



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-naïve patients with early stage RMSR. The study consisted of screening period up to 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, Data analyst, Carer, 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 Participants | | | | |
| 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 & hand function 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: | |
| <p>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. 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.</p> | |
| 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 at Week 48 (n=602) | 2.48 (± 10.12) | | | |
| Change at Week 96 (n=563) | 1.89 (± 9.98) | | | |
| Change at Week 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 PAPILOMA 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 |
| CERVICOBACHIAL 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 JIROVECI 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