



## Clinical trial results:

### An Open-Label Study To Evaluate the Efficacy and Safety of Ocrelizumab in Subjects With Relapsing Multiple Sclerosis Who Have A Suboptimal Response to an Adequate Course of Disease-Modifying Treatment

#### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2015-005597-38                         |
| Trial protocol           | GB IE SE ES EE DK DE NL BE CZ FI FR IT |
| Global end of trial date |  |

#### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 24 December 2021  |
| First version publication date | 29 October 2020   |
| Version creation reason        | <ul style="list-style-type: none"><li>New data added to full data set</li></ul> Results maintenance |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | MA30005 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02861014 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Interim          |
| Date of interim/final analysis                       | 20 December 2019 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 25 October 2019  |
| Global end of trial reached?                         | No               |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this prospective, multicenter, open-label, efficacy, and safety study is to assess the efficacy and safety of ocrelizumab in subjects with Relapsing Remitting Multiple Sclerosis (RRMS) who have had a suboptimal response to an adequate course of a Disease-Modifying Treatment (DMT).

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following: - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines - Applicable ICH Good Clinical Practice (GCP) Guidelines - Applicable laws and regulations

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 09 September 2016 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Safety            |
| Long term follow-up duration                              | 2 Years           |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 98          |
| Country: Number of subjects enrolled | Sweden: 10         |
| Country: Number of subjects enrolled | Switzerland: 3     |
| Country: Number of subjects enrolled | Turkey: 26         |
| Country: Number of subjects enrolled | United Kingdom: 48 |
| Country: Number of subjects enrolled | Belgium: 28        |
| Country: Number of subjects enrolled | Czech Republic: 44 |
| Country: Number of subjects enrolled | Denmark: 17        |
| Country: Number of subjects enrolled | Estonia: 15        |
| Country: Number of subjects enrolled | Finland: 2         |
| Country: Number of subjects enrolled | France: 30         |
| Country: Number of subjects enrolled | Germany: 139       |
| Country: Number of subjects enrolled | Ireland: 5         |
| Country: Number of subjects enrolled | Italy: 200         |
| Country: Number of subjects enrolled | Netherlands: 9     |
| Country: Number of subjects enrolled | Norway: 6          |
| Worldwide total number of subjects   | 680                |
| EEA total number of subjects         | 651                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 680 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

One additional subject was initially enrolled in error and the information provided is based on the ITT population.

### Pre-assignment

Screening details:

The study consists of a Screening period (up to 4 weeks), an Open-label treatment period (96 weeks; with last dose administered at Week 72), and a Safety Follow-up period of at least 2 years.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|           |             |
|-----------|-------------|
| Arm title | Ocrelizumab |
|-----------|-------------|

Arm description:

Participants received Ocrelizumab as two 300 mg IV infusions on Days 1 and 15 followed by one 600 mg IV infusions administered at Weeks 24, 48, and 72.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Ocrelizumab           |
| Investigational medicinal product code |                       |
| Other name                             | RO4964913             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Ocrelizumab is administered as two 300 mg IV infusions on Days 1 and 15 followed by one 600 mg IV infusions administered at Weeks 24, 48, and 72.

| Number of subjects in period 1 | Ocrelizumab |
|--------------------------------|-------------|
| Started                        | 680         |
| Completed                      | 641         |
| Not completed                  | 39          |
| Physician decision             | 2           |
| Consent withdrawn by subject   | 14          |
| Adverse event, non-fatal       | 7           |
| Study Terminated By Sponsor    | 3           |
| Death                          | 1           |
| Pregnancy                      | 4           |
| Commercial Ocrelizumab         | 3           |
| Lack of efficacy               | 3           |
| Protocol deviation             | 2           |



## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Ocrelizumab |
|-----------------------|-------------|

Reporting group description:

Participants received Ocrelizumab as two 300 mg IV infusions on Days 1 and 15 followed by one 600 mg IV infusions administered at Weeks 24, 48, and 72.

| Reporting group values                             | Ocrelizumab | Total |  |
|--|-------------|-------|--|
| Number of subjects                                 | 680         | 680   |  |
| 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)                               | 680         | 680   |  |
| From 65-84 years                                   | 0           | 0     |  |
| 85 years and over                                  | 0           | 0     |  |
| Age Continuous                                     |             |       |  |
| Units: Years                                       |             |       |  |
| arithmetic mean                                    | 34.2        |       |  |
| standard deviation                                 | ± 8.6       | -     |  |
| Sex: Female, Male                                  |             |       |  |
| Units: Participants                                |             |       |  |
| Female   | 436         | 436   |  |
| Male   | 244         | 244   |  |
| Race (NIH/OMB)                                     |             |       |  |
| Units: Subjects                                    |             |       |  |
| American Indian or Alaska Native                   | 0           | 0     |  |
| Asian  | 3           | 3     |  |
| Native Hawaiian or Other Pacific Islander          | 0           | 0     |  |
| Black or African American                          | 1           | 1     |  |
| White  | 625         | 625   |  |
| More than one race                                 | 2           | 2     |  |
| Unknown or Not Reported                            | 49          | 49    |  |
| Ethnicity (NIH/OMB)                                |             |       |  |
| Units: Subjects                                    |             |       |  |
| Hispanic or Latino                                 | 27          | 27    |  |
| Not Hispanic or Latino                             | 579         | 579   |  |
| Unknown or Not Reported                            | 74          | 74    |  |

## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Ocrelizumab |
| Reporting group description:  |             |
| Participants received Ocrelizumab as two 300 mg IV infusions on Days 1 and 15 followed by one 600 mg IV infusions administered at Weeks 24, 48, and 72. |             |

### Primary: Percentage of Participants With No Evidence of Disease Activity (NEDA) as per Protocol Defined Events During a 96-Week Period

|  |  |
|--|--|
| End point title  | Percentage of Participants With No Evidence of Disease Activity (NEDA) as per Protocol Defined Events During a 96-Week Period <sup>[1]</sup> |
| End point description:   |  |
| A protocol-defined event of disease activity was defined by the occurrence of at least one of the following while on treatment with ocrelizumab: - A protocol-defined relapse (PDR) - 24-week CDP based on increase in EDSS while on treatment with ocrelizumab - A T1 Gd-enhanced lesion after Week 8 - A new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| Week 96  |  |
| 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 statistical analyses provided  |  |

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Ocrelizumab         |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 658                 |  |  |  |
| Units: Percentage                |                     |  |  |  |
| number (confidence interval 95%) | 74.8 (71.3 to 78.0) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Free From a Protocol-Defined Event of Disease Activity During 24 Weeks Period

|  |  |
|--|--|
| End point title  | Percentage of Participants Free From a Protocol-Defined Event of Disease Activity During 24 Weeks Period |
| End point description:   |  |
| A protocol-defined event of disease activity was defined by the occurrence of at least one of the following while on treatment with ocrelizumab: - A protocol-defined relapse (PDR) - 24-week CDP based on increase in EDSS while on treatment with ocrelizumab - A T1 Gd-enhanced lesion after Week 8 - A new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline up to 24 weeks  |  |

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Ocrelizumab         |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 673                 |  |  |  |
| Units: Percentage                |                     |  |  |  |
| number (confidence interval 95%) | 87.1 (84.3 to 89.5) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Free From a Protocol-Defined Event of Disease Activity During 48 Weeks Period

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants Free From a Protocol-Defined Event of Disease Activity During 48 Weeks Period |
|-----------------|--|

End point description:

A protocol-defined event of disease activity was defined by the occurrence of at least one of the following while on treatment with ocrelizumab: - A protocol-defined relapse (PDR) - 24-week CDP based on increase in EDSS while on treatment with ocrelizumab - A T1 Gd-enhanced lesion after Week 8 - A new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 48 weeks

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Ocrelizumab         |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 665                 |  |  |  |
| Units: Percentage                |                     |  |  |  |
| number (confidence interval 95%) | 82.6 (79.5 to 85.4) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to First Protocol-Defined Event of Disease Activity

|                 |  |
|-----------------|--|
| End point title | Time to First Protocol-Defined Event of Disease Activity |
|-----------------|--|

End point description:

9999 = The median time to onset could not be estimated because more than 50% of the mITT population were event-free at the end of the study.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|



End point timeframe:  
Baseline up to 96 Weeks

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Ocrelizumab         |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 680                 |  |  |  |
| Units: Weeks                     |                     |  |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Adjusted mean change from baseline to Week 96 in Expanded Disability Status Scale (EDSS)

|                 |  |
|-----------------|--|
| End point title | Adjusted mean change from baseline to Week 96 in Expanded Disability Status Scale (EDSS) |
|-----------------|--|

End point description:

The EDSS is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks: 24, 48, 72, 96

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Ocrelizumab     |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 680             |  |  |  |
| Units: Points on scale               |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Week 24                              | -0.02 (± 0.64)  |  |  |  |
| Week 48                              | 0.01 (± 0.82)   |  |  |  |
| Week 72                              | -0.03 (± 0.85)  |  |  |  |
| Week 96                              | -0.01 (± 0.85)  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Confirmed Disability Improvement (CDI), Confirmed Disability Progression (CDP), or Stable Disability, as Assessed Using EDSS Scale

|   |  |
|---|--|
| End point title   | Percentage of Participants With Confirmed Disability Improvement (CDI), Confirmed Disability Progression (CDP), or Stable Disability, as Assessed Using EDSS Scale |
| End point description:<br>The EDSS is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Up to Week 96   |  |

|                                  |                 |  |  |  |
|----------------------------------|-----------------|--|--|--|
| <b>End point values</b>          | Ocrelizumab     |  |  |  |
| Subject group type               | Reporting group |  |  |  |
| Number of subjects analysed      | 640             |  |  |  |
| Units: Percentage                |                 |  |  |  |
| number (not applicable)          |                 |  |  |  |
| Confirmed Disability Progression | 13.4            |  |  |  |
| Stable Disability                | 72.2            |  |  |  |
| Confirmed Disability Improvement | 14.4            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with a baseline EDSS score $\geq 2$ with CDI at Week 96

|   |  |
|---|--|
| End point title   | Number of participants with a baseline EDSS score $\geq 2$ with CDI at Week 96 |
| End point description:<br>The EDSS is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Week 96   |  |

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Ocrelizumab     |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 339             |  |  |  |
| Units: Percentage           |                 |  |  |  |
| number (not applicable)     | 17.3            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Annualized protocol-defined relapse rate at Week 96**

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|                 |   |
|-----------------|---|
| End point title | Annualized protocol-defined relapse rate at Week 96 |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 96

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|                                  |                        |  |  |  |
|----------------------------------|------------------------|--|--|--|
| <b>End point values</b>          | Ocrelizumab            |  |  |  |
| Subject group type               | Reporting group        |  |  |  |
| Number of subjects analysed      | 680                    |  |  |  |
| Units: Rate                      |                        |  |  |  |
| number (confidence interval 95%) | 0.030 (0.023 to 0.038) |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Time to onset of 24-week Confirmed Disability Progression**

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|                 |   |
|-----------------|---|
| End point title | Time to onset of 24-week Confirmed Disability Progression |
|-----------------|---|

End point description:

9999 = The median time to onset could not be estimated because more than 50% of the mITT population were event-free at the end of the study.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 96 Weeks

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|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Ocrelizumab         |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 680                 |  |  |  |
| Units: Weeks                     |                     |  |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Time to Onset of First Protocol-Defined Relapse**

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|                 |   |
|-----------------|---|
| End point title | Time to Onset of First Protocol-Defined Relapse |
|-----------------|---|

End point description:

9999 = The median time to onset could not be estimated because more than 50% of the mITT population were event-free at the end of the study.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 96 Weeks

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|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Ocrelizumab         |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 680                 |  |  |  |
| Units: Weeks                     |                     |  |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Time to onset of first new and/or enlarging T2 lesion**

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|                 |   |
|-----------------|---|
| End point title | Time to onset of first new and/or enlarging T2 lesion |
|-----------------|---|

End point description:

9999 = The median time to event could not be estimated because more than 50% of the ITT population were event-free at the end of the study.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 96 Weeks

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|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Ocrelizumab         |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 680                 |  |  |  |
| Units: Weeks                     |                     |  |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Mean number of T1 Gd-enhancing lesions per MRI scan**

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|  |   |
|--|---|
| End point title  | Mean number of T1 Gd-enhancing lesions per MRI scan |
| End point description:<br>9999 = No result could be obtained for Week 96, as the model did not converge. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Weeks: 24, 48, 96  |   |

|                                  |                        |  |  |  |
|----------------------------------|------------------------|--|--|--|
| <b>End point values</b>          | Ocrelizumab            |  |  |  |
| Subject group type               | Reporting group        |  |  |  |
| Number of subjects analysed      | 680                    |  |  |  |
| Units: Rate                      |                        |  |  |  |
| number (confidence interval 95%) |                        |  |  |  |
| Week 24                          | 0.004 (0.001 to 0.014) |  |  |  |
| Week 48                          | 0.004 (0.001 to 0.011) |  |  |  |
| Week 96                          | 9999 (9999 to 9999)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to Week 96 in total T2 lesion volume detected by brain MRI from

|   |  |
|---|--|
| End point title                           | Change from baseline to Week 96 in total T2 lesion volume detected by brain MRI from |
| End point description:                    |  |
| End point type                            | Secondary  |
| End point timeframe:<br>Baseline, Week 96 |  |

|                                      |                        |  |  |  |
|--------------------------------------|------------------------|--|--|--|
| <b>End point values</b>              | Ocrelizumab            |  |  |  |
| Subject group type                   | Reporting group        |  |  |  |
| Number of subjects analysed          | 632                    |  |  |  |
| Units: mL                            |                        |  |  |  |
| arithmetic mean (standard deviation) | -558.6 ( $\pm$ 1194.6) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

**Secondary: Percentage change from baseline to Week 96 in total T2 lesion volume detected by brain MRI**

|                 |  |
|-----------------|--|
| End point title | Percentage change from baseline to Week 96 in total T2 lesion volume detected by brain MRI |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 96

|                                      |                    |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| <b>End point values</b>              | Ocrelizumab        |  |  |  |
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 632                |  |  |  |
| Units: mL                            |                    |  |  |  |
| arithmetic mean (standard deviation) | -8.5 ( $\pm$ 18.2) |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Volume of new and/or enlarging T2 hyperintense lesions volume of lesions per MRI scan**

|                 |   |
|-----------------|---|
| End point title | Volume of new and/or enlarging T2 hyperintense lesions volume of lesions per MRI scan |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 96

|                                      |                     |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| <b>End point values</b>              | Ocrelizumab         |  |  |  |
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 680                 |  |  |  |
| Units: uL                            |                     |  |  |  |
| arithmetic mean (standard deviation) |                     |  |  |  |
| Week 24                              | 21.4 ( $\pm$ 241.7) |  |  |  |
| Week 48                              | 23.1 ( $\pm$ 510.2) |  |  |  |
| Week 96                              | 3.7 ( $\pm$ 41.6)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean number of new and/or enlarging T2 hyperintense lesions per MRI scan

|                 |  |
|-----------------|--|
| End point title | Mean number of new and/or enlarging T2 hyperintense lesions per MRI scan |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 24, 48, 96

| End point values                          | Ocrelizumab            |  |  |  |
|---|------------------------|--|--|--|
| Subject group type                        | Reporting group        |  |  |  |
| Number of subjects analysed               | 680                    |  |  |  |
| Units: Rate                               |                        |  |  |  |
| arithmetic mean (confidence interval 95%) |                        |  |  |  |
| Week 24                                   | 0.053 (0.038 to 0.075) |  |  |  |
| Week 48                                   | 0.009 (0.004 to 0.017) |  |  |  |
| Week 96                                   | 0.011 (0.006 to 0.020) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline at Week 48 and 96 in T1 hypointense lesion volume

|                 |  |
|-----------------|--|
| End point title | Change from baseline at Week 48 and 96 in T1 hypointense lesion volume |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 48, 96

|                                      |                        |  |  |  |
|--------------------------------------|------------------------|--|--|--|
| <b>End point values</b>              | Ocrelizumab            |  |  |  |
| Subject group type                   | Reporting group        |  |  |  |
| Number of subjects analysed          | 680                    |  |  |  |
| Units: mL                            |                        |  |  |  |
| arithmetic mean (standard deviation) |                        |  |  |  |
| Week 48                              | -416.5 ( $\pm$ 1224.3) |  |  |  |
| Week 96                              | -528.5 ( $\pm$ 1144.7) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change from baseline at Week 48 and 96 in T1 hypointense lesion volume

|                        |   |
|------------------------|---|
| End point title        | Percentage change from baseline at Week 48 and 96 in T1 hypointense lesion volume |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Weeks 48, 96           |   |

|                                      |                     |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| <b>End point values</b>              | Ocrelizumab         |  |  |  |
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 680                 |  |  |  |
| Units: Percentage                    |                     |  |  |  |
| arithmetic mean (standard deviation) |                     |  |  |  |
| Week 48                              | -4.0 ( $\pm$ 149.7) |  |  |  |
| Week 96                              | -12.5 ( $\pm$ 21.1) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Adjusted mean change from baseline at Week 48 and 96 in T1 hypointense lesion volume

|                        |  |
|------------------------|--|
| End point title        | Adjusted mean change from baseline at Week 48 and 96 in T1 hypointense lesion volume |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Weeks 48, 96           |  |



|   |                           |  |  |  |
|---|---------------------------|--|--|--|
| <b>End point values</b>                   | Ocrelizumab               |  |  |  |
| Subject group type                        | Reporting group           |  |  |  |
| Number of subjects analysed               | 680                       |  |  |  |
| Units: mL                                 |                           |  |  |  |
| arithmetic mean (confidence interval 95%) |                           |  |  |  |
| Week 48                                   | -461.8 (-613.8 to -309.7) |  |  |  |
| Week 96                                   | -576.5 (-727.0 to -426.1) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Adjusted mean percentage change from baseline in brain volume

|                        |   |
|------------------------|---|
| End point title        | Adjusted mean percentage change from baseline in brain volume |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Weeks 24, 48, 96       |   |

|   |                           |  |  |  |
|---|---------------------------|--|--|--|
| <b>End point values</b>                   | Ocrelizumab               |  |  |  |
| Subject group type                        | Reporting group           |  |  |  |
| Number of subjects analysed               | 680                       |  |  |  |
| Units: Percentage                         |                           |  |  |  |
| arithmetic mean (confidence interval 95%) |                           |  |  |  |
| Week 24                                   | -0.153 (-0.259 to -0.047) |  |  |  |
| Week 48                                   | -0.445 (-0.556 to -0.334) |  |  |  |
| Week 96                                   | -0.805 (-0.940 to -0.669) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Adjusted mean percentage change from baseline in cortical grey matter

**volume**

|                 |  |
|-----------------|--|
| End point title | Adjusted mean percentage change from baseline in cortical grey matter volume |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 48, 96

| End point values                          | Ocrelizumab               |  |  |  |
|---|---------------------------|--|--|--|
| Subject group type                        | Reporting group           |  |  |  |
| Number of subjects analysed               | 680                       |  |  |  |
| Units: Percentage                         |                           |  |  |  |
| arithmetic mean (confidence interval 95%) |                           |  |  |  |
| Week 48                                   | -0.312 (-0.606 to -0.019) |  |  |  |
| Week 96                                   | -0.618 (-0.928 to -0.308) |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Adjusted mean percentage change from baseline in white matter volume**

|                 |  |
|-----------------|--|
| End point title | Adjusted mean percentage change from baseline in white matter volume |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 48, 96

| End point values                          | Ocrelizumab               |  |  |  |
|---|---------------------------|--|--|--|
| Subject group type                        | Reporting group           |  |  |  |
| Number of subjects analysed               | 680                       |  |  |  |
| Units: Percentage                         |                           |  |  |  |
| arithmetic mean (confidence interval 95%) |                           |  |  |  |
| Week 48                                   | -0.382 (-0.609 to -0.154) |  |  |  |
| Week 96                                   | -0.745 (-0.983 to -0.507) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - SDMT Score

|                 |   |
|-----------------|---|
| End point title | Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - SDMT Score |
|-----------------|---|

End point description:

Brief International Cognitive Assessment for MS (BICAMS) is assessing cognitive processing speed and verbal and visual memory. Symbol Digits Modalities Test (SDMT) is assessing processing speed/working memory.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 48, 96

|                                      |                   |  |  |  |
|--------------------------------------|-------------------|--|--|--|
| <b>End point values</b>              | Ocrelizumab       |  |  |  |
| Subject group type                   | Reporting group   |  |  |  |
| Number of subjects analysed          | 680               |  |  |  |
| Units: Points on scale               |                   |  |  |  |
| arithmetic mean (standard deviation) |                   |  |  |  |
| Week 48                              | 2.5 ( $\pm$ 9.8)  |  |  |  |
| Week 96                              | 1.3 ( $\pm$ 10.2) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - BVMT-R Score

|                 |   |
|-----------------|---|
| End point title | Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - BVMT-R Score |
|-----------------|---|

End point description:

Brief International Cognitive Assessment for MS (BICAMS) is assessing cognitive processing speed and verbal and visual memory. Brief Visuospatial Memory Test-Revised (BVMT-R) is assessing learning and visuospatial memory.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 48, 96

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Ocrelizumab     |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 680             |  |  |  |
| Units: Points on scale               |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Week 48                              | -1.9 (± 5.3)    |  |  |  |
| Week 96                              | -1.5 (± 5.4)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - SDMT Score

|   |  |
|---|--|
| End point title   | Percentage change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - SDMT Score |
| End point description:<br>Brief International Cognitive Assessment for MS (BICAMS) is assessing cognitive processing speed and verbal and visual memory. Symbol Digits Modalities Test (SDMT) is assessing processing speed/working memory. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Weeks 48, 96  |  |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Ocrelizumab     |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 680             |  |  |  |
| Units: Percentage                    |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Week 48                              | 7.2 (± 30.8)    |  |  |  |
| Week 96                              | 4.8 (± 30.6)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - BVMT-R Score

|                 |  |
|-----------------|--|
| End point title | Percentage change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS - BVMT-R |
|-----------------|--|

|   |           |
|---|-----------|
|   | Score     |
| End point description:  |           |
| Brief International Cognitive Assessment for MS (BICAMS) is assessing cognitive processing speed and verbal and visual memory. Brief Visuospatial Memory Test-Revised (BVRT-R) is assessing learning and visuospatial memory. |           |
| End point type  | Secondary |
| End point timeframe:  |           |
| Weeks 48, 96  |           |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Ocrelizumab     |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 680             |  |  |  |
| Units: Percentage                    |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Week 48                              | -4.4 (± 31.1)   |  |  |  |
| Week 96                              | -2.0 (± 33.7)   |  |  |  |

### 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 approximately 3 years 2 months |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| <b>End point values</b>                       | Ocrelizumab     |  |  |  |
| Subject group type                            | Reporting group |  |  |  |
| Number of subjects analysed                   | 680             |  |  |  |
| Units: Percentage                             |                 |  |  |  |
| number (not applicable)                       |                 |  |  |  |
| Any AE  | 89.1            |  |  |  |
| SAE   | 7.2             |  |  |  |
| Deaths  | 0.1             |  |  |  |
| AEs leading to study drug discontinuation     | 1.0             |  |  |  |
| SAEs leading to study drug discontinuation    | 0.7             |  |  |  |
| AEs leading to dose modification/interruption | 15.0            |  |  |  |

|                                   |      |  |  |  |
|-----------------------------------|------|--|--|--|
| Infusion-related reactions (IRRs) | 43.2 |  |  |  |
| Serious IRRs                      | 0.1  |  |  |  |
| Infections                        | 66.9 |  |  |  |
| Serious infections                | 1.6  |  |  |  |
| Malignancies                      | 0.4  |  |  |  |
| Pregnancies                       | 0.7  |  |  |  |
| AE of Grade $\geq 3$              | 11.9 |  |  |  |

## Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline to primary cutoff date (up to 3 years 2 months)

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Ocrelizumab |
|-----------------------|-------------|

Reporting group description:

Participants received Ocrelizumab as two 300 mg IV infusions on Days 1 and 15 followed by one 600 mg IV infusions administered at Weeks 24, 48, and 72.

| Serious adverse events  | Ocrelizumab      |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed   | 49 / 680 (7.21%) |  |  |
| number of deaths (all causes)                                       | 1                |  |  |
| number of deaths resulting from adverse events                      | 0                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| BASAL CELL CARCINOMA  |                  |  |  |
| subjects affected / exposed   | 1 / 680 (0.15%)  |  |  |
| occurrences causally related to treatment / all                     | 1 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| BENIGN NEOPLASM OF THYMUS   |                  |  |  |
| subjects affected / exposed   | 1 / 680 (0.15%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| SQUAMOUS CELL CARCINOMA OF THE CERVIX                               |                  |  |  |
| subjects affected / exposed   | 1 / 680 (0.15%)  |  |  |
| occurrences causally related to treatment / all                     | 1 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Vascular disorders  |                  |  |  |
| SHOCK HAEMORRHAGIC  |                  |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Pregnancy, puerperium and perinatal conditions       |                 |  |  |
| ABORTION SPONTANEOUS                                 |                 |  |  |
| subjects affected / exposed                          | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| OEDEMA   |                 |  |  |
| subjects affected / exposed                          | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Reproductive system and breast disorders             |                 |  |  |
| TESTICULAR INFARCTION                                |                 |  |  |
| subjects affected / exposed                          | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| HAEMORRHAGIC OVARIAN CYST                            |                 |  |  |
| subjects affected / exposed                          | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders      |                 |  |  |
| NASAL ULCER  |                 |  |  |
| subjects affected / exposed                          | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Psychiatric disorders                                |                 |  |  |
| COMPLETED SUICIDE                                    |                 |  |  |
| subjects affected / exposed                          | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |
| DELIRIUM   |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| DEPRESSION                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| DEPRESSION SUICIDAL                             |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| HALLUCINATION                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| SUICIDE ATTEMPT                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| ANKLE FRACTURE                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| FACIAL BONES FRACTURE                           |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| INFUSION RELATED REACTION                       |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| RIB FRACTURE                                    |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>TENDON INJURY</b>                            |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>URETERIC INJURY</b>                          |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>UTERINE RUPTURE</b>                          |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cardiac disorders</b>                        |                 |  |  |
| <b>ANGINA PECTORIS</b>                          |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>MYOCARDIAL INFARCTION</b>                    |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Nervous system disorders</b>                 |                 |  |  |
| <b>CEREBRAL VENOUS SINUS THROMBOSIS</b>         |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>GENERALISED TONIC-CLONIC SEIZURE</b>         |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| HEADACHE  |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| MIGRAINE  |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| MULTIPLE SCLEROSIS RELAPSE                      |                 |  |  |
| subjects affected / exposed                     | 3 / 680 (0.44%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| STATUS MIGRAINOSUS                              |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| SUBARACHNOID HAEMORRHAGE                        |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| GRANULOCYTOPENIA                                |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ear and labyrinth disorders                     |                 |  |  |
| VERTIGO   |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| ABDOMINAL PAIN LOWER                            |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| ANAL FISTULA                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| COLITIS ULCERATIVE                              |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| CROHN'S DISEASE                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| ENTEROCOLITIS                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| LUMBAR HERNIA                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| MELAENA   |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| TOOTHACHE                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| HEPATITIS                                       |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| DERMATITIS ATOPIC                               |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| DERMATITIS ALLERGIC                             |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| GUTTATE PSORIASIS                               |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| URTICARIA                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| INTERVERTEBRAL DISC PROTRUSION                  |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| OSTEONECROSIS                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| ANAL ABSCESS                                    |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>GASTROENTERITIS</b>                          |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>OESOPHAGITIS BACTERIAL</b>                   |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>ORAL BACTERIAL INFECTION</b>                 |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>SEPSIS</b>                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>PNEUMONIA</b>                                |                 |  |  |
| subjects affected / exposed                     | 2 / 680 (0.29%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>SINUSITIS</b>                                |                 |  |  |
| subjects affected / exposed                     | 3 / 680 (0.44%) |  |  |
| occurrences causally related to treatment / all | 3 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>SUPERINFECTION FUNGAL</b>                    |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>URINARY TRACT INFECTION</b>                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>VARICELLA ZOSTER VIRUS INFECTION</b>         |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>VIRAL INFECTION</b>                          |                 |  |  |
| subjects affected / exposed                     | 1 / 680 (0.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | Ocrelizumab        |  |  |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 531 / 680 (78.09%) |  |  |
| Injury, poisoning and procedural complications        |                    |  |  |
| <b>INFUSION RELATED REACTION</b>                      |                    |  |  |
| subjects affected / exposed                           | 294 / 680 (43.24%) |  |  |
| occurrences (all)                                     | 569                |  |  |
| Nervous system disorders                              |                    |  |  |
| <b>HEADACHE</b>                                       |                    |  |  |
| subjects affected / exposed                           | 154 / 680 (22.65%) |  |  |
| occurrences (all)                                     | 320                |  |  |
| <b>PARAESTHESIA</b>                                   |                    |  |  |
| subjects affected / exposed                           | 34 / 680 (5.00%)   |  |  |
| occurrences (all)                                     | 47                 |  |  |
| General disorders and administration site conditions  |                    |  |  |
| <b>FATIGUE</b>  |                    |  |  |
| subjects affected / exposed                           | 67 / 680 (9.85%)   |  |  |
| occurrences (all)                                     | 106                |  |  |
| <b>PYREXIA</b>  |                    |  |  |

|   |                          |  |  |
|---|--------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 47 / 680 (6.91%)<br>62   |  |  |
| Gastrointestinal disorders<br>DIARRHOEA<br>subjects affected / exposed<br>occurrences (all)                       | 42 / 680 (6.18%)<br>52   |  |  |
| NAUSEA<br>subjects affected / exposed<br>occurrences (all)  | 38 / 680 (5.59%)<br>40   |  |  |
| Respiratory, thoracic and mediastinal disorders<br>COUGH<br>subjects affected / exposed<br>occurrences (all)      | 47 / 680 (6.91%)<br>56   |  |  |
| OROPHARYNGEAL PAIN<br>subjects affected / exposed<br>occurrences (all)  | 42 / 680 (6.18%)<br>55   |  |  |
| Psychiatric disorders<br>INSOMNIA<br>subjects affected / exposed<br>occurrences (all)                             | 34 / 680 (5.00%)<br>43   |  |  |
| Musculoskeletal and connective tissue disorders<br>ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all) | 37 / 680 (5.44%)<br>40   |  |  |
| BACK PAIN<br>subjects affected / exposed<br>occurrences (all)   | 57 / 680 (8.38%)<br>74   |  |  |
| PAIN IN EXTREMITY<br>subjects affected / exposed<br>occurrences (all)   | 47 / 680 (6.91%)<br>58   |  |  |
| Infections and infestations<br>INFLUENZA<br>subjects affected / exposed<br>occurrences (all)                      | 92 / 680 (13.53%)<br>137 |  |  |
| NASOPHARYNGITIS   |                          |  |  |



|                                   |                    |  |  |
|-----------------------------------|--------------------|--|--|
| subjects affected / exposed       | 210 / 680 (30.88%) |  |  |
| occurrences (all)                 | 449                |  |  |
| ORAL HERPES                       |                    |  |  |
| subjects affected / exposed       | 55 / 680 (8.09%)   |  |  |
| occurrences (all)                 | 116                |  |  |
| SINUSITIS                         |                    |  |  |
| subjects affected / exposed       | 36 / 680 (5.29%)   |  |  |
| occurrences (all)                 | 58                 |  |  |
| UPPER RESPIRATORY TRACT INFECTION |                    |  |  |
| subjects affected / exposed       | 51 / 680 (7.50%)   |  |  |
| occurrences (all)                 | 81                 |  |  |
| URINARY TRACT INFECTION           |                    |  |  |
| subjects affected / exposed       | 70 / 680 (10.29%)  |  |  |
| occurrences (all)                 | 108                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 03 June 2016     | Updates to AE reporting period and safety information and selection criteria. Recommendation on subject observation added. Updates to screening assessments. Update to infusion preparation instructions. Extension of window for laboratory sample collection.                               |
| 28 March 2017    | Change in sample size from 600 to 750 (more subjects were recruited than expected, a result of screening rate being higher than anticipated)  |
| 05 October 2017  | Updates to core safety text. Requirement added for antihistamine pre-treatment. Removal of California Verbal Learning Test 2 from the BICAMS test battery. Removal of the serum sampling for antibody assay. Extension of time window for laboratory assessments before ocrelizumab infusion. |
| 04 November 2018 | Updates to safety risks (substantial change). Information on use of the optional patient diary. Clarification on treatment discontinuation rules for subjects who become pregnant.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported