# Clinical trial results:
# A Phase 3, Multi-center, Randomized, Double-Blind, Double-Dummy, Active-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients

## Summary

| | |
|---|---|
| EudraCT number | 2014-002320-27 |
| Trial protocol | EE PT LV SE NL BG PL ES LT HU GB HR |
| Global end of trial date | 22 December 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 14 January 2018 |
| First version publication date | 14 January 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | RPC01-301 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02294058 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Celgene International Sarle II |
| Sponsor organisation address | Rue des Moulins 4, 2108 Couvet, Switzerland, |
| Public contact | ClinicalTrialDisclosure, Celgene Corporation, +1 8882601599, ClinicalTrialDisclosure@celgene.com |
| Scientific contact | James Sheffield, Celgene Corporation, +1 619-371-1506, JSheffield@Celgene.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 08 February 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 22 December 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess whether the clinical efficacy of RPC1063 is superior to interferon (IFN) β-1a (Avonex®) in reducing the rate of clinical relapses in patients with Relapsing Multiple Sclerosis (RMS).

Protection of trial subjects:

Patient Confidentiality. This study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 03 December 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Belarus: 123 |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 12 |
| Country: Number of subjects enrolled | Bulgaria: 16 |
| Country: Number of subjects enrolled | Croatia: 2 |
| Country: Number of subjects enrolled | Estonia: 16 |
| Country: Number of subjects enrolled | Georgia: 62 |
| Country: Number of subjects enrolled | Germany: 14 |
| Country: Number of subjects enrolled | Latvia: 6 |
| Country: Number of subjects enrolled | Lithuania: 4 |
| Country: Number of subjects enrolled | Moldova, Republic of: 5 |
| Country: Number of subjects enrolled | New Zealand: 7 |
| Country: Number of subjects enrolled | Poland: 259 |
| Country: Number of subjects enrolled | Portugal: 25 |
| Country: Number of subjects enrolled | Romania: 29 |
| Country: Number of subjects enrolled | Russian Federation: 272 |
| Country: Number of subjects enrolled | Serbia: 65 |
| Country: Number of subjects enrolled | Spain: 9 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | Ukraine: 382 |
| Country: Number of subjects enrolled | United States: 36 |

| | |
|---|---|
| Worldwide total number of subjects | 1346 |
| EEA total number of subjects | 382 |

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 1346 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted in the United States, Eastern and Western Europe and New Zealand. 1346 participants were randomized from 152 sites in 20 countries,

### Pre-assignment

Screening details:

Participant were randomized 1:1:1 ratio to one of three treatment groups. Randomization was stratified by baseline Expanded Disability Status Scale (EDSS) score (≤ 3.5, > 3.5) and country.

### Period 1

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

Blinding implementation details:

A "dual assessor" approach was used to evaluate efficacy and safety to prevent potential unblinding as result of observed efficacy, AEs, or laboratory changes. Each site had 2 investigators: a principal or treating investigator and a blinded evaluator who was the EDSS evaluator. The EDSS evaluator was responsible for the administering the EDSS and did not have access to other patient data prior to EDSS data when performing exams.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Interferon Beta-1a (IFN β-1a) |

Arm description:

Participants received IFN β-1a 30 µg intramuscular (IM) injection weekly and matching placebo capsules (identical in physical appearance to ozanimod) orally every day for at least one year.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo capsules (identical in physical appearance to Ozanimod) orally every day for one year

| | |
|---|---|
| Investigational medicinal product name | Interferon Beta-1a (IFN β-1a) |
| Investigational medicinal product code | |
| Other name | Avonex |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

IFN β-1a 30 µg IM weekly for one year

| | |
|---|---|
| **Arm title** | Ozanimod 1 mg |

Arm description:

Participants received ozanimod 1 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for at least one year.

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

| | |
|---|---|
| Investigational medicinal product name | Ozanimod |
| Investigational medicinal product code | RPC-1063 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Ozanimod 1 mg capsules PO daily for one year

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Intramuscular placebo injection (identical in physical appearance to IFN β-1a) every week for one year

| | |
|---|---|
| **Arm title** | Ozanimod 0.5 mg |

Arm description:

Participants received ozanimod 0.5 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for at least one year.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ozanimod |
| Investigational medicinal product code | RPC-1063 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Ozanimod 0.5 mg capsules PO daily for one year

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Intramuscular placebo injection (identical in physical appearance to IFN β-1a) every week for one year

| **Number of subjects in period 1** | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg |
|---|---|---|---|
| Started | 448 | 447 | 451 |
| Completed | 412 | 418 | 425 |
| Not completed | 36 | 29 | 26 |
| Consent withdrawn by subject | 10 | 13 | 14 |
| Physician decision | 2 | - | 1 |
| Adverse event, non-fatal | 16 | 13 | 7 |
| Miscellaneous | 4 | 1 | 1 |
| Lost to follow-up | 1 | 2 | - |
| Lack of efficacy | 3 | - | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Interferon Beta-1a (IFN β-1a) |
| Reporting group description: | |
| Participants received IFN β-1a 30 µg intramuscular (IM) injection weekly and matching placebo capsules (identical in physical appearance to ozanimod) orally every day for at least one year. | |
| Reporting group title | Ozanimod 1 mg |
| Reporting group description: | |
| Participants received ozanimod 1 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for at least one year. | |
| Reporting group title | Ozanimod 0.5 mg |
| Reporting group description: | |
| Participants received ozanimod 0.5 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for at least one year. | |

| Reporting group values | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg |
|---|---|---|---|
| Number of subjects | 448 | 447 | 451 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 448 | 447 | 451 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 35.9 | 34.8 | 36.0 |
| standard deviation | ± 9.11 | ± 9.24 | ± 9.43 |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female | 300 | 283 | 311 |
| Male | 148 | 164 | 140 |
| Race<br>Units: Subjects | | | |
| White | 447 | 446 | 447 |
| Black | 0 | 0 | 2 |
| Asian | 0 | 1 | 1 |
| Other | 1 | 0 | 1 |
| Region, Category<br>Units: Subjects | | | |
| Eastern Europe | 419 | 415 | 419 |
| Rest of World | 29 | 32 | 32 |

| | | | |
|---|---|---|---|
| Age at MS Symptom Onset (years)<br>Units: years | | | |
| arithmetic mean | 29.5 | 28.4 | 29.3 |
| standard deviation | ± 8.92 | ± 8.42 | ± 9.25 |
| Age at MS Diagnosis<br>Units: Years | | | |
| arithmetic mean | 32.7 | 31.6 | 32.7 |
| standard deviation | ± 9.01 | ± 8.81 | ± 9.49 |
| Years Since MS Diagnosis<br>Units: Years | | | |
| arithmetic mean | 3.71 | 3.60 | 3.70 |
| standard deviation | ± 4.361 | ± 4.193 | ± 4.518 |
| Expanded Disability Status Scale (EDSS) at Baseline | | | |
| The EDSS is a scale for assessing disability in 8 functional systems (visual, brain stem, pyramidal, cerebellar, sensory, bowel & bladder, cerebral, ambulation and other functions). Based on scores in these 8 functional systems, an overall score ranging from 0 (normal) to 10 (death due to MS) is assigned. Participants with EDSS scores of 0.0 to 4.5 are fully ambulatory; patients with EDSS scores of 5.0 to 9.5 have impaired ambulation. | | | |
| Units: units on a scale | | | |
| arithmetic mean | 2.62 | 2.61 | 2.65 |
| standard deviation | ± 1.138 | ± 1.160 | ± 1.135 |
| Years Since MS Symptom Onset<br>Units: years | | | |
| arithmetic mean | 6.88 | 7.16 | 6.85 |
| standard deviation | ± 5.877 | ± 6.255 | ± 6.449 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 1346 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 1346 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female | 894 | | |
| Male | 452 | | |
| Race<br>Units: Subjects | | | |
| White | 1340 | | |
| Black | 2 | | |

| | | | |
|---|---|---|---|
| Asian | 2 | | |
| Other | 2 | | |
| Region, Category<br>Units: Subjects | | | |
| Eastern Europe | 1253 | | |
| Rest of World | 93 | | |
| Age at MS Symptom Onset (years)<br>Units: years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Age at MS Diagnosis<br>Units: Years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Years Since MS Diagnosis<br>Units: Years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Expanded Disability Status Scale (EDSS) at Baseline | | | |
| The EDSS is a scale for assessing disability in 8 functional systems (visual, brain stem, pyramidal, cerebellar, sensory, bowel & bladder, cerebral, ambulation and other functions). Based on scores in these 8 functional systems, an overall score ranging from 0 (normal) to 10 (death due to MS) is assigned. Participants with EDSS scores of 0.0 to 4.5 are fully ambulatory; patients with EDSS scores of 5.0 to 9.5 have impaired ambulation. | | | |
| Units: units on a scale<br>arithmetic mean<br>standard deviation | <br><br>- | | |
| Years Since MS Symptom Onset<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br>- | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Interferon Beta-1a (IFN β-1a) |
| Reporting group description: | |
| Participants received IFN β-1a 30 µg intramuscular (IM) injection weekly and matching placebo capsules (identical in physical appearance to ozanimod) orally every day for at least one year. | |
| Reporting group title | Ozanimod 1 mg |
| Reporting group description: | |
| Participants received ozanimod 1 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for at least one year. | |
| Reporting group title | Ozanimod 0.5 mg |
| Reporting group description: | |
| Participants received ozanimod 0.5 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for at least one year. | |
| Subject analysis set title | IFN β-1a |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Participants received IFN β-1a 30 µg intramuscular (IM) injection weekly and matching placebo capsules (identical in physical appearance to Ozanimod) orally every day for one year. | |
| Subject analysis set title | Ozanimod 1 mg |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Participants received Ozanimod 1 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to Interferon) weekly for one year. | |
| Subject analysis set title | Ozanimod 0.5 mg |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Participants received Ozanimod 0.5 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to Interferon) weekly for one year. | |

### Primary: Adjusted Annualized Relapse Rate (ARR) During the Treatment Period

| | |
|---|---|
| End point title | Adjusted Annualized Relapse Rate (ARR) During the Treatment Period |
| End point description: | |
| The relapse rate was based on confirmed relapses. Relapses that met the clinical criteria for a relapse and were accompanied by objective neurological worsening (based upon EDSS evaluated by an independent, blinded EDSS evaluator) were confirmed by the treating investigator. A relapse was defined as new or recurrent neurological symptoms preceded by a relatively stable or improving neurological state of at least 30 days (less than 30 days following the onset of a protocol-defined relapse was considered part of the same relapse). Symptoms must have persisted for >24 hours and should not be attributable to confounding clinical factors. The adjusted annualized relapse rate is based on the Poisson regression model, adjusted for region (Eastern Europe vs Rest of World), age at Baseline, and the baseline number of GdE lesions, and included the natural log transformation of time on study as an offset term. The Intent to Treat Population was included. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 2.5 years | |

| End point values | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 448 | 447 | 451 | |
| Units: Relapses/year | | | | |
| least squares mean (confidence interval 95%) | 0.350 (0.279 to 0.440) | 0.181 (0.140 to 0.236) | 0.241 (0.188 to 0.308) | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |
| Number of subjects included in analysis | 895 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | < 0.0001 [2] |
| Method | Poisson regression model |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.518 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.405 |
| upper limit | 0.663 |

Notes:

[1] - To account for multiple comparisons, each of the 2 treatment comparisons was tested at the alpha = 0.025 level.

[2] - Adjusted for region, baseline age, number of Gadolinium Enhancing (GdE) lesions and included the natural log transformation of time as an offset term.

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 0.5 mg |
| Number of subjects included in analysis | 899 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.0013 [4] |
| Method | Poisson Regression Model |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.688 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.547 |
| upper limit | 0.864 |

Notes:

[3] - To account for multiple comparisons, each of the 2 treatment comparisons was tested at the alpha = 0.025 level.

[4] - Adjusted for region, age at baseline, and the baseline number of GdE lesions, and included the natural log transformation of time on study as an offset term.

**Secondary: Adjusted Mean Number of New or Enlarging Hyperintense T2-Weighted**

| Brain Magnetic Resonance Imaging (MRI) Lesions per Scan over 12 months | |
|---|---|
| End point title | Adjusted Mean Number of New or Enlarging Hyperintense T2-Weighted Brain Magnetic Resonance Imaging (MRI) Lesions per Scan over 12 months |

End point description:

The number of new or enlarging hyperintense T2-weighted brain MRI lesions was based on the cumulative number of new or enlarging T2 lesions since baseline over 12 months. Includes participants with non-missing MRI results and included to the analysis population.

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

End point timeframe:

12 month treatment period; MRI scans were assessed at months 6 and 12

| End point values | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 382 | 388 | 397 | |
| Units: T2 Lesions/scan | | | | |
| least squares mean (confidence interval 95%) | 2.836 (2.331 to 3.451) | 1.465 (1.203 to 1.784) | 2.139 (1.777 to 2.575) | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |
| Number of subjects included in analysis | 770 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[5] |
| P-value | < 0.0001 [6] |
| Method | Negative Binomial Regression Model |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.517 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.427 |
| upper limit | 0.625 |

Notes:

[5] - To account for multiple comparisons, each of the 2 treatment comparisons was tested at the alpha = 0.05 level.

[6] - Observed data, adjusted for region, age at baseline, and baseline number of GdE lesions. The natural log transformation of the number of available MRI scans over 12 months is used as an offset term.

| Statistical analysis title | Statistical Analysis 2 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 0.5 mg |

| | |
|---|---|
| Number of subjects included in analysis | 779 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[7] |
| P-value | = 0.0032 [8] |
| Method | Negative binomial regression model |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.754 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.625 |
| upper limit | 0.91 |

Notes:

[7] - To account for multiple comparisons, each of the 2 treatment comparisons was tested at the alpha = 0.05 level.
[8] - Observed data, adjusted for region, age at baseline, and baseline number of GdE lesions. The natural log transformation of the number of available MRI scans over 12 months is used as an offset term.

## Secondary: Adjusted Mean Number of Gadolinium Enhancing (GdE) Brain MRI Lesions at Month 12

| | |
|---|---|
| End point title | Adjusted Mean Number of Gadolinium Enhancing (GdE) Brain MRI Lesions at Month 12 |

End point description:

The number of Gd-enhancing T1-lesions per MRI scan was measured as the total number of Gd-enhancing T1-lesions that occurred at month 12. Includes participants with non-missing MRI results and included to the analysis population.

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

End point timeframe:

Month 12

| **End point values** | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 382 | 388 | 397 | |
| Units: Lesions | | | | |
| least squares mean (confidence interval 95%) | 0.433 (0.295 to 0.635) | 0.160 (0.106 to 0.242) | 0.287 (0.197 to 0.418) | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |

| | |
|---|---|
| Number of subjects included in analysis | 770 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[9] |
| P-value | < 0.0001 [10] |
| Method | Negative Binomial Regression Model |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.256 |
| upper limit | 0.536 |

Notes:

[9] - To account for multiple comparisons, each of the 2 treatment comparisons was tested at the alpha = 0.05 level.
[10] - Adjusted for region, age at baseline, and the baseline number of GdE lesions. The natural log transformation of number of available MRI scans at 12 month (1 scan per subject) is used as an offset term.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 0.5 mg |
| Number of subjects included in analysis | 779 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[11] |
| P-value | < 0.0182 [12] |
| Method | Negative binomial regression model |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.662 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.471 |
| upper limit | 0.932 |

Notes:

[11] - To account for multiple comparisons, each of the 2 treatment comparisons was tested at the alpha = 0.05 level.
[12] - Adjusted for region, age at baseline, and the baseline number of GdE lesions. The natural log transformation of number of available MRI scans at 12 month (1 scan per subject) is used as an offset term.

## Secondary: Time to 3-month Confirmed Disability Worsening on Expanded Disability Status Scale (EDSS)

| End point title | Time to 3-month Confirmed Disability Worsening on Expanded Disability Status Scale (EDSS) |
|---|---|

End point description:

The Expanded Disability Status Scale (EDSS) is an ordinal scale instrument widely accepted to evaluate disability status at a particular time and disability progression over time in patients and MS clinical studies. The disability level is based on a neurological examination to obtain scores in seven neurologic functional systems (FSs) and an ambulation score that are combined to determine the overall EDSS score (step) ranging from 0 (normal) to 10 (death due to MS). The FSs are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral. Ambulation is measured based on if restriction is present and assisted required as well as minimum distance level achieved.

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

End point timeframe:

Time to Onset of Confirmed Disability Progression (CDP) for at Least 12 Weeks During the Double-Blind Treatment Period.

| End point values | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 448[13] | 447[14] | 451[15] | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| 3 months\| | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | |

Notes:

[13] - Not estimable as there were insufficient disability events at 3 months

[14] - Not estimable as there were insufficient disability events at 3 months

[15] - Not estimable as there were insufficient disability events at 3 months

## Statistical analyses

| Statistical analysis title | Analysis of confirmation after 3 months |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |
| Number of subjects included in analysis | 895 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3055 [16] |
| Method | Cox proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.34 |
| upper limit | 1.402 |

Notes:

[16] - Based on the Cox proportional hazard model with factors for treatment group, adjusted for region, age at baseline, and baseline EDSS score.

| Statistical analysis title | Analysis of confirmation after 3 months |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 0.5 mg |
| Number of subjects included in analysis | 899 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7163 [17] |
| Method | Cox proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.886 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 1.705 |

Notes:

[17] - Based on the Cox proportional hazard model with factors for treatment group, adjusted for region, age at Baseline, and Baseline EDSS score.

## Secondary: Percentage of Patients who Were Gadolinium Enhancing (GdE) Lesion-Free at Month 12

| End point title | Percentage of Patients who Were Gadolinium Enhancing (GdE) Lesion-Free at Month 12 |
|---|---|

End point description:

Participants were considered lesion free at Month 12 if they did not show evidence of GdE lesions from the date of the first study treatment to their month 12 MRI Scan. The ITT population consisted of all randomized participants who received at least 1 dose of study medication. Non-responder imputation was used.

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

End point timeframe:

Month 12

| **End point values** | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 448 | 447 | 451 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 74.1 (69.7 to 78.5) | 85.3 (81.8 to 88.8) | 77.6 (73.5 to 81.7) | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |
| Number of subjects included in analysis | 895 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [18] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentages |
| Point estimate | 11.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.59 |
| upper limit | 16.86 |

Notes:

[18] - Based on the Cochran-Mantel-Haenszel test stratified by region and Expanded Disability Status Scale category per Interactive Voice Response System (IVRS).

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 0.5 mg |

| | |
|---|---|
| Number of subjects included in analysis | 899 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.281 [19] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentages |
| Point estimate | 3.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.51 |
| upper limit | 9.51 |

Notes:

[19] - Based on the Cochran-Mantel-Haenszel test stratified by region and Expanded Disability Status Scale category per Interactive Voice Response System.

## Secondary: Percentage of Patients Who Were T2 Lesion-Free at Month 12

| | |
|---|---|
| End point title | Percentage of Patients Who Were T2 Lesion-Free at Month 12 |

End point description:

Participants were considered T2 lesion free at Month 12 if they did not show evidence of a relapse in T2 lesions from the date of the first study treatment to study completion at month 12. The ITT population consisted of all randomized participants who received at least 1 dose of study medication; analysis included non-responder imputation.

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

End point timeframe:

Month 12

| End point values | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 448 | 447 | 451 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 27.5 (23.0 to 32.0) | 32.2 (27.6 to 36.9) | 30.0 (25.5 to 34.5) | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |
| Number of subjects included in analysis | 895 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1523 [20] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentages |
| Point estimate | 4.73 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.73 |
| upper limit | 11.18 |

Notes:

[20] - Based on the Cochran-Mantel-Haenszel test stratified by region and Expanded Disability Status Scale category per IVRS.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 0.5 mg |
| Number of subjects included in analysis | 899 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4628 [21] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Percentages |
| Point estimate | 2.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.86 |
| upper limit | 8.84 |

Notes:

[21] - Based on the Cochran-Mantel-Haenszel test stratified by region and Expanded Disability Status Scale category per IVRS.

## Secondary: Percent Change in Normalized Brain Volume (Atrophy) on Brain MRI Scans from Baseline to Month 12

| End point title | Percent Change in Normalized Brain Volume (Atrophy) on Brain MRI Scans from Baseline to Month 12 |
|---|---|

End point description:

Brain volumes were reported in cm^3. If the data were collected in mm3, then a transformation was applied by dividing the result in mm3 by 1000 to convert to cm3 prior to analysis. Atrophy was measured by MRI scan. Actual brain volumes, change from baseline to each visit, and percent change from baseline to each visit was measured. The ITT population consisted of all randomized participants who received at least 1 dose of study medication. Last Observation Carried Forward (LOCF). Imputation was used.

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

End point timeframe:

Baseline to Month 12

| **End point values** | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 445 | 447 | 450 | |
| Units: Percent Change | | | | |
| median (full range (min-max)) | | | | |
| Baseline | 1445.526 (1222.70 to 1635.16) | 1458.301 (1190.84 to 1662.99) | 1453.033 (1195.40 to 1642.53) | |

| | | | | |
|---|---|---|---|---|
| Change from baseline at month 12 | -0.57 (-3.7 to 1.1) | -0.39 (-2.8 to 2.1) | -0.50 (-2.7 to 1.4) | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |
| Number of subjects included in analysis | 892 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [22] |
| Method | ANCOVA |
| Parameter estimate | Median difference (final values) |
| Point estimate | 0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 0.28 |

Notes:

[22] - Rank Ancova

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |
| Number of subjects included in analysis | 892 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0615 [23] |
| Method | ANCOVA |
| Parameter estimate | Median difference (final values) |
| Point estimate | 0.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.03 |
| upper limit | 0.2 |

Notes:

[23] - Rank Ancova

**Secondary: Change from Baseline in Multiple Sclerosis Functional Composite (MSFC) Score (Including the Low-Contrast Letter Acuity Test [LCLA] to Month 12**

| End point title | Change from Baseline in Multiple Sclerosis Functional Composite (MSFC) Score (Including the Low-Contrast Letter Acuity Test [LCLA] to Month 12 |
|---|---|

End point description:

The MSFC-LCLA is a battery including the following 4 individual scales: • The Timed 25-Foot Walk is an ambulation measure of walking 25 feet with time taken recorded in seconds • The 9-Hole Peg Test (9HPT) is a quantitative measure of upper extremity (arm and hand) function • The Symbol Digit Modalities Test (SDMT) is a measure of executive cognitive function that assesses processing speed,

flexibility, and calculation ability • Low-Contrast Letter Acuity Test (LCLA) used a standardized set of charts to assess low contrast visual acuity Z-scores were calculated for the MSFC for each component and averaged to create an overall composite score. A score of +1 indicates that, on average, an individual scored 1 standard deviation (SD) better than the reference population and a score of -1 indicates that an individual scored 1 SD worse than the reference population. The ITT population consisted of all randomized participants who received at least 1 dose of study medication.

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

End point timeframe:

Baseline to Month 12

| **End point values** | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 447 | 447 | 450 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.022 (± 0.334) | 0.003 (± 0.328) | -0.007 (± 0.351) | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |
| Number of subjects included in analysis | 894 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.129 [24] |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Mean |
| Point estimate | 0.034 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.01 |
| upper limit | 0.077 |

Notes:

[24] - Adjusted for region, EDSS category per IVRS and the baseline MSFC score.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 0.5 mg |
| Number of subjects included in analysis | 897 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4942 [25] |
| Method | ANCOVA |
| Parameter estimate | Difference in LS Mean |
| Point estimate | 0.015 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.028 |
| upper limit | 0.059 |

Notes:

[25] - Adjusted for region, EDSS category per IVRS and the baseline MSFC score.

## Secondary: Mean Change in Multiple Sclerosis Quality of Life (MSQOL)-54 Score from Baseline to Month 12

| End point title | Mean Change in Multiple Sclerosis Quality of Life (MSQOL)-54 Score from Baseline to Month 12 |
|---|---|

End point description:

The MSQOL-54 is a multidimensional health-related QOL measure that combines both generic and MS-specific items into a single instrument. The instrument generates 12 subscales along with two summary scores, and two additional single-item measures. The subscales are: physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function. The summary scores are the physical health composite summary and the mental health composite summary. The change for the summary scores for the physical health and mental health composite, including statistical analysis are reported. The single item measures are satisfaction with sexual function and change in health. Each domain has a range from 0 to 100 where higher means better.

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

End point timeframe:

Baseline to Month 12

| **End point values** | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 448 | 447 | 451 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical health composite summary\| | 0.046 (± 12.578) | 1.925 (± 11.870) | 1.414 (± 12.343) | |
| Mental health composite summary\| | -0.123 (± 15.240) | 0.260 (± 15.800) | 0.283 (± 15.686) | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Analysis of Physical Health Composite Summary

| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 895 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0364 [26] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.642 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.104 |
| upper limit | 3.18 |

Notes:

[26] - Adjusted for region, EDSS category per IVRS, and the baseline summary scores of interest.

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

Analysis of Physical Health Composite Summary

| | |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 0.5 mg |
| Number of subjects included in analysis | 899 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1905 [27] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.024 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.51 |
| upper limit | 2.559 |

Notes:

[27] - Adjusted for region, EDSS category per IVRS, and the baseline summary scores of interest.

| **Statistical analysis title** | Statistical Analysis 3 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |
| Number of subjects included in analysis | 895 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[28] |
| P-value | = 0.7104 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.356 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.523 |
| upper limit | 2.2234 |

Notes:
[28] - Analysis of Mental Health Composite

| **Statistical analysis title** | Statistical Analysis 4 |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |
| Number of subjects included in analysis | 895 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[29] |
| P-value | = 0.8587 [30] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.045 |
| upper limit | 1.705 |

Notes:
[29] - Analysis of Mental Health Composite
[30] - Adjusted for region, EDSS category per IVRS, and the baseline summary scores of interest.

## Secondary: Number of Subjects with Treatment Emergent Adverse Events

| End point title | Number of Subjects with Treatment Emergent Adverse Events |
|---|---|

End point description:

An AE is any untoward medical occurrence that does not necessarily have a causal relationship with the investigational product (IP). An AE can be any unfavorable or unintended sign, including an abnormal laboratory finding, symptom or disease temporally associated with the use of an IP whether or not considered related to the IP. A treatment-emergent adverse event (TEAE) = an AE with a start date on or after the date of first dose of IP, up through the lst dose of IP in the open-label extension Study RPC01-3001 for those who continued into the open-label extension. A serious AE (SAE) is any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalization or prolongation of existing inpatient hospitalization. The investigator assessed the severity of AEs as mild, moderate, or severe. Safety population.

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

End point timeframe:

From date of first dose of study medication to 28 days following the final dose of study medication; the mean duration of exposure to study drug was 410.3 days for IFN, 412.7 days for Ozanimod 0.5 mg and 414.1 days for Ozanimod 1 mg

| **End point values** | IFN β-1a | Ozanimod 1 mg | Ozanimod 0.5 mg | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 445 | 448 | 453 | |
| Units: participants | | | | |
| Any TEAE | 336 | 268 | 259 | |
| Any Moderate or Severe TEAE | 182 | 138 | 113 | |
| Any Severe TEAE | 10 | 7 | 10 | |
| Any Suspected TEAE | 83 | 91 | 76 | |
| Any Related TEAE | 13 | 7 | 8 | |
| Any Serious TEAE | 11 | 13 | 16 | |
| Any Suspected Serious TEAE | 0 | 3 | 0 | |

| | | | | |
|---|---|---|---|---|
| Any Related Serious TEAE | 0 | 1 | 0 | |
| Any TEAE Leading to Stopping of Study Drug | 16 | 13 | 7 | |
| Any TEAE Leading to Study Withdrawal | 16 | 13 | 7 | |
| Any Death | 0 | 0 | 0 | |
| Any Death related to Study Drug | 0 | 0 | 0 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to 6-month Confirmed Disability Worsening on Expanded Disability Status Scale (EDSS)

| End point title | Time to 6-month Confirmed Disability Worsening on Expanded Disability Status Scale (EDSS) |
|---|---|

End point description:

The Expanded Disability Status Scale (EDSS) is an ordinal scale instrument widely accepted to evaluate disability status at a particular time and disability progression over time in patients and MS clinical studies. The disability level is based on a neurological examination to obtain scores in seven neurologic functional systems (FSs) and an ambulation score that are combined to determine the overall EDSS score (step) ranging from 0 (normal) to 10 (death due to MS). The FSs are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral. Ambulation is measured based on if restriction is present and assisted required as well as minimum distance level achieved.

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

End point timeframe:

Time to Onset of Confirmed Disability Progression (CDP) for at Least 12 Weeks During the Double-Blind Treatment Period.

| **End point values** | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 448[31] | 447[32] | 451[33] | |
| Units: days | | | | |
| median (confidence interval 95%) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | |

Notes:

[31] - Not estimable as there were insufficient disability events at 3 months

[32] - Not estimable as there were insufficient disability events at 3 months

[33] - Not estimable as there were insufficient disability events at 3 months

### Statistical analyses

| **Statistical analysis title** | Analysis of confirmation after 6 months |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 1 mg |

| | |
|---|---|
| Number of subjects included in analysis | 895 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6725 [34] |
| Method | Cox proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.238 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 3.337 |

Notes:

[34] - Based on the Cox proportional hazard model with factors for treatment group, adjusted for region, age at baseline and baseline EDSS score

| **Statistical analysis title** | Analysis of confirmation after 6 months |
|---|---|
| Comparison groups | Interferon Beta-1a (IFN β-1a) v Ozanimod 0.5 mg |
| Number of subjects included in analysis | 899 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3755 [35] |
| Method | Cox proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.535 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.595 |
| upper limit | 3.963 |

Notes:

[35] - Based on the Cox proportional hazard model with factors for treatment group, adjusted for region, age at baseline and baseline EDSS score

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the start of study medication treatment until 28 days following the last dose of treatment with the study drug.

Adverse event reporting additional description:

The mean exposure to study drug was 410.3 days for IFN, 412.7 days for Ozanimod 0.5 mg and 414.1 days for Ozanimod 1 mg

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Interferon Beta-1a (IFN β-1a) |

Reporting group description:

Participants received IFN β-1a 30 µg intramuscular (IM) injection weekly and matching placebo capsules (identical in physical appearance to Ozanimod) orally every day for one year.

| | |
|---|---|
| Reporting group title | Ozanimod 1 mg |

Reporting group description:

Participants received Ozanimod 1 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to Interferon) weekly for one year.

| | |
|---|---|
| Reporting group title | Ozanimod 0.5 mg |

Reporting group description:

Participants received Ozanimod 0.5 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to Interferon) weekly for one year.

| Serious adverse events | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 445 (2.47%) | 13 / 448 (2.90%) | 16 / 453 (3.53%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal Cell Carcinoma | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign Ovarian Tumour | | | |
| subjects affected / exposed | 1 / 445 (0.22%) | 0 / 448 (0.00%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibroadenoma Of Breast | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive Breast Carcinoma | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Testicular Seminoma (Pure) Stage I | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine Leiomyoma | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion Spontaneous | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Menometrorrhagia | | | |
| subjects affected / exposed | 1 / 445 (0.22%) | 0 / 448 (0.00%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postmenopausal Haemorrhage | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Fibrin D Dimer Increased | | | |
| subjects affected / exposed | 1 / 445 (0.22%) | 0 / 448 (0.00%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle Fracture | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye Injury | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial Bones Fracture | | | |
| subjects affected / exposed | 1 / 445 (0.22%) | 0 / 448 (0.00%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural Haematoma | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial Fibrillation | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus Bradycardia | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Supraventricular Tachycardia | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral Infarction | | | |
| subjects affected / exposed | 1 / 445 (0.22%) | 0 / 448 (0.00%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical Radiculopathy | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple Sclerosis Relapse | | | |
| subjects affected / exposed | 2 / 445 (0.45%) | 0 / 448 (0.00%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelopathy | | | |
| subjects affected / exposed | 1 / 445 (0.22%) | 0 / 448 (0.00%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular Encephalopathy | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Duodenal Ulcer | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Gallbladder Polyp | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal Colic | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral Disc Disorder | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendiceal Abscess | | | |
| subjects affected / exposed | 1 / 445 (0.22%) | 0 / 448 (0.00%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 445 (0.00%) | 0 / 448 (0.00%) | 1 / 453 (0.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lyme Disease | | | |
| subjects affected / exposed | 1 / 445 (0.22%) | 0 / 448 (0.00%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative Abscess | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis Acute | | | |
| subjects affected / exposed | 1 / 445 (0.22%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous Abscess | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 0 / 445 (0.00%) | 1 / 448 (0.22%) | 0 / 453 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Interferon Beta-1a (IFN β-1a) | Ozanimod 1 mg | Ozanimod 0.5 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 273 / 445 (61.35%) | 57 / 448 (12.72%) | 88 / 453 (19.43%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 25 / 445 (5.62%) | 34 / 448 (7.59%) | 27 / 453 (5.96%) |
| occurrences (all) | 39 | 46 | 47 |
| General disorders and administration | | | |

| | | | |
|---|---|---|---|
| site conditions | | | |
| Influenza Like Illness | | | |
| subjects affected / exposed | 227 / 445 (51.01%) | 17 / 448 (3.79%) | 18 / 453 (3.97%) |
| occurrences (all) | 706 | 23 | 20 |
| Pyrexia | | | |
| subjects affected / exposed | 28 / 445 (6.29%) | 5 / 448 (1.12%) | 5 / 453 (1.10%) |
| occurrences (all) | 299 | 6 | 13 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 36 / 445 (8.09%) | 30 / 448 (6.70%) | 44 / 453 (9.71%) |
| occurrences (all) | 50 | 47 | 64 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 24 / 445 (5.39%) | 18 / 448 (4.02%) | 31 / 453 (6.84%) |
| occurrences (all) | 29 | 21 | 39 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 26 August 2014 | The following changes were made in response to US Food and Drug Administration (FDA) correspondence dated 28 February 2013 and agreed upon under a Special Protocol Assessment (SPA): The duration of the study was increased to provide additional data for assessment of accumulation of disability and the investigational plan, study schedule, objectives, endpoints, and statistical plans were updated accordingly; Planned statistical analyses text was updated; An MRI assessment at 6 months was added, text was updated to clarify that disability progression cannot be evaluated during a relapse, exclusion criteria was updated to allow enrollment of more subjects with diabetes mellitus, PK sampling schedule was clarified. • Minor changes to procedures, excluded medications, screening criteria/procedures Changes previously made for RPC01-201 Protocol Amendment 2 dated 09 August 2013 (Serial No. 0024) and agreed to on 03 December 2013 • Administrative changes - minor clarifications, corrections of inconsistencies between sections of the protocol, and correction of typographical errors |
| 27 July 2015 | • The sponsor’s address was updated • The Schedule of Assessments was modified to clarify the End of Treatment visit procedures • A maximum dose was added for citalopram in the table of prohibited cardiac medications • The Expanded Disability Status Scale functional system categories were corrected • Clarified that the use of an automated BP device is not required • Minor editorial and typographical corrections |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported