Clinical trial results:
A Phase III, multicenter, randomized, parallel-group, double blinded, placebo controlled study to evaluate the efficacy and safety of ocrelizumab in adults with Primary Progressive Multiple Sclerosis

Summary

EudraCT number	2010-020338-25
Trial protocol	LT ES BE FR HU NL CZ GB DE PT AT FI IT GR BG DK PL
Global end of trial date	

Results information

Result version number	v2
This version publication date	07 May 2017
First version publication date	08 July 2016
Version creation reason	• Correction of full data set revisions

Trial information

Trial identification

Sponsor protocol code	WA25046

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01194570
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	Interim
Date of interim/final analysis	24 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2015
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of ocrelizumab compared with placebo in subjects with primary progressive multiple sclerosis (PPMS).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	11 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 58
Country: Number of subjects enrolled	Portugal: 18
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Spain: 74
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Czech Republic: 20
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	France: 106
Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Brazil: 11
Country: Number of subjects enrolled	Canada: 32

Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Peru: 5
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Ukraine: 74
Country: Number of subjects enrolled	United States: 101
Worldwide total number of subjects	732
EEA total number of subjects	465

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)	732
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 943 subjects were screened and 732 were randomized into the study, of which 725 received at least one dose of placebo or ocrelizumab. A total of 549 subjects were ongoing with double-blind treatment at the clinical cut-off date (CCOD).

Period 1

Period 1 title	Double-Blind Treatment Period (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

Arm description:

Subjects with primary progressive multiple sclerosis (PPMS) received placebo matched to ocrelizumab at a schedule interval of 24 weeks up to at least 120 weeks.

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:

Subjects received placebo infusions matching ocrelizumab infusions of 300 milligram (mg) separated by 14 days, at a schedule interval of 24 weeks.

Arm title	Ocrelizumab 600 mg

Arm description:

Subjects with PPMS received ocrelizumab as two IV infusions of 300 mg separated by 14 days at a scheduled interval of every 24 weeks up to at least 120 weeks.

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:

Subjects received ocrelizumab 600 mg intraveous (IV) as 300 mg infusions separated by 14 days, at a scheduled interval of every 24 weeks.

Number of subjects in period 1	Placebo	Ocrelizumab 600 mg
Started	244	488
Completed	0	0
Not completed	244	488
Physician decision	2	6
Protocol violation	-	2
Death	1	3
Other	13	20
Pregnancy	1	1
Adverse event	12	18
Non-compliance	2	2
Non-compliance with study drug	2	2
Ongoing at CCOD	162	387
Lost to follow-up	1	4
Lack of efficacy	27	21
Withdrawal by subject	21	22

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects with primary progressive multiple sclerosis (PPMS) received placebo matched to ocrelizumab at a schedule interval of 24 weeks up to at least 120 weeks.	
Reporting group title	Ocrelizumab 600 mg
Reporting group description:	
Subjects with PPMS received ocrelizumab as two IV infusions of 300 mg separated by 14 days at a scheduled interval of every 24 weeks up to at least 120 weeks.	

Reporting group values	Placebo	Ocrelizumab 600 mg	Total
Number of subjects	244	488	732
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	44.4	44.7	
standard deviation	± 8.3	± 7.9	-
Gender categorical Units: Subjects			
Female	124	237	361
Male	120	251	371

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects with primary progressive multiple sclerosis (PPMS) received placebo matched to ocrelizumab at a schedule interval of 24 weeks up to at least 120 weeks.

Reporting group title	Ocrelizumab 600 mg

Reporting group description:

Subjects with PPMS received ocrelizumab as two IV infusions of 300 mg separated by 14 days at a scheduled interval of every 24 weeks up to at least 120 weeks.

Primary: Time to Onset of Clinical Disability Progression (CDP) Sustained for at Least 12 Weeks During the Double-Blind Treatment Period

End point title	Time to Onset of Clinical Disability Progression (CDP) Sustained for at Least 12 Weeks During the Double-Blind Treatment Period

End point description:

The time to onset of CDP was defined as the time from baseline to the first disability progression, which is confirmed at the next regularly scheduled visit >=12 weeks (>=84 days) after the initial disability progression. Baseline for the time to onset of CDP is the date of randomization, independent of the first day of dosing. Disability progression is defined as an increase of >= 1.0 point from baseline EDSS score, if the baseline EDSS value is <=5.5 points (inclusive), or an increase of >=0.5 points, if the baseline EDSS is >5.5 points. ITT population included all randomised subjects in the study. Here, 99999 indicates median, -99999 minimum and 99999 maximum of full range as value observed were censored.

End point type	Primary

End point timeframe:

Up to clinical cut-off date (CCOD) 24 July 2015 (up to 216 week)

End point values	Placebo	Ocrelizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	487[1]		
Units: weeks				
median (full range (min-max))	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Notes:

[1] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

Statistical analyses

Statistical analysis title	Time to onset of CDP sustained for 12 weeks

Statistical analysis description:

Hazard ratios were estimated by stratified Cox regression. Stratified by geographical region (United States [US] vs. rest of the world [ROW]) and age (<= 45, >45 years).

Comparison groups	Placebo v Ocrelizumab 600 mg

Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0321
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.98

Secondary: Time to Onset of Clinical Disability Progression (CDP) Sustained for at Least 24 Weeks During the Double-Blind Treatment Period

End point title	Time to Onset of Clinical Disability Progression (CDP) Sustained for at Least 24 Weeks During the Double-Blind Treatment Period

End point description:

The time to onset of CDP was defined as the time from baseline to the first disability progression, which is confirmed at the next regularly scheduled visit >=24 weeks (>=161 days) after the initial disability progression. Baseline for the time to onset of CDP is the date of randomisation, independent of the first day of dosing. Disability progression is defined as an increase of >= 1.0 point from baseline EDSS score, if the baseline EDSS value is <=5.5 points (inclusive), or an increase of >=0.5 points, if the baseline EDSS is >5.5 points. ITT population included all randomised subjects in the study. Here, 99999 indicates median, -99999 minimum and 99999 maximum of full range as value observed were censored.

End point type	Secondary

End point timeframe:

Up to clinical CCOD 24 July 2015 (up to 216 weeks)

End point values	Placebo	Ocrelizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	487[2]		
Units: weeks				
median (full range (min-max))	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Notes:

[2] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

Statistical analyses

Statistical analysis title	Time to onset of CDP sustained for 24 weeks

Statistical analysis description:

Hazard ratios were estimated by stratified Cox regression. Stratified by geographical region (US vs. ROW) and age (<= 45, >45 years).

Comparison groups	Placebo v Ocrelizumab 600 mg

Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0365
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.98

Secondary: Percent Change From Baseline in Timed 25-Foot Walk (T25-FW) at Week 120

End point title	Percent Change From Baseline in Timed 25-Foot Walk (T25-FW) at Week 120

End point description:

ITT population included all randomised subjects in the study. Here, n signifies the number of subjects evaluable for the specified category. Here, least square mean is indicating adjusted geometric mean.

End point type	Secondary

End point timeframe:

Baseline, Week 120

End point values	Placebo	Ocrelizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239[3]	473[4]		
Units: percent change				
least squares mean (confidence interval 95%)				
Change from Baseline at Week 120 (n= 174, 397)	55.097 (39.855 to 71.999)	38.933 (29.222 to 49.374)		

Notes:

[3] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

[4] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

Statistical analyses

Statistical analysis title	T25-FW change from baseline at Week 120

Statistical analysis description:

Estimates (back-transformed) based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix: log(Post-baseline(BL)/BL) = log(BL 25-FTW) + Geographical Region (US vs. ROW) + Age (<=45, > 45 years) + Week + Treatment + Treatment*Week (repeated values over Week) + log (BL 25-FTW)*Week. Relative reduction was calculated as -Relative change = -(OCR response-Placebo response)/Placebo response*100%. The 95% CI for relative reduction was obtained using the Bootstrap method.

Comparison groups	Placebo v Ocrelizumab 600 mg

Number of subjects included in analysis	712
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0404 [5]
Method	Ranked ANCOVA
Parameter estimate	Relative Reduction (%)
Point estimate	29.337
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.618
upper limit	51.456

Notes:

[5] - P-value from a ranked ANCOVA on Percent Change from BL adjusting for rank of BL 25-Foot Timed Walk (25-FTW), Geographical Region (US vs ROW) and Age (<=45, > 45 years); missing observations imputed with LOCF.

Secondary: Percent Change From Baseline in Total Volume of T2 Lesions at Week 120

End point title	Percent Change From Baseline in Total Volume of T2 Lesions at Week 120

End point description:

ITT population included all randomised subjects in the study. Here, n signifies the number of subjects evaluable for the specified category. Here, least square mean is indicating adjusted geometric mean.

End point type	Secondary

End point timeframe:

From Baseline to Week 120

End point values	Placebo	Ocrelizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234[6]	464[7]		
Units: percent change				
least squares mean (confidence interval 95%)				
% Change from Baseline to Week 120 (n=183, 400)	7.426 (4.967 to 9.942)	-3.366 (-4.987 to -1.718)		

Notes:

[6] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

[7] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

Statistical analyses

Statistical analysis title	Total Volume of T2 Lesions change at Week 120

Statistical analysis description:

Estimates (back-transformed) are based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix: log(Post-BL/BL) = log(BL T2 lesion volume) + Geographical Region (US vs. ROW) + Age (<=45, > 45 years) + Week + Treatment + Treatment*Week (repeated values over Week) + log (BL T2 lesion volume)*Week.

Comparison groups	Ocrelizumab 600 mg v Placebo

Number of subjects included in analysis	698
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Ranked ANCOVA
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.876
upper limit	0.924

Notes:

[8] - P-value is from ranked ANCOVA on Percent Change from BL adjusting for rank of BL T2 lesion volume, Geographical Region (US vs ROW) and Age (<=45, > 45 years); missing observations imputed with LOCF.

Secondary: Percent Change in Total Brain Volume From Week 24 to Week 120

End point title	Percent Change in Total Brain Volume From Week 24 to Week 120

End point description:

ITT population included all randomised subjects in the study. Here, least square mean is indicating adjusted mean.

End point type	Secondary

End point timeframe:

From Week 24 to Week 120

End point values	Placebo	Ocrelizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[9]	407[10]		
Units: percent change				
least squares mean (confidence interval 95%)	-1.093 (-1.236 to -0.951)	-0.902 (-1.004 to -0.799)		

Notes:

[9] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

[10] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

Statistical analyses

Statistical analysis title	Percent change in total brain volume

Statistical analysis description:

Estimates are from analysis based on MMRM using unstructured covariance matrix: Percentage Change = Brain Volume at Week 24 + Geographical Region (US vs. ROW) + Age (<=45, > 45 years) + Week + Treatment + Treatment*Week (repeated values over Week) + Brain Volume at Week 24*Week. Relative reduction was calculated as – Relative change = - (OCR response-Placebo response)/Placebo response*100%. The 95% CI for relative reduction was obtained using Bootstrap method.

Comparison groups	Placebo v Ocrelizumab 600 mg

Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0206
Method	MMRM
Parameter estimate	Relative Reduction (%)
Point estimate	17.475
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.206
upper limit	29.251

Secondary: Change in From Baseline Physical Component Summary Score (PCS) SF-36 Health Survey (SF-36) at Week 120

End point title	Change in From Baseline Physical Component Summary Score (PCS) SF-36 Health Survey (SF-36) at Week 120

End point description:

The SF-36v2 is a 36-item, self- reported, generic measure of quality of life that has been widely used in multiple disease areas. It is composed of 8 health domains: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), and Mental Health (ME). In brief, scoring for each health domain scale involves (a) recoding item response values, (b) summing recoded response values for all items in a given scale to obtain the scale raw score, (c) transforming scale raw score to a 0−100 score. The PCS score was derived based on the SF-36 V2 User's Manual. It is computed by (a) multiplying each health domain z score by a scale-specific physical factor score coefficient, (b) summing the resulting products, (c) converting the product total to T score. ITT population. Here, n= number of subjects evaluable for the specified category. Here, least square mean is indicating adjusted mean.

End point type	Secondary

End point timeframe:

From Baseline to Week 120

End point values	Placebo	Ocrelizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128[11]	292[12]		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Change at Week 120 (n= 128, 292)	-1.108 (-2.394 to 0.177)	-0.731 (-1.655 to 0.193)		

Notes:

[11] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

[12] - Number of subjects analysed is the total subjects who were evaluable for this endpoint.

Statistical analyses

Statistical analysis title	SF-36 PCS change from baseline at Week 120

Statistical analysis description:

Estimates are from analysis based on MMRM using unstructured covariance matrix: Change = Baseline PCS Score + Geographical Region (US vs. ROW) + Age (<=45, > 45 years) + Week + Treatment +

Treatment*Week (repeated values over Week) + Baseline PCS Score*Week.

Comparison groups	Placebo v Ocrelizumab 600 mg
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6034
Method	MMRM
Parameter estimate	Difference in Adjusted Means
Point estimate	0.377
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.048
upper limit	1.802
Variability estimate	Standard error of the mean
Dispersion value	0.725

Secondary: Percentage of Subjects With at Least one Adverse Event (AE)

End point title	Percentage of Subjects With at Least one Adverse Event (AE)

End point description:

AEs included infusion related reactions (IRRs) and serious multiple sclerosis (MS) relapses, but excluded non-serious MS relapses. The safety population includes all subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From the first infusion up to the study clinical cut-off date 24 July 2015 (up to 216 weeks)

End point values	Placebo	Ocrelizumab 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	486		
Units: percentage of subjects				
number (not applicable)	90	95.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first infusion up to the study clinical cut-off date 24 July 2015 (up to 216 weeks)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Matching placebo to ocrelizumab was administered as two intravenous infusions separated by 14 days at a schedule interval of 24 weeks in subjects with PPMS.

Reporting group title	Ocrelizumab 600 mg

Reporting group description:

Subjects with PPMS received ocrelizumab as two IV infusions of 300 mg separated by 14 days at a scheduled interval of every 24 weeks up to at least 120 weeks.

Serious adverse events	Placebo	Ocrelizumab 600 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 239 (22.18%)	99 / 486 (20.37%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of the cervix			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaplastic large-cell lymphoma			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign vaginal neoplasm			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondroma			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive breast carcinoma			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant fibrous histiocytoma			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			

subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Parathyroid tumour benign			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rosai-Dorfman syndrome			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry gangrene			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Gait disturbance			
subjects affected / exposed	1 / 239 (0.42%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug intolerance			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical polyp			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metrorrhagia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 239 (0.42%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Depression suicidal			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 239 (0.00%)	5 / 486 (1.03%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 239 (0.84%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 239 (0.42%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fibula fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative fever			

subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural intestinal perforation			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	2 / 239 (0.84%)	5 / 486 (1.03%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 239 (0.84%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasticity			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures with secondary generalisation			

subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Primary progressive multiple sclerosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uhthoff's phenomenon			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 239 (0.42%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agranulocytosis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			

subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	2 / 239 (0.84%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 239 (0.42%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			

subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus allergic			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 239 (0.42%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 239 (0.84%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			

subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 239 (0.42%)	4 / 486 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 239 (0.42%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			

subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 239 (0.84%)	6 / 486 (1.23%)	
occurrences causally related to treatment / all	1 / 3	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	2 / 239 (0.84%)	5 / 486 (1.03%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	3 / 239 (1.26%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendictis			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	1 / 239 (0.42%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 239 (0.00%)	2 / 486 (0.41%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess of eyelid			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			

subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural cellulitis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pericarditis			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 239 (0.00%)	1 / 486 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 239 (0.42%)	0 / 486 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Ocrelizumab 600 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	179 / 239 (74.90%)	400 / 486 (82.30%)	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	61 / 239 (25.52%)	191 / 486 (39.30%)	
occurrences (all)	145	480	
Contusion			
subjects affected / exposed	19 / 239 (7.95%)	14 / 486 (2.88%)	
occurrences (all)	22	19	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 239 (3.77%)	25 / 486 (5.14%)	
occurrences (all)	9	25	
Nervous system disorders			

Headache			
subjects affected / exposed	32 / 239 (13.39%)	65 / 486 (13.37%)	
occurrences (all)	46	97	
Dizziness			
subjects affected / exposed	10 / 239 (4.18%)	25 / 486 (5.14%)	
occurrences (all)	13	30	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	23 / 239 (9.62%)	27 / 486 (5.56%)	
occurrences (all)	31	29	
Oedema peripheral			
subjects affected / exposed	12 / 239 (5.02%)	24 / 486 (4.94%)	
occurrences (all)	14	26	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	12 / 239 (5.02%)	23 / 486 (4.73%)	
occurrences (all)	14	26	
Nausea			
subjects affected / exposed	16 / 239 (6.69%)	19 / 486 (3.91%)	
occurrences (all)	20	21	
Diarrhoea			
subjects affected / exposed	12 / 239 (5.02%)	22 / 486 (4.53%)	
occurrences (all)	15	36	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 239 (3.35%)	29 / 486 (5.97%)	
occurrences (all)	8	36	
Psychiatric disorders			
Depression			
subjects affected / exposed	30 / 239 (12.55%)	37 / 486 (7.61%)	
occurrences (all)	33	38	
Insomnia			
subjects affected / exposed	12 / 239 (5.02%)	27 / 486 (5.56%)	
occurrences (all)	12	30	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	36 / 239 (15.06%)	55 / 486 (11.32%)	
occurrences (all)	50	65	
Arthralgia			
subjects affected / exposed	21 / 239 (8.79%)	38 / 486 (7.82%)	
occurrences (all)	28	43	
Pain in extremity			
subjects affected / exposed	25 / 239 (10.46%)	32 / 486 (6.58%)	
occurrences (all)	34	35	
Musculoskeletal pain			
subjects affected / exposed	12 / 239 (5.02%)	19 / 486 (3.91%)	
occurrences (all)	12	23	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	65 / 239 (27.20%)	110 / 486 (22.63%)	
occurrences (all)	117	184	
Urinary tract infection			
subjects affected / exposed	53 / 239 (22.18%)	96 / 486 (19.75%)	
occurrences (all)	114	214	
Influenza			
subjects affected / exposed	21 / 239 (8.79%)	56 / 486 (11.52%)	
occurrences (all)	24	69	
Upper respiratory tract infection			
subjects affected / exposed	14 / 239 (5.86%)	53 / 486 (10.91%)	
occurrences (all)	21	72	
Bronchitis			
subjects affected / exposed	12 / 239 (5.02%)	29 / 486 (5.97%)	
occurrences (all)	18	36	
Gastroenteritis			
subjects affected / exposed	12 / 239 (5.02%)	20 / 486 (4.12%)	
occurrences (all)	15	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2011	1. Clarification of the implementation of 2 separate infusions 14 days apart throughout the study. Implementation of the amended re-treatment regimen consisting of two 300 mg ocrelizumab infusions administered 14 days apart at a scheduled interval of every 24 weeks for all treatment doses of Study WA25046. 2. Revision of inclusion / exclusion criteria. The main changes included: 1) the inclusion of subjects with higher age (<=55 years) for a broader PPMS study population and 2) modification of the exclusion criteria to reduce the potential risk of infection to study subjects and to improve clarity of screening criteria. 3. Clarifications on prior experience with ocrelizumab development programs in lupus, rheumatoid arthritis (RA) and relapsing-remitting multiple sclerosis (RRMS).
15 June 2012	1. Dosing preparation and infusion guidance were revised to simplify the preparation of infusion bags and dosing procedures. 2. Specific eligibility cut-off values for immunoglobulin M (IgM) and immunoglobulin G (IgG) were modified to reflect the central lab reference ranges. 3. Sites were informed of additional, optional sub-studies conducted at select centers in which subjects could be eligible to participate.
06 February 2015	1. An update to the Statistical Considerations and Analytical Plan section of the protocol in line with the Statistical Analysis Plan (SAP) for the study. 2. Conversion of optional investigator-sponsored Roche-supported sub-studies to Roche supported exploratory substudies as per current policy of the sponsor. 3. Revision of the pre-specified mandatory biomarker analysis plan. 4. Inclusion of more detail with respect to the open-label extension phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported