 5. Clarified that randomisation could occur within 24 hours or exceptionally within 72 hours prior to administration of blinded study infusion 6. In the schedule of assessments added an assessment of rheumatoid manifestations; included new safety assessment for Hepatitis B viral DNA and separated inflammatory related biomarkers and Apolipoprotein A1 and B at baseline and every 24 weeks from the blood biochemistry assessments to reduce their collection time points 7. In the schedule of assessments added an assessment of rheumatoid manifestations; included new safety assessment for Hepatitis B viral DNA and separated inflammatory related biomarkers and Apolipoprotein A1 and B at baseline and every 24 weeks from the blood biochemistry assessments to reduce their collection time points 8. Recommended that IV infusion bags containing diluted ocrelizumab solutions be used within 48 hours of preparation for stability reasons 9. Provided guidance on the administration of rescue medication during the study 10. Included detailed information on the Hepatitis B screening process for inclusion into the study including information on viral DNA monitoring and separated the screening process from that for Hepatitis C
28 August 2008	1. Reduced the number of samples collected during the double-blind and study extension periods and amended the scheduled of assessments and procedures accordingly 2. Clarified the basis for the administration of Day 15 infusions for patients who develop infections between Day 1 and Day 15 of a course of study treatment 3. Clarified the circumstances under which pregnant patients and subjects who develop skin malignancy during the study could be given study treatment
12 July 2010	Terminates treatment and mandates transitioning of all subjects to safety follow up
06 September 2012	Terminates the Safety Follow up for all subjects

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/21905001

http://www.ncbi.nlm.nih.gov/pubmed/24498318