



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
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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
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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	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 μ g 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 μ g IM weekly for one year

Arm title	Ozanimod 1 mg
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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
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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
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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 μ g 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 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 Units: years			
arithmetic mean	35.9	34.8	36.0
standard deviation	\pm 9.11	\pm 9.24	\pm 9.43
Gender, Male/Female Units: Subjects			
Female	300	283	311
Male	148	164	140
Race Units: Subjects			
White	447	446	447
Black	0	0	2
Asian	0	1	1
Other	1	0	1
Region, Category Units: Subjects			
Eastern Europe	419	415	419
Rest of World	29	32	32

Age at MS Symptom Onset (years) Units: years arithmetic mean standard deviation	29.5 ± 8.92	28.4 ± 8.42	29.3 ± 9.25
Age at MS Diagnosis Units: Years arithmetic mean standard deviation	32.7 ± 9.01	31.6 ± 8.81	32.7 ± 9.49
Years Since MS Diagnosis Units: Years arithmetic mean standard deviation	3.71 ± 4.361	3.60 ± 4.193	3.70 ± 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 standard deviation	2.62 ± 1.138	2.61 ± 1.160	2.65 ± 1.135
Years Since MS Symptom Onset Units: years arithmetic mean standard deviation	6.88 ± 5.877	7.16 ± 6.255	6.85 ± 6.449

Reporting group values	Total		
Number of subjects	1346		
Age categorical 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 Units: years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	894		
Male	452		
Race Units: Subjects			
White	1340		
Black	2		

Asian	2		
Other	2		
Region, Category			
Units: Subjects			
Eastern Europe	1253		
Rest of World	93		
Age at MS Symptom Onset (years)			
Units: years			
arithmetic mean			
standard deviation	-		
Age at MS Diagnosis			
Units: Years			
arithmetic mean			
standard deviation	-		
Years Since MS Diagnosis			
Units: Years			
arithmetic mean			
standard deviation	-		
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			
standard deviation	-		
Years Since MS Symptom Onset			
Units: years			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Interferon Beta-1a (IFN β -1a)
Reporting group description: Participants received IFN β -1a 30 μ g 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 μ g 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)
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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
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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
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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
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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
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End point description:

Brain volumes were reported in cm³. 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
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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)	
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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
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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 (\pm 0.334)	0.003 (\pm 0.328)	-0.007 (\pm 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
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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
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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 (\pm 12.578)	1.925 (\pm 11.870)	1.414 (\pm 12.343)	
Mental health composite summary	-0.123 (\pm 15.240)	0.260 (\pm 15.800)	0.283 (\pm 15.686)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Analysis of Physical Health Composite Summary

Comparison groups	Interferon Beta-1a (IFN β -1a) v Ozanimod 1 mg
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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
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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 1st 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
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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)
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

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