Clinical trial results:
An Open-label, Single-arm Study to Evaluate the Effectiveness and Safety of Ocrelizumab in Patients With Early Stage Relapsing Remitting Multiple Sclerosis

Summary

EudraCT number	2016-002937-31
Trial protocol	NO SE AT DK DE PT BE HU PL SK ES BG SI NL GB FR HR IT
Global end of trial date	27 April 2023

Results information

Result version number	v2 (current)
This version publication date	15 February 2025
First version publication date	12 May 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MA30143

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4058
Public contact	Roche Trial Information Hotline, Hoffmann-La Roche, +41 61 6878333,
Scientific contact	Medical Communications, Hoffmann-La Roche, +1 8008218590, genentech@druginfo.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	27 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2023
Global end of trial reached?	Yes
Global end of trial date	27 April 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effectiveness and safety of ocrelizumab in patients with early stage relapsing remitting multiple sclerosis.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) guidelines according to the regulations and procedures described in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 14
Country: Number of subjects enrolled	Australia: 55
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 39
Country: Number of subjects enrolled	Bulgaria: 28
Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	Canada: 67
Country: Number of subjects enrolled	Switzerland: 21
Country: Number of subjects enrolled	Germany: 78
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	France: 69
Country: Number of subjects enrolled	United Kingdom: 52
Country: Number of subjects enrolled	Croatia: 36
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Italy: 60
Country: Number of subjects enrolled	Kuwait: 5
Country: Number of subjects enrolled	Lebanon: 6
Country: Number of subjects enrolled	Mexico: 72
Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	Norway: 6

Country: Number of subjects enrolled	Poland: 153
Country: Number of subjects enrolled	Portugal: 27
Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	Slovakia: 28
Country: Number of subjects enrolled	Slovenia: 12
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	Türkiye: 47
Country: Number of subjects enrolled	United States: 203
Worldwide total number of subjects	1225
EEA total number of subjects	662

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)	1225
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A prospective, multicenter, open-label, single-arm effectiveness and safety study enrolled 1225 eligible treatment-naive patients with early stage RMSR. The study consisted of screening period up 4 weeks and open-label treatment with ocrelizumab period up to 192 week.

Pre-assignment

Screening details:

The efficacy analyses were performed on the main study cohort enrolled as per original study protocol, and safety analyses on all enrolled participants.

Period 1

Period 1 title	Overall Study
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Main Study - Ocrelizumab

Arm description:

Ocrelizumab was administered intravenously (IV) as two 300-milligram (mg) infusions on Days 1 and 15, followed by one 600-mg infusion dose every 24 weeks (+/- 14 days) for a maximum of 8 doses throughout the 192 weeks treatment period.

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

Dosage and administration details:

Ocrelizumab was administered IV as two 300-mg infusions on Days 1 and 15, followed by one 600-mg infusion dose every 24 weeks (+/- 14 days).

Number of subjects in period 1	Main Study - Ocrelizumab
Started	1225
Completed	1010
Not completed	215
Adverse event, serious fatal	12
Site Closure	3
Physician decision	13
planned pregnancy	17
Consent withdrawn by subject	77
Changed to Commercial Ocrelizumab	4
Adverse event, non-fatal	25
Pregnancy	7

Terminated By Sponsor	14
Lost to follow-up	17
disease progression	1
Protocol deviation	15
Lack of efficacy	10

Period 2

Period 2 title	Substudy (Week 24 to Week 144)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Substudy - Conventional Infusion

Arm description:

Ocrelizumab was administered as 600 mg IV infused over approximately 3.5 hours every 24 weeks throughout the treatment period.

Arm type	Experimental
Investigational medicinal product name	Ocrelizumab
Investigational medicinal product code	RO4964913
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion, Concentrate and solvent for solution for infusion, Concentrate and solvent for solution for infusion
Routes of administration	Subcutaneous use, Subcutaneous use, Subcutaneous use

Dosage and administration details:

Ocrelizumab was administered as 600 mg IV infused over approximately 3.5 hours every 24 weeks.

Arm title	Substudy - Shorter Infusion

Arm description:

Ocrelizumab was administered as 600 mg IV infused over approximately 2 hours and saline for remaining 1.5 hours, every 24 weeks throughout the treatment period.

Arm type	Experimental
Investigational medicinal product name	Ocrelizumab
Investigational medicinal product code	RO4964913
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Ocrelizumab was administered as 600 mg IV infused over approximately 2 hours every 24 weeks.

Number of subjects in period 2[1]	Substudy - Conventional Infusion	Substudy - Shorter Infusion
Started	373	372
Completed	0	2
Not completed	373	370
Consent withdrawn by subject	5	7
Substudy stopped by sponsor	355	352
Reason Not Specified	13	8
Withdrawal due to infusion related reaction (IRR)	-	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Participants who consented to participate in the sub-study were enrolled.

Baseline characteristics

Reporting groups	
Reporting group title	Main Study - Ocrelizumab

Reporting group description:

Ocrelizumab was administered intravenously (IV) as two 300-milligram (mg) infusions on Days 1 and 15, followed by one 600-mg infusion dose every 24 weeks (+/- 14 days) for a maximum of 8 doses throughout the 192 weeks treatment period.

Reporting group values	Main Study - Ocrelizumab	Total	
Number of subjects	1225	1225	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	1225	1225	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	32.7		
standard deviation	± 9.1	-	
Sex: Female, Male Units:			
Female	784	784	
Male	441	441	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	11	11	
Asian	19	19	
Native Hawaiian or Other Pacific Islander	2	2	
Black or African American	34	34	
White	1007	1007	
More than one race	37	37	
Unknown or Not Reported	115	115	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	145	145	
Not Hispanic or Latino	960	960	
Unknown or Not Reported	120	120	

End points

End points reporting groups

Reporting group title	Main Study - Ocrelizumab
Reporting group description:	
Ocrelizumab was administered intravenously (IV) as two 300-milligram (mg) infusions on Days 1 and 15, followed by one 600-mg infusion dose every 24 weeks (+/- 14 days) for a maximum of 8 doses throughout the 192 weeks treatment period.	
Reporting group title	Substudy - Conventional Infusion
Reporting group description:	
Ocrelizumab was administered as 600 mg IV infused over approximately 3.5 hours every 24 weeks throughout the treatment period.	
Reporting group title	Substudy - Shorter Infusion
Reporting group description:	
Ocrelizumab was administered as 600 mg IV infused over approximately 2 hours and saline for remaining 1.5 hours, every 24 weeks throughout the treatment period.	

Primary: Time to Onset of Confirmed Disability Progression (CDP) Sustained for at Least 24 Weeks and 48 Weeks as Measured Using Expanded Disability Status Scale (EDSS)

End point title	Time to Onset of Confirmed Disability Progression (CDP) Sustained for at Least 24 Weeks and 48 Weeks as Measured Using Expanded Disability Status Scale (EDSS)[1]
End point description:	
The EDSS-Expanded Disability Status Scale is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death). Disability progression as measured by EDSS is defined as ≥1 point increase in EDSS score from a baseline EDSS score of 1-5 inclusive, a 0.5-increase from a baseline EDSS score higher than 5 and a 1.5-increase from a baseline EDSS score from 0 to 1 exclusive. Disability progression was considered confirmed if a sustained change in EDSS for a minimum of 24 weeks (-2 weeks) from the initial progression event was seen i.e. the change in EDSS must have been sustained at all available visits for a minimum of 24 weeks/48 weeks. Treatment efficacy was measured for this First Enrollment Cohort ITT population. 9999=Median (corresponds to a probability of 50%) and 95% CI was not reached due to low number of participants with the event at the end of the study.	
End point type	Primary
End point timeframe:	
Baseline up to 4 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: weeks				
median (confidence interval 95%)				
CPD Sustained for at Least 24 weeks	9999 (9999 to 9999)			
CDP Sustained for at Least 48 weeks	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with 24-Week and 48-Week Confirmed Disability Improvement (CDI) During the Year 1 Treatment Period, as Measured Using EDSS

End point title	Percentage of Participants with 24-Week and 48-Week Confirmed Disability Improvement (CDI) During the Year 1 Treatment Period, as Measured Using EDSS[2]

End point description:

CDI is defined as an improvement of ≥1 point on the EDSS score confirmed at a regular scheduled visit at least 24/48 weeks after the initial documentation of neurological worsening (measured only participants with a baseline EDSS of ≥2.0). EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death). Treatment efficacy was measured for this First Enrollment Cohort ITT population. Overall number analyzed is the number of participants with data available for analyses. Number analyzed is the number of participants with data available for analyses at the specified timepoints.

End point type	Primary

End point timeframe:

At Weeks 24 and 48 during Year 1

Notes:

[2] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	309			
Units: Percentage %				
number (confidence interval 95%)				
CDI Sustained for 24 weeks: At Week 24 (n=293)	95.11 (92.03 to 97.03)			
CDI Sustained for 24 weeks: At Week 48 (n=205)	83.50 (78.81 to 87.24)			
CDI Sustained for 48 weeks: At Week 48 (n=213)	87.54 (83.28 to 90.77)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with 24-Week and 48-Week CDI During the Year 2 Treatment Period, as Measured Using EDSS

End point title	Percentage of Participants with 24-Week and 48-Week CDI During the Year 2 Treatment Period, as Measured Using EDSS[3]

End point description:

CDI is defined as an improvement of 1 point on the EDSS score confirmed at a regular scheduled visit at least 24/48 weeks after the initial documentation of neurological worsening (measured only participants with a baseline EDSS of ≥2.0). EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death). Treatment efficacy was measured for this First Enrollment Cohort ITT population. Overall number analyzed is the number of participants with data available for analyses. Number analyzed is the number of participants with data available for analyses at the specified timepoints.

End point type	Primary

End point timeframe:

At Weeks 48, 72 and 96 during Year 2

Notes:

[3] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	252			
Units: Percentage of Participants				
number (confidence interval 95%)				
CDI Sustained for 24 weeks: At Week 48 (n=252)	100.0 (100.00 to 100.00)			
CDI Sustained for 48 weeks: At Week 48 (n=252)	100.0 (100.0 to 100.0)			
CDI Sustained for 24 weeks: At Week 72 (n=243)	97.20 (94.22 to 98.66)			
CDI Sustained for 48 weeks: At Week 72 (n=244)	97.60 (94.74 to 98.91)			
CDI Sustained for 24 weeks: At Week 96 (n=166)	90.29 (85.71 to 93.46)			
CDI Sustained for 48 weeks: At Week 96 (n=169)	92.55 (88.41 to 92.55)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Event-free for CDP Sustained for at Least 24 and 48 Weeks at Year 2, as Measured Using EDSS

End point title	Percentage of Participants Event-free for CDP Sustained for at Least 24 and 48 Weeks at Year 2, as Measured Using EDSS[4]

End point description:

EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death). Disability progression as measured by EDSS is defined as ≥1 point increase in EDSS score from a baseline EDSS score of 1-5 inclusive, a 0.5-increase from a baseline EDSS score higher than 5 & a 1.5-increase from a baseline EDSS score from 0 to 1 exclusive. Disability progression was considered confirmed if a sustained change in EDSS for a minimum of 24 weeks (-2 weeks) from initial progression event was seen i.e. change in EDSS must have been sustained at all available visits (during Year 1) for a minimum of 24 weeks/48 weeks. Percentage of participants who did not have CPD sustained for 24 & 48 weeks are reported here. Treatment efficacy was measured for First Enrollment Cohort ITT population. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed for CDP at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Primary

End point timeframe:

Year 2 (Weeks 72 and 96)

Notes:

[4] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Percentage of Particiopants				
number (confidence interval 95%)				
CDP Sustained for 24 weeks: At Week 72 (n=615)	93.97 (91.87 to 95.54)			
CDP Sustained for 48 weeks: At Week 72 (n=622)	95.18 (93.25 to 96.56)			
CDP Sustained for 24 weeks: Week 96 (n=587)	91.65 (89.26 to 93.52)			
CDP Sustained for 48 weeks: Week 96 (n=598)	93.47 (91.30 to 95.12)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With 24-Week and 48-Week CDI at Year 4, as Measured Using EDSS

End point title	Percentage of Participants With 24-Week and 48-Week CDI at Year 4, as Measured Using EDSS[5]

End point description:

CDI is defined as an improvement of 1 point on the EDSS score confirmed at a regular scheduled visit at least 24 weeks after the initial documentation of neurological worsening (measured only participants with a baseline EDSS of ≥2.0). EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death). Treatment efficacy was measured for this First Enrollment Cohort ITT population. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed for CDP at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Primary

End point timeframe:

At Weeks 144, 168 and 192 during Year 4

Notes:

[5] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Percentage of Participants				
number (confidence interval 95%)				
CDI Sustained for 24 weeks: At Week 144 (n=218)	100.00 (100.00 to 100.00)			
CDI Sustained for 48 weeks: At Week 144 (n=218)	100.00 (100.00 to 100.00)			

CDI Sustained for 24 weeks: At Week 168 (n=215)	99.54 (96.77 to 99.93)			
CDI Sustained for 48 weeks: At Week 168 (n=216)	100.00 (100.00 to 100.00)			
CDI Sustained for 24 weeks: At Week 192 (n=163)	93.77 (89.51 to 96.34)			
CDI Sustained for 48 weeks: At Week 192 (n=172)	98.01 (94.77 to 99.25)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Event-free for CDP Sustained for at Least 24 and 48 Weeks at Year 4, as Measured Using EDSS

End point title	Percentage of Participants Event-free for CDP Sustained for at Least 24 and 48 Weeks at Year 4, as Measured Using EDSS[6]

End point description:

EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death). Disability progression as measured by EDSS is defined as ≥1 point increase in EDSS score from a baseline EDSS score of 1-5 inclusive, a 0.5-increase from a baseline EDSS score higher than 5 & a 1.5-increase from a baseline EDSS score from 0 to 1 exclusive. Disability progression was considered confirmed if a sustained change in EDSS for a minimum of 24 weeks (-2 weeks) from initial progression event was seen i.e. change in EDSS must have been sustained at all available visits (during Year 1) for a minimum of 24 weeks/48 weeks. Percentage of participants who did not have CPD sustained for 24 & 48 weeks are reported here. Treatment efficacy was measured for First Enrollment Cohort ITT population. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed for CDP at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Primary

End point timeframe:

Year 4 (Weeks 168 and 192)

Notes:

[6] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Percentage of Participants				
number (confidence interval 95%)				
CDP Sustained for 24 weeks: At Week 168 (n=516)	85.98 (83.04 to 88.44)			
CDP Sustained for 48 weeks: At Week 168 (n=528)	87.98 (85.20 to 90.27)			
CDP Sustained for 24 weeks: At Week 192 (n=402)	84.18 (81.08 to 86.81)			
CDP Sustained for 48 weeks: At Week 192 (n=414)	86.48 (83.54 to 88.93)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline in EDSS Score at Week 24

End point title	Mean Change From Baseline in EDSS Score at Week 24[7]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

From Baseline to Week 24

Notes:

[7] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	671			
Units: Change in Total EDSS Score				
arithmetic mean (standard deviation)	-0.14 (± 0.68)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline in EDSS Score at Week 120

End point title	Mean Change From Baseline in EDSS Score at Week 120[8]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Baseline, Week 120

Notes:

[8] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	579			
Units: Change in Total EDSS Score				
arithmetic mean (standard deviation)	-0.10 (± 0.94)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline in EDSS Score at Week 96

End point title	Mean Change From Baseline in EDSS Score at Week 96[9]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Baseline, Week 96

Notes:

[9] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	637			
Units: Change in Total EDSS Score				
arithmetic mean (standard error)	-0.12 (± 0.95)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline in EDSS Score at Week 72

End point title	Mean Change From Baseline in EDSS Score at Week 72[10]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

From Baseline to Week 72

Notes:

[10] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	651			
Units: Change in Total EDSS Score				
arithmetic mean (standard deviation)	-0.09 (± 0.89)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline in EDSS Score at Week 48

End point title	Mean Change From Baseline in EDSS Score at Week 48[11]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

From Baseline to Week 48

Notes:

[11] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	659			
Units: Change in Total EDSS				
arithmetic mean (standard deviation)	-0.14 (± 0.77)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline in EDSS Score at Week 144

End point title	Mean Change From Baseline in EDSS Score at Week 144[12]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Baseline, Week 144

Notes:

[12] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	561			
Units: Change in Total EDSS Score				
arithmetic mean (standard error)	-0.10 (± 1.00)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline in EDSS Score at Week 168

End point title	Mean Change From Baseline in EDSS Score at Week 168[13]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Baseline, Week 168

Notes:

[13] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	560			
Units: Change in Total EDSS Score				
arithmetic mean (standard error)	-0.05 (± 1.05)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline in EDSS Score at Week 192

End point title	Mean Change From Baseline in EDSS Score at Week 192[14]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Baseline, Week 192

Notes:

[14] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	562			
Units: Change in Total EDSS Score				
arithmetic mean (standard deviation)	-0.06 (± 1.06)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Have Improved, Stable, or Worsened Disability Compared to Baseline at Year 2, As Measured Using EDSS

End point title	Percentage of Participants Who Have Improved, Stable, or Worsened Disability Compared to Baseline at Year 2, As Measured Using EDSS[15]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Year 2 (Week 96)

Notes:

[15] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	632			
Units: Percentage of Participants				
number (not applicable)				
Week 96 Stable (Change <= 0.5 and >= -0.5)	76.6			
Week 96 Improved (<-0.5)	11.6			
Week 96 Improved (<-0.5)	11.6			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Have Improved, Stable, or Worsened Disability Compared to Baseline at Year 1, As Measured Using EDSS

End point title	Percentage of Participants Who Have Improved, Stable, or Worsened Disability Compared to Baseline at Year 1, As Measured Using EDSS[16]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Year 1 (Week 48)

Notes:

[16] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	659			
Units: Percentage of Participants				
number (not applicable)				
Week 48 Stable (Change <= 0.5 and >= -0.5)	73.3			
Week 48 Improved (<-0.5)	17.5			
Week 48 Improved (<-0.5)	17.5			

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Relapse Rate

End point title	Annualized Relapse Rate[17]

End point description:

Relapse is defined as occurrence of new or worsening neurological symptoms attributable to MS, as determined using EDSS/FSS assessment. The adjusted annualized relapse rate is reported which is: Adjusted by age at disease diagnosis, Baseline EDSS, Presence of T1 Gd-enhanced lesion at screening and Presence of relapses in the last year prior to enrollment. Log-transformed exposure time is included as an offset variable. The report contains data up to week 192 of the treatment period of each individual participant. First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort.

End point type	Primary

End point timeframe:

Baseline up to 4 years

Notes:

[17] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: events per participant per year				
least squares mean (confidence interval 95%)	0.02 (0.015 to 0.027)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Have Improved, Stable, or Worsened Disability at Year 3, As Measured Using EDSS

End point title	Percentage of Participants Who Have Improved, Stable, or Worsened Disability at Year 3, As Measured Using EDSS[18]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Year 3

Notes:

[18] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	557			
Units: Percentage of Participants				
number (not applicable)				
Worsened (>0.5)	9.3			
Stable (Change <= 0.5 and >= -0.5)	81.5			
Improved (<-0.5)	9.2			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Have Improved, Stable, or Worsened Disability at Year 4, As Measured Using EDSS

End point title	Percentage of Participants Who Have Improved, Stable, or Worsened Disability at Year 4, As Measured Using EDSS[19]

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Overall number analyzed is the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Year 4

Notes:

[19] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	562			
Units: Percentage of Participants				
number (not applicable)				
Worsened (>0.5)	18.0			
Stable (Change <= 0.5 and >= -0.5)	59.3			
Improved (<-0.5)	22.8			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Event-Free for CDP Sustained for at Least 24 and 48 Weeks at Year 1, as Measured Using EDSS

End point title	Percentage of Participants Event-Free for CDP Sustained for at Least 24 and 48 Weeks at Year 1, as Measured Using EDSS[20]

End point description:

EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death). Disability progression as measured by EDSS is defined as ≥1 point increase in EDSS score from a baseline EDSS score of 1-5 inclusive, a 0.5-increase from a baseline EDSS score higher than 5 & a 1.5-increase from a baseline EDSS score from 0 to 1 exclusive. Disability progression was considered confirmed if a sustained change in EDSS for a minimum of 24 weeks (-2 weeks) from initial progression event was seen i.e. change in EDSS must have been sustained at all available visits (during Year 1) for a minimum of 24 weeks/48 weeks. Percentage of participants who did not have CPD sustained for 24 & 48 weeks are reported here. Treatment efficacy was measured for First Enrollment Cohort ITT population. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed for CDP at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Primary

End point timeframe:

Year 1 (Weeks 24 and 48)

Notes:

[20] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Percentage of Participants				
number (confidence interval 95%)				
CDP Sustained for 24 weeks: At Week 24 (n=668)	99.55 (98.62 to 99.86)			
CDP Sustained for 24 weeks: At Week 48 (n=645)	97.30 (95.75 to 98.29)			
CDP Sustained for 48 weeks: At Week 48 (n=649)	98.05 (96.67 to 98.87)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants without Protocol-Defined Event of Disease Activity

End point title	Percentage of Participants without Protocol-Defined Event of Disease Activity[21]

End point description:

Protocol-defined event of disease activity is defined as having at least one of the following: (1). protocol defined relapse (occurrence of new or worsening neurological symptoms attributable to Multiple Sclerosis [MS], as determined using EDSS/Functional Systems Score [FSS] assessment). (2). CDP, as determined using EDSS. (3). a T1 Gd-enhanced lesion after Week 8 (4). a new and/or enlarging T2 hyperintense lesion on magnetic resonance imaging (MRI) after Week 8 compared to the Week 8 MRI scan. First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed at that timepoint. Different participants may have contributed data for each timepoint

End point type	Primary

End point timeframe:

Baseline up to 4 years

Notes:

[21] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Percentage of participants				
number (confidence interval 95%)				
Week 24 (n=646)	95.98 (94.20 to 97.23)			
Week 48 (n=590)	88.94 (86.30 to 91.09)			
Week 72 (n=549)	83.94 (80.92 to 86.52)			
Week 96 (n=517)	80.38 (77.14 to 83.21)			
Week 120 (n=488)	77.38 (73.99 to 80.39)			
Week 144 (n=463)	75.76 (72.28 to 78.86)			
Week 168 (n=436)	72.79 (69.18 to 76.05)			
Week 192 (n=340)	70.67 (66.97 to 74.04)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants without Relapse

End point title	Percentage of Participants without Relapse[22]

End point description:

Relapse is defined as occurrence of new or worsening neurological symptoms attributable to MS, as determined using EDSS/FSS assessment. First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Primary

End point timeframe:

Baseline up to 4 years

Notes:

[22] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 24 (n=661)	98.52 (97.26 to 99.20)			
Week 48 (n=649)	97.91 (96.50 to 98.76)			
Week 72 (n=631)	96.25 (94.49 to 97.45)			
Week 96 (n=610)	95.32 (93.41 to 96.69)			
Week 120 (n=593)	93.90 (91.78 to 95.49)			
Week 144 (n=570)	93.09 (90.85 to 94.79)			
Week 168 (n=554)	92.43 (90.10 to 94.23)			
Week 192 (n=439)	91.56 (89.12 to 93.48)			

Statistical analyses

No statistical analyses for this end point

Primary: Sub Study: Number of Participants with IRRs Occurring During or Within 24 Hours Following the First Infusion After Randomization to the Shorter Infusion Substudy

End point title	Sub Study: Number of Participants with IRRs Occurring During or Within 24 Hours Following the First Infusion After Randomization to the Shorter Infusion Substudy[23]

End point description:

ITT Population included all randomized participants in shorter infusion sub study.

End point type	Primary

End point timeframe:

Week 24 through Week 144

Notes:

[23] - 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: No formal statistical analysis was planned for this endpoint.

End point values	Substudy - Conventional Infusion	Substudy - Shorter Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	372		
Units: Participants	101	107		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Are Relapse Free

End point title	Percentage of Participants Who Are Relapse Free

End point description:

Relapse is defined as occurrence of new or worsening neurological symptoms attributable to MS, as determined using EDSS/FSS assessment.

End point type	Secondary

End point timeframe:

Week 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	624			
Units: Percentage of Participants				
median (confidence interval 95%)	92.00 (89.7 to 94.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With no Evidence of Progression Sustained for At Least 24 Weeks and no Active Disease (NEPAD)

End point title	Percentage of Participants With no Evidence of Progression Sustained for At Least 24 Weeks and no Active Disease (NEPAD)

End point description:

NEPAD is defined as no progression on all of the three components of NEP (CDP, T25FWT, 9HPT), no new relapse and no enlarging or new T2 or T1 Gd-enhancing lesion. CDP will be assessed using EDSS. Relapse is defined as occurrence of new or worsening neurological symptoms attributable to MS, as determined using EDSS/FSS assessment. First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

Weeks 96, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 192 (n=277)	58.89 (54.96 to 62.60)			
Week 192	58.89 (54.96 to 62.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With No Evidence of Protocol Defined Disease Activity

End point title	Percentage of Participants With No Evidence of Protocol Defined Disease Activity

End point description:

Protocol-defined disease activity is defined as having at least one of the following: (1). protocol defined relapse (occurrence of new or worsening neurological symptoms attributable to Multiple Sclerosis [MS], as determined using EDSS/Functional Systems Score [FSS] assessment). (2). CDP, as determined using EDSS. (3). a T1 Gd-enhanced lesion after Week 8. (4). a new and/or enlarging T2 hyperintense lesion on magnetic resonance imaging (MRI) after Week 8 compared to the Week 8 MRI scan. Event-free rate. First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

Weeks 96, 144, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Percentage of Participants				
median (confidence interval 95%)				
Week 96	80.38 (77.14 to 83.21)			
Week 144	75.76 (72.28 to 78.86)			
Week 192	70.67 (66.97 to 74.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MSFC Composite Timed 25 Foot Walk Test (T25FW) Score

End point title	Change from Baseline in MSFC Composite Timed 25 Foot Walk Test (T25FW) Score

End point description:

The change in the mean score of T25FW is reported below. The time taken to walk 25 feet, typically measured in seconds. The longer it takes to walk, the higher score, which indicates deterioration. Lower times indicate better performance and greater mobility. Higher times indicate worse performance and greater impairment. Subsequently, the lower the mean change in the score over time, the better performance. Treatment efficacy was measured for this First Enrollment Cohort ITT population. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed at the specified timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, 72, 96, 120, 144, 168, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: seconds				
arithmetic mean (standard deviation)				
Week 24 (n=650)	-0.31 (± 6.62)			
Week 48 (n=647)	-0.49 (± 6.88)			
Week 72 (n=627)	-0.56 (± 6.99)			
Week 96 (n=617)	-0.62 (± 6.95)			
Week 120 (n=560)	-0.44 (± 7.94)			
Week 144 (n=562)	-0.97 (± 6.25)			
Week 168 (n=554)	-0.83 (± 6.64)			
Week 192 (n=543)	0.09 (± 9.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MSFC Composite 9 Hole Peg Test (9HPT) Score

End point title	Change from Baseline in MSFC Composite 9 Hole Peg Test (9HPT) Score

End point description:

Mean change in 9HPT-score is reported. Participants are instructed to place pegs one by one into each of nine holes arranged in a board stabilized with a plastic nonslip sheet on a solid table, and then to remove these pegs from the holes. Both the dominant and non-dominant hands are tested twice (two consecutive trials for each hand). The participants are required to complete two successful trials for each hand. The amount of time (in seconds) required to place and remove all nine pegs is recorded for each trial. The number of seconds it takes to complete the test, the higher raw scores, which indicates deterioration. The lower mean change in the score over time, the better the performance. Treatment efficacy was measured for this First Enrollment Cohort ITT population. Number analyzed per timepoint

are unique number of participants out of all the participants who were assessed at the specified timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

Weeks 24, 48, 72, 96, 120, 144, 168, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: seconds				
arithmetic mean (standard deviation)				
Week 24 (n=650)	-0.47 (± 14.44)			
Week 48 (n=648)	-1.22 (± 11.54)			
Week 72 (n=628)	-1.78 (± 8.09)			
Week 96 (n=618)	-1.67 (± 10.91)			
Week 120 (n=551)	-0.87 (± 15.21)			
Week 144 (n=560)	-1.91 (± 8.70)			
Week 168 (n=555)	-1.84 (± 10.68)			
Week 192 (n=544)	-0.73 (± 17.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MSFC Composite (Paced Auditory Serial Addition Test [PASAT]) Score

End point title	Change from Baseline in MSFC Composite (Paced Auditory Serial Addition Test [PASAT]) Score

End point description:

PASAT measures cognitive function. A total of 60 single digit numbers are presented by an audiotape/CD-rom at a constant rate in every 3 seconds (PASAT-3). Participants are required to add each new number to the one immediately before it. Due to the relative complexity of this test, a practice trial with a set of 10 numbers should be performed before the original test. Participants are allowed up to 3 practice trials. Two sets of numbers (forms A & B) are developed to be used alternatively in every visit to minimize memorizing. Number of correct answers is recorded. PASAT score range: 0-60. Higher values=better outcome in cognitive processing speed. Subsequently, higher values in mean changes from baseline=improvement in cognitive function. First Enrollment Cohort ITT population. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed at the specified timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

Weeks 24, 48, 72, 96, 120, 144, 168, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 24 (n=251)	4.18 (± 9.26)			
Week 48 (n=453)	5.40 (± 9.52)			
Week 72 (n=320)	6.33 (± 11.59)			
Week 96 (n=435)	7.66 (± 10.93)			
Week 120 (n=290)	7.69 (± 12.95)			
Week 144 (n=372)	8.45 (± 10.02)			
Week 168 (n=285)	8.47 (± 11.79)			
Week 192 (n=344)	9.64 (± 11.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of T1 Gd-Enhancing Lesions as Detected by Brain MRI

End point title	Total Number of T1 Gd-Enhancing Lesions as Detected by Brain MRI
End point description:	
Number of Lesions are categorized as followed: 1, 2, 3, >1, >3	
End point type	Secondary
End point timeframe:	
Weeks 24, 48, 96, 144, 192	

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Number of Lesions				
Week 24 Number of Lesions 0	659			
Week 24 Number of Lesions 1	6			
Week 24 Number of Lesions 2	2			
Week 24 Number of Lesions >1	2			
Week 48 Number of Lesions 0	650			
Week 48 Number of Lesions 1	7			
Week 96 Number of Lesions 0	629			
Week 96 Number of Lesions 1	1			
Week 144 Number of Lesions 0	567			
Week 144 Number of Lesions 1	1			

Week 144 Number of Lesions 3	1			
Week 144 Number of Lesions >1	1			
Week 192 Number of Lesions 0	545			
Week 192 Number of Lesions 1	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of New and/or Enlarging T2 Lesion as Detected by Brain MRI

End point title	Total Number of New and/or Enlarging T2 Lesion as Detected by Brain MRI
End point description:	
Number of Lesions are categorized as followed: 1, 2, 3, >1, >3	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 24, 48, 96, 144, 192	

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Number of Lesions				
Week 24 Number of Lesions 0	651			
Week 24 Number of Lesions 1	13			
Week 24 Number of Lesions 2	3			
Week 24 Number of Lesions >1	3			
Week 48 Number of Lesions 0	644			
Week 48 Number of Lesions 1	11			
Week 48 Number of Lesions 2	3			
Week 48 Number of Lesions 3	2			
Week 48 Number of Lesions >1	5			
Week 96 Number of Lesions 0	624			
Week 96 Number of Lesions 1	8			
Week 96 Number of Lesions 2	1			
Week 96 Number of Lesions >1	1			
Week 144 Number of Lesions 0	564			
Week 144 Number of Lesions 1	6			
Week 144 Number of Lesions 2	1			
Week 144 Number of Lesions 3	1			
Week 144 Number of Lesions >1	2			
Week 192 Number of Lesions 0	546			
Week 192 Number of Lesions 1	4			
Week 192 Number of Lesions 2	1			
Week 192 Number of Lesions >1	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total T1 hypointense lesion volume as Detected by Brain MRI

End point title	Change from baseline in total T1 hypointense lesion volume as Detected by Brain MRI

End point description:

End point type	Secondary

End point timeframe:

Baseline, Weeks 48, 96, 144, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Change in Volume				
arithmetic mean (standard deviation)				
Week 48	-310.63 (± 708.07)			
Week 96	-405.61 (± 755.99)			
Week 144	-359.76 (± 761.84)			
Week 192	-307.64 (± 797.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Change from Baseline in Multiple Sclerosis Functional Composite Score (MSFC) Total

End point title	Secondary: Change from Baseline in Multiple Sclerosis Functional Composite Score (MSFC) Total

End point description:

MSFC combines the following: Timed 25 Foot Walk Test [T25FWT] for leg function &ambulation measured in seconds (sec). The longer it takes to walk, higher the score indicating deterioration; 9 Hole Peg Test [9HPT] for arm & handf unction measured in sec. Higher score=more time taken to complete test indicating deterioration. Paced Auditory Serial Addition Test [PASAT] for cognitive function (score range: 0-60, higher score=better cognitive processing speed). MSFC composite={[Average(1/9-HPT)-Baseline Mean(1/9-HPT)/Baseline Std Dev(1/9-HPT)]+[-(Average T25FWT-Baseline Mean T25FWT)

/Baseline Std-Dev T25FWT]+[(PASAT-3-BaselineMean PASAT-3)/Baseline Std Dev PASAT-3]}/ 3.0. MSFC is based on the concept that scores for these 3 dimensions are combined to create a single score to detect change over time in a group of MS patients. Higher composite score=better overall function. Lower score=worse overall function. Higher mean change in total MSFC score=functional improvement at cohort level.

End point type	Secondary

End point timeframe:

Weeks 24, 48, 72, 96, 120, 144, 168, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 24 (n=595)	0.09 (± 0.67)			
Week 48 (n=601)	0.11 (± 0.54)			
Week 78 (n=588)	0.12 (± 0.45)			
Week 96 (n=566)	0.14 (± 0.53)			
Week 120 (n=511)	0.16 (± 0.61)			
Week 144 (n=513)	0.16 (± 0.48)			
Week 168 (n=498)	0.18 (± 0.56)			
Week 192 (n=492)	0.19 (± 0.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Fluid-Attenuated Inversion-Recovery (FLAIR) Lesion as Detected by Brain MRI

End point title	Total Number of Fluid-Attenuated Inversion-Recovery (FLAIR) Lesion as Detected by Brain MRI

End point description:

End point type	Secondary

End point timeframe:

Baseline, Weeks 8, 24, 48, 96, 144, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Number of Lesions				
Baseline Week 8 0	633			
Baseline Week 8 1	6			
Week 24 0	635			

Week 24 1	6			
Week 48 0	631			
Week 48 1	6			
Week 96 0	611			
Week 96 1	7			
Week 144 0	550			
Week 144 1	5			
Week 192 0	530			
Week 192 1	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Brain Volume as Detected by Brain MRI

End point title	Change From Baseline in Brain Volume as Detected by Brain MRI

End point description:

Percentage change from Normalized brain volume in cm3 (cubic centimeter)values are reported

End point type	Secondary

End point timeframe:

From Baseline to Weeks 24, 48, 96, 144, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Percentage Change in Volume (cm3)				
arithmetic mean (standard deviation)				
Week 24	-0.189 (± 0.564)			
Week 48	-0.479 (± 0.733)			
Week 96	-0.909 (± 0.930)			
Week 144	-1.283 (± 1.156)			
Week 192	-1.535 (± 1.311)			

Statistical analyses

No statistical analyses for this end point

Secondary: Employment Status: Work Productivity and Activity Impairment Questionnaire (WAPI) Score

End point title	Employment Status: Work Productivity and Activity Impairment Questionnaire (WAPI) Score

End point description:

WPAI scale measures impact of health problems on work productivity and regular activities:
Absenteeism (Work Time Missed) measuring % of work time missed due to health issues;
Presenteeism:Calculated as the percentage of impairment while working due to health problems. Overall Work Impairment:Calculated by combining absenteeism and presenteeism using the formula:Overall Work Impairment=Absenteeism+(1−Absenteeism)×Presenteeism Overall Work Impairment=Absenteeism(1−Absenteeism)×Presenteeism. This formula accounts for both the time missed and the reduced productivity while at work.
Activity Impairment: Calculated as the percentage of impairment in regular activities outside of work.
Range: Each component is scored as 0%-100%). Higher % indicate greater impairment and worse outcomes.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, 96, 120, 144, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: WAPI Sub-Score				
arithmetic mean (standard deviation)				
Work productivity Baseline (n=369)	26.33 (± 31.84)			
Work productivity Week 24 (n=401)	17.65 (± 25.04)			
Work productivity Week 48 (n=404)	18.83 (± 25.92)			
Work productivity Week 96 (n=420)	16.46 (± 23.10)			
Work productivity Week 144 (n=368)	16.78 (± 23.85)			
Work productivity Week 192 (n=369)	15.80 (± 22.25)			
Activity Impairment Baseline (n=640)	23.23 (± 24.79)			
Activity Impairment Week 24 (n=634)	18.09 (± 22.15)			
Presenteeism Week 48 (n=635)	18.85 (± 23.37)			
Activity Impairment Week 96 (n=605)	17.79 (± 22.92)			
Activity Impairment Week 144 (n=563)	17.80 (± 23.74)			
Activity Impairment Week 192 (n=521)	18.18 (± 23.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: SymptoMScreen Composite Score

End point title	SymptoMScreen Composite Score

End point description:

The SMSS consists of 12 items which are assessed on a seven-point Likert scale that ranges from 0 (not at all affected) to 6 (total limitation) [7]. The total score ranges from 0 to 72, with higher scores indicating more severe symptom endorsement. First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, 96, 144, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Change in SymptoMScreen Composite Score				
arithmetic mean (standard deviation)				
Week 24 (n=651)	-0.1 (± 0.9)			
Week 48 (n=648)	-0.1 (± 1.0)			
Week 96 (n=621)	0.0 (± 1.1)			
Week 144 (n=568)	0.0 (± 1.1)			
Week 192 (n=538)	0.0 (± 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life: Multiple Sclerosis Impact Scale (MSIS)-29 Questionnaire Score

End point title	Quality of Life: Multiple Sclerosis Impact Scale (MSIS)-29 Questionnaire Score

End point description:

The 29-item Multiple Sclerosis Impact Scale (MSIS-29) is a questionnaire to examine the impact of multiple sclerosis (MS) on physical and psychological functioning from a patient’s perspective, which includes 29 items self-reported measures associated with a physical scale and 9 items with a psychological scale. MSIS-29 scales are generated by summing items and it's ranging from 29-145'. The higher total MSIS-29 scores indicate a greater degree of disability. The mean change in MSIS-29 scores from baseline is reported. The decreasing values in the mean change from baseline indicate functional improvement from participants’ perspective. First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, 96, 144, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Change in MSIS-29 Score				
arithmetic mean (standard deviation)				
Week 24 (n=656)	-2.43 (± 12.13)			
Week 48 (n=650)	-2.15 (± 13.04)			
Week 96 (n=627)	-1.26 (± 14.31)			
Week 144 (n=571)	-0.73 (± 14.83)			
Week 192 (n=543)	-0.63 (± 16.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 4 years

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	1225			
Units: Percentage of Participants				
number (not applicable)				
Adverse Events	95.8			
Serious Adverse Events	15.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants without Treatment Discontinuation

End point title	Percentage of Participants without Treatment Discontinuation

End point description:

First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort.

End point type	Secondary

End point timeframe:

Baseline up to 4 years

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: percentage of participants				
number (confidence interval 95%)				
Week 24 (n=671)	98.97 (97.85 to 99.51)			
Week 48 (n=661)	97.49 (96.00 to 98.45)			
Week 72 (n=652)	96.02 (94.25 to 97.25)			
Week 96 (n=635)	93.51 (91.38 to 95.13)			
Week 120 (n=625)	92.04 (89.73 to 93.84)			
Week 144 (n=605)	89.23 (86.65 to 91.34)			
Week 168 (n=589)	87.17 (84.41 to 89.47)			
Week 192 (n=464)	83.85 (80.85 to 86.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants without protocol-defined event of Evidence of Progression (NEP)

End point title	Percentage of Participants without protocol-defined event of Evidence of Progression (NEP)

End point description:

NEP is defined as no progression sustained for at least 24 weeks on all of the following three components (CDP; 20 percent [%] increase from baseline in timed 25 Foot Walk Test [T25FWT]; 20% increase from baseline in timed 9 hole peg test [9HPT]). CDP will be assessed using EDSS. First Enrollment Cohort ITT population. Treatment efficacy was measured for this First Enrollment Cohort. Number analyzed per timepoint are unique number of participants out of all the participants who were assessed at that timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary

End point timeframe:

Weeks 96, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	678			
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 96 (n=511)	79.60 (76.33 to 82.48)			
Week 192 (n=325)	69.16 (65.40 to 72.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With IRR Overall and by Dose at Randomization

End point title	Number of Participants With IRR Overall and by Dose at Randomization

End point description:

ITT Population included all randomized participants in shorter infusion sub study. Number analyzed is the number of participants who received an infusion.

End point type	Secondary

End point timeframe:

From Week 24 to Week 144

End point values	Substudy - Conventional Infusion	Substudy - Shorter Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	372		
Units: Participants				
All Randomized Doses (Overall) (n=373, 372)	155	172		
1st Randomized Dose (n=373, 372)	101	107		
2nd Randomized Dose (n=367, 355)	84	96		
3rd Randomized Dose (n=305, 300)	62	82		
4th Randomized Dose (n=147, 136)	14	17		
5th Randomized Dose (n=23, 21)	1	3		
6th Randomized Dose (n=6, 4)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Cognitive Performance as Measured by Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) - Symbol Digits Modalities Test (SDMT)

End point title	Change from baseline in Cognitive Performance as Measured by Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) - Symbol Digits Modalities Test (SDMT)

End point description:

BICAMS is assessing cognitive processing speed and verbal and visual memory. SDMT assesses processing speed/working memory. The SDMT presents a series of nine symbols, each paired with a single digit in a key at the top of a standard sheet of paper. Participants are asked to voice the digit associated with each symbol as rapidly as possible for 90 sec. There is a single outcome measure - the number correct over the 90 second time span. The higher the results, the better processing speed/working memory. Treatment efficacy was measured for this First Enrollment Cohort ITT population. Overall number analyzed is the number of participants with data available for analyses. Number analyzed is the number of participants with data available for analyses at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Weeks 48, 96, 144, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	602			
Units: responses over 90 seconds				
arithmetic mean (standard deviation)				
Change atWeek 48 (n=602)	2.48 (± 10.12)			
Change atWeek 96 (n=563)	1.89 (± 9.98)			
Change atWeek 144 (n=506)	3.33 (± 9.31)			
Change at Week 192 (n=506)	4.38 (± 10.38)			

Statistical analyses

No statistical analyses for this end point

Secondary: Substudy: IRRs Leading to Treatment Discontinuation

End point title	Substudy: IRRs Leading to Treatment Discontinuation

End point description:

ITT Population included all randomized participants in shorter infusion sub study.

End point type	Secondary

End point timeframe:

From Week 24 to Week 144

End point values	Substudy - Conventional Infusion	Substudy - Shorter Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	372		
Units: symptoms	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Substudy: Severity of IRRs

End point title	Substudy: Severity of IRRs

End point description:

The number of participants with IRRs by most extreme intensity were reported (Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 =life-threatening, grade 5 = fatal). Multiple IRRs in one participant are counted only once at the most extreme (highest) intensity observed. ITT Population included all randomized participants in shorter infusion sub study. Number analyzed is the number of participants with IRR.

End point type	Secondary

End point timeframe:

From Week 24 to Week 144

End point values	Substudy - Conventional Infusion	Substudy - Shorter Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	372		
Units: Participants				
Grade 1 (Mild)	88	92		
Grade 2 (Moderate)	66	76		
Grade 3 (Severe)	1	4		
Grade 4 (Life-Threatening)	0	0		
Grade 5 (Fatal)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Substudy: Number of IRR Symptoms

End point title	Substudy: Number of IRR Symptoms

End point description:

ITT Population included all randomized participants in shorter infusion sub study. Overall number of participants analyzed is the number of participants with data available for analyses. Number analyzed is the number of participants with an infusion.

End point type	Secondary

End point timeframe:

From Week 24 to Week 144

End point values	Substudy - Conventional Infusion	Substudy - Shorter Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	372		
Units: symptoms				
1st randomized dose Overall Participants with IRR	471	458		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Cognitive Performance as Measured by BICAMS -California Verbal Learning Test-II (CVLT-II)

End point title	Change from baseline in Cognitive Performance as Measured by BICAMS -California Verbal Learning Test-II (CVLT-II)

End point description:

BICAMS assesses cognitive processing speed and verbal and visual memory. The CLVT-II is an assessment of verbal learning and memory which measures recall and recognition scores, encoding strategies, learning rates and error types. A list learning task with 16 words from 4 semantic categories are read over a series of 5 list presentations. Recall is assessed after learning and at a 20-minute delay. The maximum possible score is 80 and a minimum is 0. A higher score indicated better recall. Treatment efficacy was measured for this First Enrollment Cohort ITT population. Overall number analyzed is the number of participants with data available for analyses. Number analyzed is the number of participants with data available for analyses at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Weeks 48, 96, 144, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	130			
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Week 48 (n=130)	2.02 (± 8.29)			
Change at Week 96 (n=119)	2.71 (± 9.25)			
Change at Week 144 (n=97)	3.99 (± 7.60)			
Change at Week 192 (n=108)	4.28 (± 13.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Cognitive Performance as Measured by BICAMS - Brief Visuospatial Memory Test-Revised (BVMT-R)

End point title	Change from baseline in Cognitive Performance as Measured by BICAMS - Brief Visuospatial Memory Test-Revised (BVMT-R)

End point description:

BICAMS assesses cognitive processing speed and verbal and visual memory. BVMT-R assesses visuospatial memory. In this test, six abstract designs are presented for 10 sec. The display is removed from view and patients render the stimuli via pencil on paper manual responses. Each design receives from 0 to 2 points representing accuracy and location. There are three learning trials, and the outcome measure is the total number of points earned over the three learning trials, thus the scale range is 0-36. The higher the result, the better visual/spatial memory. Treatment efficacy was measured for this First Enrollment Cohort ITT population. Overall number analyzed is the number of participants with data available for analyses. Number analyzed is the number of participants with data available for analyses at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Weeks 48, 96, 144, 192

End point values	Main Study - Ocrelizumab			
Subject group type	Reporting group			
Number of subjects analysed	643			
Units: points on a scale				
arithmetic mean (standard deviation)				
Baseline (n=643)	23.69 (± 6.44)			
Change at Week 48 (n=587)	-0.71 (± 5.31)			
Change at Week 96 (n=566)	0.82 (± 5.68)			
Change at Week 144 (n=489)	3.15 (± 5.37)			
Change at Week 192 (n=489)	1.06 (± 7.09)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Main study: Up to 4 Years
Sub-study: Week 24 to Week 144

Adverse event reporting additional description:

Safety population included all enrolled participants who received any dose or part of a dose of ocrelizumab. Three participants from the 'Substudy - Conventional Infusion' arm received shorter infusions of ocrelizumab. Hence, these participants are represented in the 'Substudy - Shorter Infusion' arm for safety assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Ocrelizumab

Reporting group description:

Ocrelizumab was administered IV as two 300-mg infusions on Days 1 and 15, followed by one 600-mg infusion dose every 24 weeks (+/- 14 days) for a maximum of 8 doses throughout the 192 weeks treatment period.

Reporting group title	Substudy - Conventional Infusion

Reporting group description:

Ocrelizumab was administered as 600 mg IV infused over approximately 3.5 hours every 24 weeks throughout the treatment period.

Reporting group title	Substudy - Shorter Infusion

Reporting group description:

Ocrelizumab was administered as 600 mg IV infused over approximately 2 hours and saline for remaining 1.5 hours, every 24 weeks throughout the treatment period.

Serious adverse events	Ocrelizumab	Substudy - Conventional Infusion	Substudy - Shorter Infusion
Total subjects affected by serious adverse events			
subjects affected / exposed	184 / 1225 (15.02%)	21 / 370 (5.68%)	19 / 375 (5.07%)
number of deaths (all causes)	13	2	1
number of deaths resulting from adverse events	4	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BENIGN BREAST NEOPLASM			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
NEOPLASM PROGRESSION			

subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALIGNANT MELANOMA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	3 / 1225 (0.24%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTRADUCTAL PAPILLOMA OF BREAST			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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
PAPILLARY THYROID CANCER			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
UTERINE LEIOMYOMA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
Vascular disorders			
PHLEBITIS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
HYPOTENSION			

subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	4 / 1225 (0.33%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
ABORTION			
subjects affected / exposed	3 / 1225 (0.24%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABORTION SPONTANEOUS			
subjects affected / exposed	7 / 1225 (0.57%)	1 / 370 (0.27%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	2 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHAGE IN PREGNANCY			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
Ectopic pregnancy			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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
General disorders and administration site conditions			
PAIN			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
OEDEMA PERIPHERAL			

subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST PAIN			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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			
IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Reproductive system and breast disorders			
OVARIAN CYST			
subjects affected / exposed	2 / 1225 (0.16%)	0 / 370 (0.00%)	0 / 375 (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
CERVICAL DYSPLASIA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENDOMETRIOSIS			
subjects affected / exposed	2 / 1225 (0.16%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE POLYP			
subjects affected / exposed	2 / 1225 (0.16%)	0 / 370 (0.00%)	0 / 375 (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
VULVOVAGINAL PAIN			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
NASAL SEPTUM DEVIATION			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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
NASAL TURBINATE HYPERTROPHY			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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
PNEUMOTHORAX			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHMA			
subjects affected / exposed	2 / 1225 (0.16%)	1 / 370 (0.27%)	0 / 375 (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
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 1225 (0.16%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
MENTAL STATUS CHANGES			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MAJOR DEPRESSION			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
DEPRESSIVE SYMPTOM			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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

DEPRESSION			
subjects affected / exposed	2 / 1225 (0.16%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMPLETED SUICIDE			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
BIPOLAR DISORDER			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
ANXIETY			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
POST-TRAUMATIC STRESS DISORDER			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
SOMATIC SYMPTOM DISORDER			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
SUICIDAL IDEATION			
subjects affected / exposed	2 / 1225 (0.16%)	1 / 370 (0.27%)	0 / 375 (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
SUICIDE ATTEMPT			
subjects affected / exposed	2 / 1225 (0.16%)	0 / 370 (0.00%)	0 / 375 (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
Investigations			

TRANSAMINASES INCREASED			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CAPILLARY PERMEABILITY INCREASED			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
Injury, poisoning and procedural complications			
FIBULA FRACTURE			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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
FRACTURE DISPLACEMENT			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANKLE FRACTURE			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
CONCUSSION			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
FEMUR FRACTURE			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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

INFUSION RELATED REACTION			
subjects affected / exposed	6 / 1225 (0.49%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	7 / 7	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIGAMENT RUPTURE			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
LIGAMENT SPRAIN			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
MULTIPLE INJURIES			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
RADIUS FRACTURE			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKIN LACERATION			
subjects affected / exposed	2 / 1225 (0.16%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TENDON RUPTURE			

subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
WRIST FRACTURE			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
Congenital, familial and genetic disorders			
CRI DU CHAT SYNDROME			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
PERICARDITIS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
PALPITATIONS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
DYSTONIA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
CERVICOBRACHIAL SYNDROME			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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

MIGRAINE			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
MULTIPLE SCLEROSIS RELAPSE			
subjects affected / exposed	9 / 1225 (0.73%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEURALGIA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
TRIGEMINAL NEURALGIA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
TOXIC ENCEPHALOPATHY			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
SYNCOPE			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
SEIZURE			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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
RADICULOPATHY			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
PRESYNCOPE			

subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
Blood and lymphatic system disorders			
NEUTROPENIA			
subjects affected / exposed	2 / 1225 (0.16%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
VISUAL IMPAIRMENT			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ANAL FISTULA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
ABDOMINAL PAIN			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
SMALL INTESTINAL PERFORATION			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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

OESOPHAGEAL SPASM			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INGUINAL HERNIA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
COLITIS ULCERATIVE			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
VOMITING			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
BILE DUCT STONE			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
CHOLELITHIASIS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
ERYTHEMA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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 and urinary disorders			
URINARY RETENTION			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
NEPHROLITHIASIS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
THYROID CYST			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRITIS			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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
BACK PAIN			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
OSTEOARTHRITIS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	5 / 1225 (0.41%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPIDIDYMITIS			

subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
FALLOPIAN TUBE ABSCESS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
COVID-19			
subjects affected / exposed	23 / 1225 (1.88%)	2 / 370 (0.54%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	6 / 23	0 / 2	0 / 1
deaths causally related to treatment / all	2 / 7	0 / 0	0 / 0
CELLULITIS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
BRONCHITIS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 PNEUMONIA			
subjects affected / exposed	17 / 1225 (1.39%)	0 / 370 (0.00%)	2 / 375 (0.53%)
occurrences causally related to treatment / all	6 / 18	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 1
GASTROENTERITIS			
subjects affected / exposed	3 / 1225 (0.24%)	1 / 370 (0.27%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OTITIS MEDIA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
ORCHITIS			

subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIC SEPSIS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS VIRAL			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
MENINGITIS BACTERIAL			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
INFLUENZA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
HEPATITIS A			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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
GENITAL HERPES			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
GASTROENTERITIS VIRAL			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
PENILE ABSCESS			

subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONSILLAR ABSCESS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
URINARY TRACT INFECTION			
subjects affected / exposed	5 / 1225 (0.41%)	0 / 370 (0.00%)	2 / 375 (0.53%)
occurrences causally related to treatment / all	2 / 5	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TYPHOID FEVER			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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
SUBACUTE ENDOCARDITIS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
RENAL ABSCESS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
PYELONEPHRITIS			
subjects affected / exposed	4 / 1225 (0.33%)	0 / 370 (0.00%)	0 / 375 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA MYCOPLASMAL			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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
PNEUMONIA			

subjects affected / exposed	8 / 1225 (0.65%)	0 / 370 (0.00%)	1 / 375 (0.27%)
occurrences causally related to treatment / all	3 / 8	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
UROSEPSIS			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
VAGINAL INFECTION			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
VARICELLA			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
VIRAL INFECTION			
subjects affected / exposed	2 / 1225 (0.16%)	0 / 370 (0.00%)	0 / 375 (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
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
DIABETES MELLITUS INADEQUATE			

CONTROL			
subjects affected / exposed	1 / 1225 (0.08%)	0 / 370 (0.00%)	0 / 375 (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
DEHYDRATION			
subjects affected / exposed	1 / 1225 (0.08%)	1 / 370 (0.27%)	0 / 375 (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

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

Non-serious adverse events	Ocrelizumab	Substudy - Conventional Infusion	Substudy - Shorter Infusion
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1110 / 1225 (90.61%)	251 / 370 (67.84%)	276 / 375 (73.60%)
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	674 / 1225 (55.02%)	154 / 370 (41.62%)	172 / 375 (45.87%)
occurrences (all)	1930	297	350
Nervous system disorders			
HEADACHE			
subjects affected / exposed	295 / 1225 (24.08%)	46 / 370 (12.43%)	37 / 375 (9.87%)
occurrences (all)	639	80	50
PARAESTHESIA			
subjects affected / exposed	98 / 1225 (8.00%)	20 / 370 (5.41%)	15 / 375 (4.00%)
occurrences (all)	124	25	17
DIZZINESS			
subjects affected / exposed	88 / 1225 (7.18%)	12 / 370 (3.24%)	10 / 375 (2.67%)
occurrences (all)	102	12	10
HYPOAESTHESIA			
subjects affected / exposed	91 / 1225 (7.43%)	17 / 370 (4.59%)	11 / 375 (2.93%)
occurrences (all)	113	20	14
General disorders and administration site conditions			

FATIGUE			
subjects affected / exposed	201 / 1225 (16.41%)	28 / 370 (7.57%)	28 / 375 (7.47%)
occurrences (all)	274	32	29
PYREXIA			
subjects affected / exposed	98 / 1225 (8.00%)	7 / 370 (1.89%)	8 / 375 (2.13%)
occurrences (all)	139	12	9
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	91 / 1225 (7.43%)	18 / 370 (4.86%)	9 / 375 (2.40%)
occurrences (all)	116	18	10
NAUSEA			
subjects affected / exposed	87 / 1225 (7.10%)	8 / 370 (2.16%)	10 / 375 (2.67%)
occurrences (all)	109	11	10
Respiratory, thoracic and mediastinal disorders			
OROPHARYNGEAL PAIN			
subjects affected / exposed	113 / 1225 (9.22%)	7 / 370 (1.89%)	9 / 375 (2.40%)
occurrences (all)	156	7	13
COUGH			
subjects affected / exposed	126 / 1225 (10.29%)	13 / 370 (3.51%)	18 / 375 (4.80%)
occurrences (all)	160	15	19
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	84 / 1225 (6.86%)	9 / 370 (2.43%)	8 / 375 (2.13%)
occurrences (all)	109	9	8
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	81 / 1225 (6.61%)	12 / 370 (3.24%)	9 / 375 (2.40%)
occurrences (all)	85	12	9
DEPRESSION			
subjects affected / exposed	75 / 1225 (6.12%)	11 / 370 (2.97%)	11 / 375 (2.93%)
occurrences (all)	88	13	14
ANXIETY			
subjects affected / exposed	62 / 1225 (5.06%)	10 / 370 (2.70%)	8 / 375 (2.13%)
occurrences (all)	69	11	8
Musculoskeletal and connective tissue disorders			

ARTHRALGIA			
subjects affected / exposed	132 / 1225 (10.78%)	17 / 370 (4.59%)	15 / 375 (4.00%)
occurrences (all)	169	21	20
MUSCLE SPASMS			
subjects affected / exposed	68 / 1225 (5.55%)	11 / 370 (2.97%)	11 / 375 (2.93%)
occurrences (all)	76	12	12
BACK PAIN			
subjects affected / exposed	115 / 1225 (9.39%)	12 / 370 (3.24%)	14 / 375 (3.73%)
occurrences (all)	147	15	16
PAIN IN EXTREMITY			
subjects affected / exposed	133 / 1225 (10.86%)	18 / 370 (4.86%)	14 / 375 (3.73%)
occurrences (all)	172	24	14
Infections and infestations			
PHARYNGITIS			
subjects affected / exposed	63 / 1225 (5.14%)	8 / 370 (2.16%)	9 / 375 (2.40%)
occurrences (all)	81	8	9
COVID-19			
subjects affected / exposed	291 / 1225 (23.76%)	14 / 370 (3.78%)	13 / 375 (3.47%)
occurrences (all)	344	14	13
SINUSITIS			
subjects affected / exposed	109 / 1225 (8.90%)	8 / 370 (2.16%)	13 / 375 (3.47%)
occurrences (all)	144	12	14
ORAL HERPES			
subjects affected / exposed	63 / 1225 (5.14%)	5 / 370 (1.35%)	9 / 375 (2.40%)
occurrences (all)	142	18	11
INFLUENZA			
subjects affected / exposed	96 / 1225 (7.84%)	8 / 370 (2.16%)	9 / 375 (2.40%)
occurrences (all)	119	8	9
BRONCHITIS			
subjects affected / exposed	62 / 1225 (5.06%)	6 / 370 (1.62%)	8 / 375 (2.13%)
occurrences (all)	84	6	11
NASOPHARYNGITIS			
subjects affected / exposed	320 / 1225 (26.12%)	58 / 370 (15.68%)	50 / 375 (13.33%)
occurrences (all)	646	81	70
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	196 / 1225 (16.00%)	28 / 370 (7.57%)	35 / 375 (9.33%)
occurrences (all)	301	34	41
URINARY TRACT INFECTION			
subjects affected / exposed	184 / 1225 (15.02%)	20 / 370 (5.41%)	24 / 375 (6.40%)
occurrences (all)	319	30	30

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 November 2016	V2
28 March 2017	V3
27 July 2018	V4
30 July 2018	V5
30 December 2018	V6
23 April 2019	V7
28 April 2020	V8
17 September 2020	V9
23 March 2021	V10

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported