



## Clinical trial results:

### A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study To Evaluate The Efficacy And Safety Of Ocrelizumab In Comparison To Interferon Beta-1a (Rebif®) In Patients With Relapsing Multiple Sclerosis Summary

|                          |   |
|--------------------------|---|
| EudraCT number           | 2010-020337-99  |
| Trial protocol           | GB FR CZ LV HU FI DE BE SK AT NL LT EE PT BG ES PL IT |
| Global end of trial date |   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 03 June 2016 |
| First version publication date | 03 June 2016 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | WA21092 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01247324 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | F. Hoffmann-La Roche AG   |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070  |
| Public contact               | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
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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                       | 02 April 2015 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 02 April 2015 |
| Global end of trial reached?                         | No            |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of ocrelizumab compared with interferon beta-1a 44 mcg subcutaneous (SC) in patients with relapsing multiple sclerosis (RMS).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 31 August 2011 |
| Long term follow-up planned                               | Yes            |
| Long term follow-up rationale                             | Safety         |
| Long term follow-up duration                              | 11 Months      |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 8           |
| Country: Number of subjects enrolled | Australia: 3           |
| Country: Number of subjects enrolled | Brazil: 18             |
| Country: Number of subjects enrolled | Chile: 1               |
| Country: Number of subjects enrolled | Israel: 4              |
| Country: Number of subjects enrolled | Mexico: 12             |
| Country: Number of subjects enrolled | Peru: 22               |
| Country: Number of subjects enrolled | Russian Federation: 67 |
| Country: Number of subjects enrolled | Serbia: 19             |
| Country: Number of subjects enrolled | Tunisia: 8             |
| Country: Number of subjects enrolled | Ukraine: 30            |
| Country: Number of subjects enrolled | South Africa: 4        |
| Country: Number of subjects enrolled | United States: 210     |
| Country: Number of subjects enrolled | Switzerland: 6         |
| Country: Number of subjects enrolled | Netherlands: 1         |
| Country: Number of subjects enrolled | Poland: 69             |
| Country: Number of subjects enrolled | Portugal: 2            |
| Country: Number of subjects enrolled | Slovakia: 7            |
| Country: Number of subjects enrolled | Spain: 13              |
| Country: Number of subjects enrolled | United Kingdom: 5      |
| Country: Number of subjects enrolled | Austria: 3             |

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Belgium: 11         |
| Country: Number of subjects enrolled | Bulgaria: 38        |
| Country: Number of subjects enrolled | Czech Republic: 130 |
| Country: Number of subjects enrolled | Estonia: 16         |
| Country: Number of subjects enrolled | Finland: 1          |
| Country: Number of subjects enrolled | France: 19          |
| Country: Number of subjects enrolled | Germany: 32         |
| Country: Number of subjects enrolled | Hungary: 14         |
| Country: Number of subjects enrolled | Italy: 19           |
| Country: Number of subjects enrolled | Latvia: 12          |
| Country: Number of subjects enrolled | Lithuania: 17       |
| Worldwide total number of subjects   | 821                 |
| EEA total number of subjects         | 409                 |

Notes:

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### 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)                      | 821 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 1051 subjects were screened for entry into the study. 821 subjects were entered into the double-blind treatment period. Subjects who completed the 96-week double-blind treatment had an option to enter a single group, active treatment open label extension, providing they fulfilled the eligibility criteria.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Double Blind Treatment Period (overall period) |
| Is this the baseline period? | Yes  |
| Allocation method            | Randomised - controlled                        |
| Blinding used                | Double blind                                   |
| Roles blinded                | Subject, Investigator, Monitor, Assessor       |

Blinding implementation details:

Treatment was administered in a double-blind, double-dummy fashion in order to maintain blinding.

### Arms

|                              |                              |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes                          |
| <b>Arm title</b>             | Interferon beta-1a 44 mcg SC |

Arm description:

Subjects with relapsing multiple sclerosis (RMS) who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received interferon beta-1a three times per week (with placebo infusions matching ocrelizumab every 24 weeks).

|  |                        |
|--|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Interferon beta-1a     |
| Investigational medicinal product code |                        |
| Other name                             | Rebif                  |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Subjects received interferon beta-1a 44 microgram (mcg) subcutaneous (SC) injections three times per week (with placebo infusions matching ocrelizumab infusions every 24 weeks).

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

Dosage and administration details:

Subjects received placebo infusions matching ocrelizumab infusions of 300 mg on Days 1 and 15 for the first dose and as a single infusion of 600 mg for all subsequent doses every 24 weeks.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Ocrelizumab |
|------------------|-------------|

Arm description:

Subjects with RMS who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received ocrelizumab every 24 weeks (with placebo injections matching interferon beta-1a SC three times per week).

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

Subjects received ocrelizumab 600 milligram (mg) IV as 300 mg infusions on Days 1 and 15 for the first dose and as a single infusion of 600 mg for all subsequent doses every 24 weeks.

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Subjects received placebo injections matching interferon beta-1a SC three times per week.

| <b>Number of subjects in period 1</b> | Interferon beta-1a<br>44 mcg SC | Ocrelizumab |
|---------------------------------------|---------------------------------|-------------|
| Started                               | 411                             | 410         |
| Completed                             | 340                             | 366         |
| Not completed                         | 71                              | 44          |
| Consent withdrawn by subject          | 13                              | 8           |
| Physician decision                    | -                               | 1           |
| Adverse Event                         | 25                              | 13          |
| Death                                 | 1                               | -           |
| Pregnancy                             | 2                               | 3           |
| Non-compliance with study drug        | 3                               | -           |
| Non-compliance                        | 2                               | -           |
| Protocol Violation                    | 1                               | 2           |
| Unspecified                           | 11                              | 8           |
| Lost to follow-up                     | 1                               | 1           |
| Lack of efficacy                      | 12                              | 8           |

## Baseline characteristics

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Interferon beta-1a 44 mcg SC |
|-----------------------|------------------------------|

Reporting group description:

Subjects with relapsing multiple sclerosis (RMS) who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received interferon beta-1a three times per week (with placebo infusions matching ocrelizumab every 24 weeks).

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

Reporting group description:

Subjects with RMS who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received ocrelizumab every 24 weeks (with placebo injections matching interferon beta-1a SC three times per week).

| Reporting group values             | Interferon beta-1a<br>44 mcg SC | Ocrelizumab | Total |
|------------------------------------|---------------------------------|-------------|-------|
| Number of subjects                 | 411                             | 410         | 821   |
| Age categorical<br>Units: Subjects |                                 |             |       |

|   |               |               |     |
|---|---------------|---------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 36.9<br>± 9.3 | 37.1<br>± 9.3 | -   |
| Gender categorical<br>Units: Subjects                                   |               |               |     |
| Female  | 272           | 270           | 542 |
| Male  | 139           | 140           | 279 |

## End points

### End points reporting groups

|  |                              |
|--|------------------------------|
| Reporting group title  | Interferon beta-1a 44 mcg SC |
| Reporting group description:<br>Subjects with relapsing multiple sclerosis (RMS) who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received interferon beta-1a three times per week (with placebo infusions matching ocrelizumab every 24 weeks). |                              |
| Reporting group title  | Ocrelizumab                  |
| Reporting group description:<br>Subjects with RMS who experienced at least either two documented clinical relapses within 2 years or one clinical relapse within 1 year prior to screening received ocrelizumab every 24 weeks (with placebo injections matching interferon beta-1a SC three times per week).                            |                              |

### Primary: Annualised Relapse Rate (ARR) in Subjects With Relapsing Multiple Sclerosis (MS) at 96 Weeks

|  |  |
|--|--|
| End point title  | Annualised Relapse Rate (ARR) in Subjects With Relapsing Multiple Sclerosis (MS) at 96 Weeks |
| End point description:<br>ARR was calculated as the total number of relapses for all subjects in the treatment group divided by the total subject-years of exposure to that treatment. Intent-to-treat (ITT) population included all randomised subjects in the study. |  |
| End point type   | Primary  |
| End point timeframe:<br>Week 96  |  |

| End point values                 | Interferon beta-1a 44 mcg SC | Ocrelizumab          |  |  |
|----------------------------------|------------------------------|----------------------|--|--|
| Subject group type               | Reporting group              | Reporting group      |  |  |
| Number of subjects analysed      | 411                          | 410                  |  |  |
| Units: relapses                  |                              |                      |  |  |
| number (confidence interval 95%) | 0.292 (0.235 to 0.361)       | 0.156 (0.122 to 0.2) |  |  |

### Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | ARR by Week 96                             |
| Statistical analysis description:<br>Adjusted by Geographical Region (US vs. Rest of World) and baseline EDSS (<4.0 vs. ≥4.0). |  |
| Comparison groups  | Interferon beta-1a 44 mcg SC v Ocrelizumab |

|   |  |
|---|--|
| Number of subjects included in analysis | 821                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.0001                                 |
| Method                                  | Negative Binomial Model                  |
| Parameter estimate                      | Ratio (Ocrelizumab / Interferon beta-1a) |
| Point estimate                          | 0.536                                    |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 0.4                                      |
| upper limit                             | 0.719                                    |

## Secondary: Time to Onset of Confirmed Disability Progression (CDP) for at Least 12 and 24 Weeks During the Double Blind Treatment Period

|                 |   |
|-----------------|---|
| End point title | Time to Onset of Confirmed Disability Progression (CDP) for at Least 12 and 24 Weeks During the Double Blind Treatment Period |
|-----------------|---|

End point description:

Disability progression was defined as an increase in the EDSS score of:

A)  $\geq 1.0$  point from the baseline EDSS score when the baseline score was less than or equal to ( $\leq$ ) 5.5

B)  $\geq 0.5$  point from the baseline EDSS score when the baseline score was  $> 5.5$

This endpoint was considered confirmatory only when results of both studies WA21092 and WA21093 were combined. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit at least 12 weeks or 24 weeks after the initial documentation of neurological worsening. ITT population included all randomised subjects in the study. Here, 99999 indicates median and -99999 and 99999 minimum and maximum of full range as less than 50% of subjects experience onset of CDP.

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

End point timeframe:

Week 96

| End point values              | Interferon beta-1a 44 mcg SC | Ocrelizumab             |  |  |
|-------------------------------|------------------------------|-------------------------|--|--|
| Subject group type            | Reporting group              | Reporting group         |  |  |
| Number of subjects analysed   | 411                          | 410                     |  |  |
| Units: weeks                  |                              |                         |  |  |
| median (full range (min-max)) | 99999 (-99999 to 99999)      | 99999 (-99999 to 99999) |  |  |

## Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | Time to onset CDP at week 12 |
|----------------------------|------------------------------|

Statistical analysis description:

Hazard ratios (HR) were estimated by stratified Cox regression. Stratification factors were Geographical Region (US vs. Rest of World) and baseline EDSS ( $< 4.0$  vs.  $\geq 4.0$ ).

|   |  |
|---|--|
| Comparison groups                       | Interferon beta-1a 44 mcg SC v Ocrelizumab |
| Number of subjects included in analysis | 821  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | = 0.0139                                   |
| Method                                  | Logrank                                    |
| Parameter estimate                      | Hazard ratio (HR)                          |
| Point estimate                          | 0.57                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.37                                       |
| upper limit                             | 0.9  |

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | Time to onset CDP at week 24 |
|-----------------------------------|------------------------------|

Statistical analysis description:

Hazard ratios (HR) were estimated by stratified Cox regression. Stratification factors were Geographical Region (US vs. Rest of World) and baseline EDSS (<4.0 vs. ≥4.0).

|   |  |
|---|--|
| Comparison groups                       | Interferon beta-1a 44 mcg SC v Ocrelizumab |
| Number of subjects included in analysis | 821  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | = 0.0278                                   |
| Method                                  | Logrank                                    |
| Parameter estimate                      | Hazard ratio (HR)                          |
| Point estimate                          | 0.57                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.34                                       |
| upper limit                             | 0.95                                       |

### **Secondary: Number of T1 Gadolinium (Gd)-Enhancing Lesions as Detected by Brain Magnetic Resonance Imaging (MRI) During the Double Blind Treatment**

|                 |  |
|-----------------|--|
| End point title | Number of T1 Gadolinium (Gd)-Enhancing Lesions as Detected by Brain Magnetic Resonance Imaging (MRI) During the Double Blind Treatment |
|-----------------|--|

End point description:

The total number of T1 gadolinium-enhancing lesions for all subjects in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96. ITT population included all randomised subjects in the study.

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

End point timeframe:

Baseline up to week 96

|                             |                              |                 |  |  |
|-----------------------------|------------------------------|-----------------|--|--|
| <b>End point values</b>     | Interferon beta-1a 44 mcg SC | Ocrelizumab     |  |  |
| Subject group type          | Reporting group              | Reporting group |  |  |
| Number of subjects analysed | 411                          | 410             |  |  |
| Units: lesions              |                              |                 |  |  |
| number (not applicable)     | 337                          | 21              |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | T1-Gd lesions                              |
| Statistical analysis description:   |  |
| Adjusted by baseline T1 Gd lesion (present or not), baseline EDSS (<4.0 vs. ≥4.0) and geographical region (US vs. ROW). |  |
| Comparison groups   | Interferon beta-1a 44 mcg SC v Ocrelizumab |
| Number of subjects included in analysis   | 821  |
| Analysis specification  | Pre-specified                              |
| Analysis type   | superiority                                |
| P-value   | < 0.0001                                   |
| Method  | Negative Binomial Model                    |
| Parameter estimate  | Adjusted rate ratio                        |
| Point estimate  | 0.058                                      |
| Confidence interval   |  |
| level   | 95 %                                       |
| sides   | 2-sided                                    |
| lower limit   | 0.032                                      |
| upper limit   | 0.104                                      |

## Secondary: Number of New, and/or Enlarging T2 Hyperintense Lesions as Detected by Brain Magnetic Resonance Imaging (MRI) During the Double Blind Treatment

|   |   |
|---|---|
| End point title   | Number of New, and/or Enlarging T2 Hyperintense Lesions as Detected by Brain Magnetic Resonance Imaging (MRI) During the Double Blind Treatment |
| End point description:  |   |
| The total number of new and/or enlarging T2 lesions for all subjects in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of lesions at Weeks 24, 48, and 96. ITT population included all randomised subjects in the study. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Baseline up to week 96  |   |

|                             |                              |                 |  |  |
|-----------------------------|------------------------------|-----------------|--|--|
| <b>End point values</b>     | Interferon beta-1a 44 mcg SC | Ocrelizumab     |  |  |
| Subject group type          | Reporting group              | Reporting group |  |  |
| Number of subjects analysed | 411                          | 410             |  |  |
| Units: lesions              |                              |                 |  |  |
| number (not applicable)     | 1916                         | 430             |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Enlarging T2 hyperintense lesions          |
| Statistical analysis description:   |  |
| Adjusted by baseline T2 lesion count, baseline EDSS (<4.0 vs. ≥4.0) and geographical region (US vs. ROW). |  |
| Comparison groups   | Interferon beta-1a 44 mcg SC v Ocrelizumab |
| Number of subjects included in analysis   | 821  |
| Analysis specification  | Pre-specified                              |
| Analysis type   | superiority                                |
| P-value   | < 0.0001                                   |
| Method  | Negative Binomial Model                    |
| Parameter estimate  | Adjusted rate ratio                        |
| Point estimate  | 0.229                                      |
| Confidence interval   |  |
| level   | 95 %                                       |
| sides   | 2-sided                                    |
| lower limit   | 0.174                                      |
| upper limit   | 0.3  |

## Secondary: Percentage of Subjects With Confirmed Disability Improvement (CDI) for at Least 12 Weeks

|  |  |
|--|--|
| End point title  | Percentage of Subjects With Confirmed Disability Improvement (CDI) for at Least 12 Weeks |
| End point description:   |  |
| Disability improvement was assessed only for the subgroup of subjects with a baseline EDSS score of ≥ 2.0. It was defined as a reduction in EDSS score of:   |  |
| A) ≥1.0 from the baseline EDSS score when the baseline score was ≥2 and ≤5.5   |  |
| B) ≥ 0.5 when the baseline EDSS score > 5.5.   |  |
| This endpoint was considered confirmatory only when results of both studies WA21092 and WA21093 were combined. ITT population included all randomised subjects in the study. Here, number of subjects analysed signifies number of subjects who were evaluable for the endpoint. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Week 96  |  |

|                                  |                              |                     |  |  |
|----------------------------------|------------------------------|---------------------|--|--|
| <b>End point values</b>          | Interferon beta-1a 44 mcg SC | Ocrelizumab         |  |  |
| Subject group type               | Reporting group              | Reporting group     |  |  |
| Number of subjects analysed      | 306 <sup>[1]</sup>           | 310                 |  |  |
| Units: percentage of subjects    |                              |                     |  |  |
| number (confidence interval 95%) | 12.42 (8.94 to 16.64)        | 20 (15.69 to 24.89) |  |  |

Notes:

[1] - Number of subjects who were evaluable for this endpoint.

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Confirmed Disability Improvement for 12 weeks |
| Statistical analysis description:  |   |
| Cochran-Mantel-Haenszel (CMH) Chi-Squared test was used, stratified by Geographical Region (US vs. Rest of World) and Baseline EDSS (<4.0 vs. ≥4.0). 95 percent (%) confidence interval (CI) of proportion was constructed using Pearson-Clopper method. |   |
| Comparison groups  | Interferon beta-1a 44 mcg SC v Ocrelizumab    |
| Number of subjects included in analysis  | 616   |
| Analysis specification   | Pre-specified                                 |
| Analysis type  | superiority                                   |
| P-value  | = 0.0106                                      |
| Method   | CMH Chi-Squared test (stratified)             |
| Parameter estimate   | Relative risk (stratified)                    |
| Point estimate   | 1.61  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided                                       |
| lower limit  | 1.11  |
| upper limit  | 2.33  |

## Secondary: Number of T1 Hypointense Lesions During the Double Blind Treatment

|   |  |
|---|--|
| End point title   | Number of T1 Hypointense Lesions During the Double Blind Treatment |
| End point description:  |  |
| The total number of new T1-Hypo-Intense Lesions (Chronic Black Holes) for all subjects in the treatment group divided by the total number of brain MRI scans. The total number of lesions is calculated as the sum of the individual number of new lesions at Weeks 24, 48, and 96. ITT population included all randomised subjects in the study. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline up to week 96  |  |

|                             |                              |                 |  |  |
|-----------------------------|------------------------------|-----------------|--|--|
| <b>End point values</b>     | Interferon beta-1a 44 mcg SC | Ocrelizumab     |  |  |
| Subject group type          | Reporting group              | Reporting group |  |  |
| Number of subjects analysed | 411                          | 410             |  |  |
| Units: lesions              |                              |                 |  |  |
| number (not applicable)     | 1307                         | 564             |  |  |

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | T1 Hypointense Lesions                     |
| Statistical analysis description:<br>Adjusted by baseline T1-hypointense lesion count, baseline EDSS (<4.0 vs. ≥4.0) and geographical region (US vs. ROW). |  |
| Comparison groups  | Interferon beta-1a 44 mcg SC v Ocrelizumab |
| Number of subjects included in analysis  | 821  |
| Analysis specification   | Pre-specified                              |
| Analysis type  | superiority                                |
| P-value  | < 0.0001                                   |
| Method   | Adjusted rate ratio                        |
| Parameter estimate   | Adjusted rate ratio                        |
| Point estimate   | 0.428                                      |
| Confidence interval  |  |
| level  | 95 %                                       |
| sides  | 2-sided                                    |
| lower limit  | 0.328                                      |
| upper limit  | 0.557                                      |

## Secondary: Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score to Week 96

|  |   |
|--|---|
| End point title  | Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score to Week 96 |
| End point description:<br>MSFC score consists of: A) Timed 25-Foot walk; B) 9-Hole Peg Test (9-HPT); and C) Paced Auditory Serial Addition Test (PASAT-3 version). The MSFCS is based on the concept that scores for these three dimensions (arm, leg, and cognitive function) are combined to create a single score (the MSFC) that can be used to detect change over time in a group of subjects with MS. Since the three primary measures differ in what they actually measure, a common composite score for the three different measures i.e., Z score was selected for the purpose. MSFC Score = {Z arm, average + Z leg, average + Zcognitive} /3.0.<br>The results from each of these three tests are transformed into Z scores and averaged to yield a composite score for each subject at each time point. ITT population included all randomised subjects in the study. Here, n signifies the number of subjects evaluable at specified time points. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Baseline, Week 96  |   |

| End point values                       | Interferon beta-1a 44 mcg SC | Ocrelizumab     |  |  |
|--|------------------------------|-----------------|--|--|
| Subject group type                     | Reporting group              | Reporting group |  |  |
| Number of subjects analysed            | 411                          | 410             |  |  |
| Units: units on a scale                |                              |                 |  |  |
| arithmetic mean (standard error)       |                              |                 |  |  |
| Unadjusted Baseline mean (n= 359, 360) | 0.028 (± 0.034)              | -0.012 (± 0.04) |  |  |
| Adjusted Week 96 mean (n= 308, 322)    | 0.174 (± 0.031)              | 0.213 (± 0.031) |  |  |

## Statistical analyses

| Statistical analysis title   | MSFC score baseline to week 96             |
|--|--|
| Statistical analysis description:  |  |
| Estimates are from analysis based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix: Change = Baseline MSFCS Score + Geographical Region + Baseline EDSS (< 4.0 vs. ≥ 4.0) + Week + Treatment + Treatment*Week (repeated values over Week) + Baseline MSFCS Score*Week. |  |
| Comparison groups  | Interferon beta-1a 44 mcg SC v Ocrelizumab |
| Number of subjects included in analysis  | 821  |
| Analysis specification   | Pre-specified                              |
| Analysis type  | superiority                                |
| P-value  | = 0.3261                                   |
| Method   | mixed-effect model of repeated measures    |
| Parameter estimate   | Difference in Adjusted Means               |
| Point estimate   | 0.039                                      |
| Confidence interval  |  |
| level  | 95 %                                       |
| sides  | 2-sided                                    |
| lower limit  | -0.039                                     |
| upper limit  | 0.116                                      |
| Variability estimate   | Standard error of the mean                 |
| Dispersion value   | 0.039                                      |

## Secondary: Percent Change in Brain Volume as Detected by Brain Magnetic Resonance Imaging (MRI) From Week 24 to Week 96

|  |  |
|--|--|
| End point title  | Percent Change in Brain Volume as Detected by Brain Magnetic Resonance Imaging (MRI) From Week 24 to Week 96 |
| End point description:   |  |
| Brain volume was recorded as an absolute "normalized" value at the baseline visit then recorded at subsequent visits as a percentage change relative to the absolute value at the baseline visit. Therefore, brain volume at Week 24 was calculated as the brain volume at the baseline visit multiplied by 1 + ([percentage change in brain volume from baseline visit to Week 24]/100). Estimates are from analysis based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix: Percentage Change = Brain Volume at Week 24 + Geographical Region (US vs. ROW) + Baseline EDSS (< 4.0 vs. ≥ 4.0) + Week + Treatment + Treatment*Week (repeated values over Week) + Brain Volume at Week 24*Week. ITT population included all randomised subjects in the study. Here, number of subjects analysed signifies number of subjects who were evaluable for the endpoint. |  |
| End point type   | Secondary  |

End point timeframe:

From Week 24 up to Week 96

|                                  |                                    |                          |  |  |
|----------------------------------|------------------------------------|--------------------------|--|--|
| <b>End point values</b>          | Interferon<br>beta-1a 44<br>mcg SC | Ocrelizumab              |  |  |
| Subject group type               | Reporting group                    | Reporting group          |  |  |
| Number of subjects analysed      | 267                                | 281                      |  |  |
| Units: percent change            |                                    |                          |  |  |
| arithmetic mean (standard error) | -0.741 ( $\pm$<br>0.046)           | -0.572 ( $\pm$<br>0.044) |  |  |

### Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Percent change in brain volume             |
| Statistical analysis description:  |  |
| Estimates are from analysis based on MMRM using unstructured covariance matrix: Percentage Change = Brain Volume at Week 24 + Geographical Region + Baseline EDSS (< 4.0 vs. $\geq$ 4.0) + Week + Treatment + Treatment*Week (repeated values over Week) + Brain Volume at Week 24*Week. |  |
| Comparison groups  | Interferon beta-1a 44 mcg SC v Ocrelizumab |
| Number of subjects included in analysis  | 548  |
| Analysis specification   | Pre-specified                              |
| Analysis type  | superiority                                |
| P-value  | = 0.0042                                   |
| Method   | MMRM                                       |
| Parameter estimate   | Difference in Adjusted Means               |
| Point estimate   | 0.168                                      |
| Confidence interval  |  |
| level  | 95 %                                       |
| sides  | 2-sided                                    |
| lower limit  | 0.053                                      |
| upper limit  | 0.283                                      |
| Variability estimate   | Standard error of the mean                 |
| Dispersion value   | 0.058                                      |

### Secondary: Change From Baseline in Short Form Health Survey-36 (SF-36) Physical Component Summary (PCS) Score at Week 96

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Short Form Health Survey-36 (SF-36) Physical Component Summary (PCS) Score at Week 96 |
|-----------------|---|

End point description:

The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores (domains) as well as psychometrically based physical and mental health summary measures. The SF-36 taps 8 health concepts: physical functioning, bodily pain, physical role functioning, emotional role functioning, emotional well-being, social functioning, vitality, and general health perceptions. The 8 scales are further summarized to 2 distinct higher-ordered clusters: the PCS and mental composite t-score (MCS). The range for all 8 domains as well as for the composite t-scores is from 0 to 100 with 100 as best possible health status and 0 as worst health status.

Descriptive statistics at baseline include subjects with assessment at baseline and at least one post-baseline value. ITT population included all randomised subjects in the study. Here, n signifies the number of subjects evaluable at specified time points.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 96    |           |

| End point values                             | Interferon beta-1a 44 mcg SC | Ocrelizumab      |  |  |
|--|------------------------------|------------------|--|--|
| Subject group type                           | Reporting group              | Reporting group  |  |  |
| Number of subjects analysed                  | 411                          | 410              |  |  |
| Units: units on a scale                      |                              |                  |  |  |
| arithmetic mean (standard error)             |                              |                  |  |  |
| Unadjusted Baseline mean (n= 338, 357)       | 45.399 (± 0.529)             | 45.065 (± 0.507) |  |  |
| Adjusted mean change at week 96(n= 276, 315) | -0.657 (± 0.475)             | 0.036 (± 0.456)  |  |  |

## Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | SF-36 PCS score at week 96                 |
| Statistical analysis description:  |  |
| Estimates are from analysis based on MMRM using unstructured covariance matrix: Change = Baseline PCS Score + Geographical Region + Baseline EDSS (< 4.0 vs. ≥ 4.0) + Week + Treatment + Treatment*Week (repeated values over Week) + Baseline PCS Score*Week. |  |
| Comparison groups  | Interferon beta-1a 44 mcg SC v Ocrelizumab |
| Number of subjects included in analysis  | 821  |
| Analysis specification   | Pre-specified                              |
| Analysis type  | superiority                                |
| P-value  | = 0.2193                                   |
| Method   | MMRM                                       |
| Parameter estimate   | Difference in Adjusted Means               |
| Point estimate   | 0.693                                      |
| Confidence interval  |  |
| level  | 95 %                                       |
| sides  | 2-sided                                    |
| lower limit  | -0.414                                     |
| upper limit  | 1.8  |
| Variability estimate   | Standard error of the mean                 |
| Dispersion value   | 0.564                                      |

## Secondary: Percentage of Subjects who Have No Evidence of Disease Activity (NEDA) up to Week 96

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects who Have No Evidence of Disease Activity (NEDA) up to Week 96 |
|-----------------|--|

**End point description:**

NEDA was defined only for subjects with a baseline EDSS score  $\geq 2.0$ . Subjects who completed the 96 week treatment period were considered as having evidence of disease activity if at least one protocol-defined relapse (PDR), a CDP event or at least one MRI scan showing MRI activity (defined as Gd-enhancing T1 lesions, or new or enlarging T2 lesions) was reported during the 96-week treatment period, otherwise the subject was considered as having NEDA. ITT population included all randomised subjects in the study. Here, number of subjects analysed signifies number of subjects who were evaluable for the endpoint.

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

**End point timeframe:**

Week 96

| End point values                 | Interferon beta-1a 44 mcg SC | Ocrelizumab         |  |  |
|----------------------------------|------------------------------|---------------------|--|--|
| Subject group type               | Reporting group              | Reporting group     |  |  |
| Number of subjects analysed      | 291 <sup>[2]</sup>           | 289 <sup>[3]</sup>  |  |  |
| Units: percentage of subjects    |                              |                     |  |  |
| number (confidence interval 95%) | 27.1 (22.1 to 32.6)          | 47.4 (41.5 to 53.3) |  |  |

**Notes:**

[2] - Number of subjects who were evaluable for this endpoint.

[3] - Number of subjects who were evaluable for this endpoint.

**Statistical analyses**

|                                   |                 |
|-----------------------------------|-----------------|
| <b>Statistical analysis title</b> | NEDA at week 96 |
|-----------------------------------|-----------------|

**Statistical analysis description:**

Analysed using CMH test, stratified by Geographical Region (US vs. Rest of World) and Baseline EDSS ( $<4.0$  vs.  $\geq 4.0$ ). 95% CI of proportion was constructed using Pearson-Clopper method

|   |  |
|---|--|
| Comparison groups                       | Interferon beta-1a 44 mcg SC v Ocrelizumab |
| Number of subjects included in analysis | 580  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | $< 0.0001$                                 |
| Method                                  | CMH Chi-Squared test (stratified)          |
| Parameter estimate                      | Relative risk (stratified)                 |
| Point estimate                          | 1.74                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 1.39                                       |
| upper limit                             | 2.17                                       |

**Secondary: Number of Subjects With Adverse Events (AEs)**

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Adverse Events (AEs) |
|-----------------|--|

**End point description:**

AEs included infusion related reactions (IRRs) and serious MS relapses, but excluded non-serious MS relapses. Serious Adverse Events (SAEs) included serious MS relapses and serious IRRs. The safety

population included all subjects who received any study drug.

|                        |           |
|------------------------|-----------|
| End point type         | Secondary |
| End point timeframe:   |           |
| Baseline up to Week 96 |           |

|                             |                                    |                 |  |  |
|-----------------------------|------------------------------------|-----------------|--|--|
| <b>End point values</b>     | Interferon<br>beta-1a 44<br>mcg SC | Ocrelizumab     |  |  |
| Subject group type          | Reporting group                    | Reporting group |  |  |
| Number of subjects analysed | 409                                | 408             |  |  |
| Units: subjects             | 331                                | 327             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Exposure to Ocrelizumab (Area Under the Concentration - Time Curve)

|                 |  |
|-----------------|--|
| End point title | Exposure to Ocrelizumab (Area Under the Concentration - Time Curve) <sup>[4]</sup> |
|-----------------|--|

End point description:

The pharmacokinetics population included all subjects in the ocrelizumab group who had at least 1 measurable concentration value.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 96              |           |

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data was only planned to be reported for Ocrelizumab reporting arm.

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Ocrelizumab     |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 393             |  |  |  |
| Units: microgram per millilitre*day  |                 |  |  |  |
| arithmetic mean (standard deviation) | 3513 (± 955)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Anti-Drug Antibodies (ADAs) to Ocrelizumab

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Anti-Drug Antibodies (ADAs) to Ocrelizumab |
|-----------------|--|

---

**End point description:**

Number of subjects positive for anti-drug antibodies (ADAs) to ocrelizumab is the number of post-baseline evaluable subjects determined to have treatment-induced ADA or treatment-enhanced ADA during the study period. Baseline evaluable subjects with an ADA assay result from a baseline sample(s). The safety population included all subjects who received any study drug. Here, n signifies the number of subjects evaluable at the specified time points.

---

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

---

**End point timeframe:**

Baseline up to week 96

---

| <b>End point values</b>                         | Interferon<br>beta-1a 44<br>mcg SC | Ocrelizumab     |  |  |
|---|------------------------------------|-----------------|--|--|
| Subject group type                              | Reporting group                    | Reporting group |  |  |
| Number of subjects analysed                     | 409                                | 408             |  |  |
| Units: subjects                                 |                                    |                 |  |  |
| Positive sample at baseline (n= 397,<br>396)    | 2                                  | 1               |  |  |
| Positive for ADA post-baseline (n= 401,<br>402) | 2                                  | 1               |  |  |

---

**Statistical analyses**

No statistical analyses for this end point

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## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline to Week 96 (Double Blind Treatment Period)

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Interferon beta-1a |
|-----------------------|--------------------|

Reporting group description:

Subjects with relapsing multiple sclerosis (RMS) who experienced at least either two documented clinical attacks within 2 years or one clinical attack within 1 year prior to screening received interferon beta-1a three times per week (with placebo infusions matching ocrelizumab every 24 weeks).

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

Reporting group description:

Subjects with RMS who experienced at least either two documented clinical attacks within 2 years or one clinical attack within 1 year prior to screening received ocrelizumab every 24 weeks (with placebo injections matching interferon beta-1a SC three times per week).

| Serious adverse events  | Interferon beta-1a | Ocrelizumab      |  |
|---|--------------------|------------------|--|
| Total subjects affected by serious adverse events                   |                    |                  |  |
| subjects affected / exposed   | 32 / 409 (7.82%)   | 28 / 408 (6.86%) |  |
| number of deaths (all causes)                                       | 1                  | 0                |  |
| number of deaths resulting from adverse events                      | 0                  | 0                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                  |  |
| Invasive ductal breast carcinoma                                    |                    |                  |  |
| subjects affected / exposed   | 0 / 409 (0.00%)    | 2 / 408 (0.49%)  |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 2            |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0            |  |
| Uterine leiomyoma   |                    |                  |  |
| subjects affected / exposed   | 2 / 409 (0.49%)    | 0 / 408 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 2              | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0            |  |
| Mantle cell lymphoma  |                    |                  |  |
| subjects affected / exposed   | 1 / 409 (0.24%)    | 0 / 408 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0            |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Renal cancer   |                 |                 |  |
| subjects affected / exposed                          | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Salivary gland adenoma                               |                 |                 |  |
| subjects affected / exposed                          | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                      |                 |                 |  |
| Mammoplasty  |                 |                 |  |
| subjects affected / exposed                          | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 0 / 409 (0.00%) | 2 / 408 (0.49%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Immune system disorders                              |                 |                 |  |
| Drug hypersensitivity                                |                 |                 |  |
| subjects affected / exposed                          | 1 / 409 (0.24%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders             |                 |                 |  |
| Endometriosis  |                 |                 |  |
| subjects affected / exposed                          | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Menorrhagia  |                 |                 |  |
| subjects affected / exposed                          | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Ovarian cyst   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Hyperventilation                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinus congestion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Depression                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 2 / 408 (0.49%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anxiety   |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Completed suicide                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Suicide attempt                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Ankle fracture                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Craniocerebral injury                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hand fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infusion related reaction                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multiple injuries                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Overdose  |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural haematoma                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural pain                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tibia fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Multiple sclerosis relapse                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 409 (0.73%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epilepsy  |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure   |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 2 / 408 (0.49%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aphasia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysarthria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ruptured cerebral aneurysm                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica  |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Leukopenia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Retinal artery occlusion                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 2 / 408 (0.49%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis chronic                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Muscle spasms                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rheumatoid Arthritis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 2 / 408 (0.49%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess limb                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 409 (0.49%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 409 (0.49%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute tonsillitis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Biliary sepsis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterocolitis infectious                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes simplex                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 409 (0.00%) | 1 / 408 (0.25%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injection site cellulitis                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Perirectal abscess                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic arthritis staphylococcal                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 409 (0.24%) | 0 / 408 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Interferon beta-1a | Ocrelizumab        |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 257 / 409 (62.84%) | 241 / 408 (59.07%) |  |
| Injury, poisoning and procedural complications        |                    |                    |  |
| Infusion related reaction                             |                    |                    |  |
| subjects affected / exposed                           | 30 / 409 (7.33%)   | 125 / 408 (30.64%) |  |
| occurrences (all)                                     | 46                 | 234                |  |
| Nervous system disorders                              |                    |                    |  |
| Headache  |                    |                    |  |
| subjects affected / exposed                           | 54 / 409 (13.20%)  | 33 / 408 (8.09%)   |  |
| occurrences (all)                                     | 64                 | 51                 |  |
| General disorders and administration site conditions  |                    |                    |  |
| Influenza like illness                                |                    |                    |  |
| subjects affected / exposed                           | 85 / 409 (20.78%)  | 15 / 408 (3.68%)   |  |
| occurrences (all)                                     | 97                 | 15                 |  |
| Injection site erythema                               |                    |                    |  |

|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 74 / 409 (18.09%)<br>76 | 0 / 408 (0.00%)<br>0    |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 28 / 409 (6.85%)<br>33  | 21 / 408 (5.15%)<br>22  |  |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)                           | 24 / 409 (5.87%)<br>24  | 28 / 408 (6.86%)<br>32  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 15 / 409 (3.67%)<br>17  | 21 / 408 (5.15%)<br>22  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 28 / 409 (6.85%)<br>29  | 25 / 408 (6.13%)<br>26  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 20 / 409 (4.89%)<br>25  | 25 / 408 (6.13%)<br>28  |  |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)        | 56 / 409 (13.69%)<br>81 | 52 / 408 (12.75%)<br>93 |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                             | 35 / 409 (8.56%)<br>44  | 59 / 408 (14.46%)<br>83 |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)   | 43 / 409 (10.51%)<br>55 | 43 / 408 (10.54%)<br>61 |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)   | 25 / 409 (6.11%)<br>27  | 19 / 408 (4.66%)<br>23  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 01 June 2011      | 1. The study design has been changed from rater blind to double blind, double dummy design to improve the robustness of the study.<br>2. The 400 mg dose of ocrelizumab has been removed leaving a single dose of ocrelizumab 600 mg; as a consequence the total number of subjects has decreased from 1200 to 800 (due to the removal of the 400 mg dose arm). The 600 mg dose of ocrelizumab has been established as the lowest, maximally effective dose, based on the results from phase II study in RRMS (WA21493/ACT4422g). |
| 15 June 2012      | 1. Dosing preparation and infusion guidance were revised to simplify the preparation of infusion bags and dosing procedures.<br>2. Specific eligibility cut-off values for immunoglobulin M (IgM) and immunoglobulin G (IgG) and the re-treatment criteria for IgG were modified to reflect the central lab reference ranges.   |
| 14 March 2013     | 1. Inclusion of an OLE phase under the same protocol.   |
| 04 September 2014 | 1. Update to the Statistical Considerations and Analytical Plan section of the protocol in line with the SAP amendment to implement European Medicines Agency (EMA) Scientific Advice and to increase statistical rigor.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported