Clinical trial results:
A Phase 2/3, Multi-center, Randomized, Double-blind, Placebo-controlled (Part A) and Double-Blind, Double-dummy, Active-controlled (Part B), Parallel Group Study to Evaluate the Efficacy and Safety of RPC1063 Administered Orally to Relapsing Multiple Sclerosis Patients

Summary

EudraCT number	2012-002714-40
Trial protocol	IT BE ES HU BG GR GB SK HR
Global end of trial date	13 April 2017

Results information

Result version number	v1 (current)
This version publication date	24 May 2018
First version publication date	24 May 2018

Trial information

Trial identification

Sponsor protocol code	RPC01-201-PartA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01628393
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene International Sarle II
Sponsor organisation address	Rue des Moulins 4, Couvet, Switzerland,
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 8882601599, ClinicalTrialDisclosure@Celgene.com
Scientific contact	James Sheffield, Celgene Corporation, 01 619-371-1506, 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	12 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A: To demonstrate the superior clinical efficacy of RPC1063 compared to placebo by showing a reduction in the cumulative number of total gadolinium enhancing (GdE) lesions from Week 12 to Week 24 in patients with relapsing multiple sclerosis (RMS). Part B: To assess whether the clinical efficacy of RPC1063 is superior to IFN-1a (Avonex®) in reducing the rate of clinical relapses at the end of Month 24 in patients with RMS.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection. 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	18 September 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Georgia: 41
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Hungary: 24
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Poland: 507
Country: Number of subjects enrolled	Romania: 34
Country: Number of subjects enrolled	Russian Federation: 140
Country: Number of subjects enrolled	Serbia: 140
Country: Number of subjects enrolled	Spain: 61
Country: Number of subjects enrolled	Ukraine: 261
Country: Number of subjects enrolled	United States: 59
Country: Number of subjects enrolled	Bulgaria: 38
Country: Number of subjects enrolled	Belarus: 116
Country: Number of subjects enrolled	Bosnia and Herzegovina: 8
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Croatia: 45

Country: Number of subjects enrolled	Moldova, Republic of: 9
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	South Africa: 18
Country: Number of subjects enrolled	United Kingdom: 16
Worldwide total number of subjects	1578
EEA total number of subjects	784

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)	1578
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Part A of the study was conducted at 55 study centers in 13 countries including the United States, Europe and Russia and consisted of a 24-week placebo-controlled period and an optional 96-week extension period. Part B was performed at 150 sites in North America, Europe, and South Africa with a overall treatment period of 24 months.

Pre-assignment

Screening details:

Part A subjects were randomly assigned to one of two daily doses of ozanimod 0.5 mg or 1 mg or placebo for 24 weeks. Those who completed 24 weeks could enter an extension phase and continue ozanimod 0.5 mg or 1 mg daily; Part B subjects were randomly assigned to one of two daily doses of ozanimod 0.5 mg or 1 mg or weekly Interferon injection.

Period 1

Period 1 title	Overall Study
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, adverse events, (AEs) or laboratory changes. A patients treatment group assignment blind was not to be broken until the end of the study unless medical treatment of that patient depened upon knowing whether the patient was receiving active drug.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Part A Core)

Arm description:

Participants received placebo capsules (identical in appearance to ozanimod) by mouth (PO) daily during the 24-week placebo-controlled phase. Participants were given the option to enter into a blinded extension phase and were re-randomized to receive ozanimod 0.5 mg or 1mg capsules PO daily for an additional 96 weeks of treatment.

Arm type	Placebo
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 appearance to ozanimod) PO daily for 24 weeks

Arm title	Ozanimod 0.5 mg (Part A Core)

Arm description:

Participants received ozanimod 0.5 mg capsules PO daily during the 24-week placebo-controlled treatment phase. Participants were given the option to enter into a blinded extension phase and continued to receive ozanimod 0.5 mg capsules PO daily for an additional 96 weeks of treatment.

Arm type	Experimental
Investigational medicinal product name	Ozanimod
Investigational medicinal product code	
Other name	RPC1063
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ozanimod 0.5 mg capsules PO daily for 24 weeks

Arm title	Ozanimod 1 mg (Part A Core)

Arm description:

Participants received ozanimod 1 mg capsules PO daily during the 24-week placebo-controlled treatment phase. These participants were given the option to enter into a blinded extension phase and continued to receive ozanimod 1 mg capsules PO daily for an additional 96 weeks of treatment.

Arm type	Experimental
Investigational medicinal product name	Ozanimod
Investigational medicinal product code	
Other name	RPC1063
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ozanimod 1 mg capsules PO daily for 24 weeks.

Arm title	Interferon Beta-1a (IFN β-1a) (Part B)

Arm description:

Participants received IFN β-1a 30 µg intramuscular (IM) injection weekly and matching placebo capsules (identical in physical appearance to ozanimod) orally daily 24 months.

Arm type	Active comparator
Investigational medicinal product name	Interferon Beta - 1a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

IFN β-1a 30 µg intramuscular (IM) injection weekly for two years.

Arm title	Ozanimod 0.5 mg (Part B)

Arm description:

Participants received ozanimod 0.5 mg capsules PO daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for 24 months.

Arm type	Experimental
Investigational medicinal product name	Ozanimod
Investigational medicinal product code	
Other name	RPC1063
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ozanimod 0.5 mg capsules PO daily for two years

Arm title	Ozanimod 1 mg (Part B)

Arm description:

Participants received ozanimod 1 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for 24 months

Arm type	Experimental

Investigational medicinal product name	Ozanimod
Investigational medicinal product code	
Other name	RPC1063
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ozanimod 1 mg capsules PO daily for two years.

Number of subjects in period 1	Placebo (Part A Core)	Ozanimod 0.5 mg (Part A Core)	Ozanimod 1 mg (Part A Core)
Started	88	87	83
Received Treatment	88	87	83
Completed	85	85	82
Not completed	3	2	1
Randomized; no study drug received	-	-	-
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	2	1	1
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-
Miscellaneous	-	-	-
Lost to follow-up	1	-	-
Protocol deviation	-	1	-
Lack of efficacy	-	-	-

Number of subjects in period 1	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)
Started	443	443	434
Received Treatment	441	439	433
Completed	376	374	388
Not completed	67	69	46
Randomized; no study drug received	2	4	1
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	30	31	19
Physician decision	7	6	5
Adverse event, non-fatal	18	13	13
Miscellaneous	2	4	6
Lost to follow-up	1	4	-
Protocol deviation	3	1	1
Lack of efficacy	4	5	1

Period 2

Period 2 title	Part A: Blinded Active Extension Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

During the blinded extension phase of Part A, the sponsor and Clinical Research Organization (CRO) were blinded until the Week 24 primary endpoint was reached by all patients and the data through Week 24 was finalized, after which the sponsor and CRO were unblinded to the treatment assignment. Investigators and patients remained blinded throughout the extension phase.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo-Ozanimod 0.5 mg (Part A Extension)

Arm description:

Participants initially randomized to placebo capsules PO daily during the 24-week placebo controlled treatment phase were re-randomized to receive ozanimod 0.5 mg capsules during the optional blinded extension period for an additional 96 weeks of treatment.

Arm type	Experimental
Investigational medicinal product name	RPC1063
Investigational medicinal product code	
Other name	Ozanimod
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ozanimod 0.5 mg capsules PO daily during the 96-week extension phase.

Arm title	Ozanimod 0.5 mg - 0.5 mg (Part A Extension)

Arm description:

Participants received ozanimod 0.5 mg capsules PO daily during the 24-week placebo-controlled treatment phase. Participants were given the option to enter into a blinded extension phase and continued to receive ozanimod 0.5 mg capsules PO daily for an additional 96 weeks of treatment.

Arm type	Experimental
Investigational medicinal product name	RPC1063
Investigational medicinal product code	
Other name	Ozanimod
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ozanimod 0.5 mg capsules PO daily during the 96-week extension phase.

Arm title	Placebo-Ozanimod 1 mg (Part A Extension)

Arm description:

Participants initially randomized to placebo capsules PO daily during the 24-week placebo controlled treatment phase were re-randomized to receive ozanimod 1 mg capsules during the optional blinded extension period for an additional 96 weeks of treatment.

Arm type	Experimental

Investigational medicinal product name	RPC1063
Investigational medicinal product code	
Other name	Ozanimod
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ozanimod 1 mg capsules PO daily during the 96-week extension phase.

Arm title	Ozanimod 1 mg - 1mg (Part A Extension)

Arm description:

Participants received ozanimod 1 mg capsules PO daily during the 24-week placebo-controlled treatment phase. Participants were given the option to enter into a blinded extension phase and continued to receive ozanimod 1 mg capsules PO daily for an additional 96 weeks of treatment.

Arm type	Experimental
Investigational medicinal product name	RPC1063
Investigational medicinal product code	
Other name	Ozanimod
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ozanimod 1 mg capsules PO daily during the 96-week extension phase.

Number of subjects in period 2[1]	Placebo-Ozanimod 0.5 mg (Part A Extension)	Ozanimod 0.5 mg - 0.5 mg (Part A Extension)	Placebo-Ozanimod 1 mg (Part A Extension)
Started	41	85	42
Completed	37	75	36
Not completed	4	10	6
Physician decision	1	3	-
Consent withdrawn by subject	-	6	2
Adverse event, non-fatal	2	1	2
Protocol deviation	1	-	-
Lack of efficacy	-	-	2

Number of subjects in period 2[1]	Ozanimod 1 mg - 1mg (Part A Extension)
Started	81
Completed	75
Not completed	6
Physician decision	2
Consent withdrawn by subject	2
Adverse event, non-fatal	-
Protocol deviation	-
Lack of efficacy	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Subjects were given the option to participate in the blinded active extension phase and some subjects chose not to participate.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (Part A Core)
Reporting group description:	
Participants received placebo capsules (identical in appearance to ozanimod) by mouth (PO) daily during the 24-week placebo-controlled phase. Participants were given the option to enter into a blinded extension phase and were re-randomized to receive ozanimod 0.5 mg or 1mg capsules PO daily for an additional 96 weeks of treatment.	
Reporting group title	Ozanimod 0.5 mg (Part A Core)
Reporting group description:	
Participants received ozanimod 0.5 mg capsules PO daily during the 24-week placebo-controlled treatment phase. Participants were given the option to enter into a blinded extension phase and continued to receive ozanimod 0.5 mg capsules PO daily for an additional 96 weeks of treatment.	
Reporting group title	Ozanimod 1 mg (Part A Core)
Reporting group description:	
Participants received ozanimod 1 mg capsules PO daily during the 24-week placebo-controlled treatment phase. These participants were given the option to enter into a blinded extension phase and continued to receive ozanimod 1 mg capsules PO daily for an additional 96 weeks of treatment.	
Reporting group title	Interferon Beta-1a (IFN β-1a) (Part B)
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 daily 24 months.	
Reporting group title	Ozanimod 0.5 mg (Part B)
Reporting group description:	
Participants received ozanimod 0.5 mg capsules PO daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for 24 months.	
Reporting group title	Ozanimod 1 mg (Part B)
Reporting group description:	
Participants received ozanimod 1 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for 24 months	

Reporting group values	Placebo (Part A Core)	Ozanimod 0.5 mg (Part A Core)	Ozanimod 1 mg (Part A Core)
Number of subjects	88	87	83
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)	88	87	83
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	39.0	38.1	38.4
standard deviation	± 8.67	± 9.17	± 40.0

Sex: Female, Male Units: Subjects			
Female	62	60	59
Male	26	27	24
Race/Ethnicity, Customized Units: Subjects			
White|	87	84	83
Black|	1	2	0
Asian|	0	1	0
Other	0	0	0
Region, Category Units: Subjects			
North America	4	4	4
Western Europe	6	4	3
Eastern Europe	78	79	76
South Africa	0	0	0
Missing	0	0	0
Age at Multiple Sclerosis Diagnosis Units: Years			
arithmetic mean	33.9	34.8	34.4
standard deviation	± 8.30	± 10.01	± 9.51
Years Since Multiple Sclerosis Diagnosis Units: Years			
arithmetic mean	4.6	2.8	3.6
standard deviation	± 5.12	± 4.98	± 4.43
Expanded Disability Status Scale (EDSS) Score 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) was 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	2.85	2.94	2.86
standard deviation	± 1.273	± 1.287	± 1.213
Years Since MS Symptom Onset Units: Years			
arithmetic mean	8.1	6.0	6.2
standard deviation	± 6.97	± 6.41	± 5.79
Number of Relapses Within the Last 12 months Prior to Screening Units: Relapses			
arithmetic mean	1.3	1.5	1.3
standard deviation	± 0.64	± 1.18	± 0.73
Number of Gadolinium Enhancing (GdE) Lesions at Baseline Units: Lesions			
arithmetic mean	1.4	0.9	1.3
standard deviation	± 3.36	± 1.42	± 2.75

Reporting group values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)
Number of subjects	443	443	434

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)	443	443	434
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	35.1	35.5	36.0
standard deviation	± 9.1	± 8.82	± 8.88
Sex: Female, Male Units: Subjects			
Female	305	289	292
Male	138	154	142
Race/Ethnicity, Customized Units: Subjects			
White|	432	431	428
Black|	7	6	5
Asian|	1	0	0
Other	3	6	1
Region, Category Units: Subjects			
North America	16	16	16
Western Europe	40	40	36
Eastern Europe	379	378	374
South Africa	6	5	7
Missing	2	4	1
Age at Multiple Sclerosis Diagnosis Units: Years			
arithmetic mean	31.6	32.0	32.1
standard deviation	± 8.82	± 8.5	± 8.95
Years Since Multiple Sclerosis Diagnosis Units: Years			
arithmetic mean	3.63	3.50	3.97
standard deviation	± 4.613	± 4.207	± 5.171
Expanded Disability Status Scale (EDSS) Score 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) was 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	2.49	2.48	2.55
standard deviation	± 1.158	± 1.166	± 1.145
Years Since MS Symptom Onset Units: Years			

arithmetic mean	6.36	6.23	6.92
standard deviation	± 6.065	± 5.547	± 6.201
Number of Relapses Within the Last 12 months Prior to Screening			
Units: Relapses			
arithmetic mean	1.3	1.4	1.3
standard deviation	± 0.58	± 0.64	± 0.60
Number of Gadolinium Enhancing (GdE) Lesions at Baseline			
Units: Lesions			
arithmetic mean	1.8	1.8	1.6
standard deviation	± 3.54	± 3.62	± 3.78

Reporting group values	Total		
Number of subjects	1578		
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)	1578		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	1067		
Male	511		
Race/Ethnicity, Customized			
Units: Subjects			
White|	1545		
Black|	21		
Asian|	2		
Other	10		
Region, Category			
Units: Subjects			
North America	60		
Western Europe	129		
Eastern Europe	1364		
South Africa	18		
Missing	7		
Age at Multiple Sclerosis Diagnosis			
Units: Years			
arithmetic mean			
standard deviation	-		

Years Since Multiple Sclerosis Diagnosis Units: Years arithmetic mean standard deviation	- -		
Expanded Disability Status Scale (EDSS) Score 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) was 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	- -		
Number of Relapses Within the Last 12 months Prior to Screening Units: Relapses arithmetic mean standard deviation	- -		
Number of Gadolinium Enhancing (GdE) Lesions at Baseline Units: Lesions arithmetic mean standard deviation	- -		

Subject analysis sets

Subject analysis set title	Placebo (Part A Core)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received placebo capsules (identical in appearance to RPC1063) by mouth (PO) daily during the 24-week placebo-controlled phase.	
Subject analysis set title	Ozanimod 0.5 mg (Part A Core)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received ozanimod 0.5 mg capsules PO daily during the 24-week placebo-controlled treatment phase	
Subject analysis set title	Ozanimod 1 mg (Part A Core)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received ozanimod 1 mg capsules PO daily during the 24-week placebo-controlled treatment phase.	
Subject analysis set title	Interferon Beta-1a (IFN β-1a) (Part B)
Subject analysis set type	Intention-to-treat
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 daily 24 months.	
Subject analysis set title	Ozanimod 0.5 mg (Part B)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received ozanimod 0.5 mg capsules PO daily and an intramuscular placebo injection	

(identical in appearance to interferon) weekly for 24 months.

Subject analysis set title	Ozanimod 1 mg (Part B)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received ozanimod 1 mg capsules PO daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for 24 months.

Reporting group values	Placebo (Part A Core)	Ozanimod 0.5 mg (Part A Core)	Ozanimod 1 mg (Part A Core)
Number of subjects	88	87	83
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)	88	87	83
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	39.0	38.1	38.4
standard deviation	± 8.67	± 9.17	± 40.0
Sex: Female, Male Units: Subjects			
Female	62	60	59
Male	26	27	27
Race/Ethnicity, Customized Units: Subjects			
White|	87	84	83
Black|	1	2	0
Asian|	0	1	0
Other	0	0	0
Region, Category Units: Subjects			
North America	4	4	4
Western Europe	6	4	3
Eastern Europe	78	79	76
South Africa	0	0	0
Missing	0	0	0
Age at Multiple Sclerosis Diagnosis Units: Years			
arithmetic mean	33.9	34.8	34.4
standard deviation	± 8.30	± 10.01	± 9.51
Years Since Multiple Sclerosis Diagnosis Units: Years			
arithmetic mean	4.6	2.8	3.6
standard deviation	± 5.12	± 4.98	± 4.43
Expanded Disability Status Scale (EDSS)			

Score 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) was 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	2.85	2.94	2.86
standard deviation	± 1.273	± 1.287	± 1.213
Years Since MS Symptom Onset			
Units: Years			
arithmetic mean	8.1	6.0	6.2
standard deviation	± 6.97	± 6.41	± 5.79
Number of Relapses Within the Last 12 months Prior to Screening			
Units: Relapses			
arithmetic mean	1.3	1.5	1.3
standard deviation	± 0.64	± 1.18	± 0.73
Number of Gadolinium Enhancing (GdE) Lesions at Baseline			
Units: Lesions			
arithmetic mean	1.4	0.9	1.3
standard deviation	± 3.36	± 1.42	± 2.75

Reporting group values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)
Number of subjects	441	439	433
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)	441	439	433
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	35.1	35.4	36.0
standard deviation	± 9.07	± 8.82	± 8.89
Sex: Female, Male			
Units: Subjects			
Female	304	287	291
Male	137	151	142
Race/Ethnicity, Customized			
Units: Subjects			
White|	432	431	428
Black|	7	6	5
Asian|	1	0	0
Other	1	2	0
Region, Category			

Units: Subjects			
North America	16	16	16
Western Europe	40	40	36
Eastern Europe	379	378	374
South Africa	6	5	7
Missing	0	0	0
Age at Multiple Sclerosis Diagnosis			
Units: Years			
arithmetic mean	31.6	32.0	32.1
standard deviation	± 8.82	± 8.5	± 8.95
Years Since Multiple Sclerosis Diagnosis			
Units: Years			
arithmetic mean	3.63	3.50	3.97
standard deviation	± 4.613	± 4.207	± 5.171
Expanded Disability Status Scale (EDSS) Score 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) was 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	2.49	2.48	2.55
standard deviation	± 1.158	± 1.166	± 1.145
Years Since MS Symptom Onset			
Units: Years			
arithmetic mean	6.36	6.23	6.92
standard deviation	± 6.065	± 5.547	± 6.201
Number of Relapses Within the Last 12 months Prior to Screening			
Units: Relapses			
arithmetic mean	1.3	1.4	1.3
standard deviation	± 0.58	± 0.64	± 0.60
Number of Gadolinium Enhancing (GdE) Lesions at Baseline			
Units: Lesions			
arithmetic mean	1.8	1.8	1.6
standard deviation	± 3.54	± 3.62	± 3.78

End points

End points reporting groups

Reporting group title	Placebo (Part A Core)
Reporting group description:	
Participants received placebo capsules (identical in appearance to ozanimod) by mouth (PO) daily during the 24-week placebo-controlled phase. Participants were given the option to enter into a blinded extension phase and were re-randomized to receive ozanimod 0.5 mg or 1mg capsules PO daily for an additional 96 weeks of treatment.	
Reporting group title	Ozanimod 0.5 mg (Part A Core)
Reporting group description:	
Participants received ozanimod 0.5 mg capsules PO daily during the 24-week placebo-controlled treatment phase. Participants were given the option to enter into a blinded extension phase and continued to receive ozanimod 0.5 mg capsules PO daily for an additional 96 weeks of treatment.	
Reporting group title	Ozanimod 1 mg (Part A Core)
Reporting group description:	
Participants received ozanimod 1 mg capsules PO daily during the 24-week placebo-controlled treatment phase. These participants were given the option to enter into a blinded extension phase and continued to receive ozanimod 1 mg capsules PO daily for an additional 96 weeks of treatment.	
Reporting group title	Interferon Beta-1a (IFN β-1a) (Part B)
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 daily 24 months.	
Reporting group title	Ozanimod 0.5 mg (Part B)
Reporting group description:	
Participants received ozanimod 0.5 mg capsules PO daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for 24 months.	
Reporting group title	Ozanimod 1 mg (Part B)
Reporting group description:	
Participants received ozanimod 1 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for 24 months	
Reporting group title	Placebo-Ozanimod 0.5 mg (Part A Extension)
Reporting group description:	
Participants initially randomized to placebo capsules PO daily during the 24-week placebo controlled treatment phase were re-randomized to receive ozanimod 0.5 mg capsules during the optional blinded extension period for an additional 96 weeks of treatment.	
Reporting group title	Ozanimod 0.5 mg - 0.5 mg (Part A Extension)
Reporting group description:	
Participants received ozanimod 0.5 mg capsules PO daily during the 24-week placebo-controlled treatment phase. Participants were given the option to enter into a blinded extension phase and continued to receive ozanimod 0.5 mg capsules PO daily for an additional 96 weeks of treatment.	
Reporting group title	Placebo-Ozanimod 1 mg (Part A Extension)
Reporting group description:	
Participants initially randomized to placebo capsules PO daily during the 24-week placebo controlled treatment phase were re-randomized to receive ozanimod 1 mg capsules during the optional blinded extension period for an additional 96 weeks of treatment.	
Reporting group title	Ozanimod 1 mg - 1mg (Part A Extension)
Reporting group description:	
Participants received ozanimod 1 mg capsules PO daily during the 24-week placebo-controlled treatment phase. Participants were given the option to enter into a blinded extension phase and continued to receive ozanimod 1 mg capsules PO daily for an additional 96 weeks of treatment.	
Subject analysis set title	Placebo (Part A Core)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received placebo capsules (identical in appearance to RPC1063) by mouth (PO) daily during the 24-week placebo-controlled phase.	

Subject analysis set title	Ozanimod 0.5 mg (Part A Core)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received ozanimod 0.5 mg capsules PO daily during the 24-week placebo-controlled treatment phase

Subject analysis set title	Ozanimod 1 mg (Part A Core)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received ozanimod 1 mg capsules PO daily during the 24-week placebo-controlled treatment phase.

Subject analysis set title	Interferon Beta-1a (IFN β-1a) (Part B)
Subject analysis set type	Intention-to-treat

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 daily 24 months.

Subject analysis set title	Ozanimod 0.5 mg (Part B)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received ozanimod 0.5 mg capsules PO daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for 24 months.

Subject analysis set title	Ozanimod 1 mg (Part B)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received ozanimod 1 mg capsules PO daily and an intramuscular placebo injection (identical in appearance to interferon) weekly for 24 months.

Primary: Part A: The Total Number of Gadolinium-Enhancing Lesions Assessed on Brain Magnetic Resonance Imaging (MRI) from Week 12 to Week 24

End point title	Part A: The Total Number of Gadolinium-Enhancing Lesions Assessed on Brain Magnetic Resonance Imaging (MRI) from Week 12 to Week 24[1]

End point description:

The number of gadolinium-enhancing lesions per MRI scan was measured as the total number of Gd-enhancing lesions that occurred from Week 12 to Week 24. Missing GdE data values were imputed using the last valid non-missing, post-baseline observation which was carried forward if the participant was only missing 1 or 2 consecutive post-baseline scans. If there were no post-baseline values to be carried forward or if the participant was missing more than 2 consecutive scans then the mean number of lesions from participants in the same treatment group at the same visit was used as the imputed value. The ITT population is defined as all randomized participants who received at least 1 dose of study drug; participants analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different. Includes participants with non-missing MRI results and included to the analysis population.

End point type	Primary

End point timeframe:

From Week 12 to Week 24

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Part A: The Total Number of Gadolinium-Enhancing Lesions Assessed on Brain Magnetic Resonance Imaging (MRI) from Week 12 to Week 24 statistical analysis was performed in the study for Part A only.

End point values	Placebo (Part A Core)	Ozanimod 0.5 mg (Part A Core)	Ozanimod 1 mg (Part A Core)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	87	83	
Units: Brain Lesions				
arithmetic mean (standard deviation)	11.1 (± 29.86)	1.5 (± 3.68)	1.5 (± 3.44)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo (Part A Core) v Ozanimod 1 mg (Part A Core)
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001 [3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Comparison between the active and placebo arms is based on a stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline.
[3] - To account for multiple comparisons, each of the 2 treatment comparisons was tested at the alpha = 0.04944 level of significance.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo (Part A Core) v Ozanimod 0.5 mg (Part A Core)
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001 [5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - Comparison between the active and placebo arms is based on a stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline
[5] - To account for multiple comparisons, each of the 2 treatment comparisons was tested at the alpha = 0.04944 level of significance

Primary: Part B: Adjusted Annualized Relapse Rate (ARR) at the End of Month 24

End point title	Part B: Adjusted Annualized Relapse Rate (ARR) at the End of Month 24

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 a blinded EDSS evaluator) were confirmed by a 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 relapse rate (per person) was calculated as the number of relapses for an individual patient divided by the number of days that patient participated in the study, and multiplied by 365.25. The adjusted ARR was performed using a Poisson regression model. The ITT population included all randomized participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

At the end of month 24

End point values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	441	439	433	
Units: Relapses/Year				
least squares mean (confidence interval 95%)	0.276 (0.234 to 0.324)	0.218 (0.183 to 0.259)	0.172 (0.142 to 0.208)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 1 mg (Part B)
Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001 [7]
Method	Poisson regression model
Parameter estimate	Rate Ratio
Point estimate	0.623
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.506
upper limit	0.768

Notes:

[6] - To account for multiple comparisons, each of the 2 treatment (0.5 mg and 1 mg ozanimod vs IFN) comparisons was tested at the alpha = 0.025 level.

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

Statistical analysis title	Statistical Analysis 2
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 0.5 mg (Part B)
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.0167 [9]
Method	Poisson Regression Model
Parameter estimate	Rate Ratio
Point estimate	0.791
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.652
upper limit	0.958

Notes:

[8] - To account for multiple comparisons, each of the 2 treatment (0.5 mg and 1 mg ozanimod vs IFN) comparisons was tested at the alpha = 0.025 level.
[9] - Adjusted for region, age at baseline and the baseline number of gadolinium-enhancing (GdE) lesions, and included the natural log transformation of time on study as an offset term.

Secondary: Part A: The Number of Gadolinium-Enhancing Lesions on Brain MRI Scan at Week 24

End point title	Part A: The Number of Gadolinium-Enhancing Lesions on Brain MRI Scan at Week 24[10]

End point description:

The number of Gd-enhancing lesions per MRI scan was measured as the total number of Gd-enhancing lesions that occurred at Week 24. The ITT population is defined as all randomized participants who received at least 1 dose of study drug. Missing GdE data values were imputed using the mean number of lesions from participants in the same treatment group at the same visit.

End point type	Secondary

End point timeframe:

At Week 24

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Part A: The Number of Gadolinium-Enhancing Lesions on Brain MRI Scan at Week 24 statistical analysis was performed in the study for Part A only

End point values	Placebo (Part A Core)	Ozanimod 0.5 mg (Part A Core)	Ozanimod 1 mg (Part A Core)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	87	83	
Units: Lesions				
arithmetic mean (standard deviation)	3.2 (± 9.80)	0.3 (± 0.86)	0.2 (± 0.59)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo (Part A Core) v Ozanimod 1 mg (Part A Core)
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - Comparison between the active and placebo arms is based on a stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo (Part A Core) v Ozanimod 0.5 mg (Part A Core)

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - Comparison between the active and placebo arms is based on a stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline.

Secondary: Part A: The Total Number of New or Enlarging Hyperintense T2-Weighted Brain MRI Lesions from Week 12 to Week 24

End point title	Part A: The Total Number of New or Enlarging Hyperintense T2-Weighted Brain MRI Lesions from Week 12 to Week 24[13]

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 from Week 12 to Week 24. The ITT population is defined as all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Week 12 to Week 24

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Part A: The Total Number of New or Enlarging Hyperintense T2-Weighted Brain MRI Lesions from Week 12 to Week 24 statistical analysis was performed in the study for Part A only.

End point values	Placebo (Part A Core)	Ozanimod 0.5 mg (Part A Core)	Ozanimod 1 mg (Part A Core)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	87	83	
Units: Brain Lesions				
arithmetic mean (standard deviation)	9.0 (± 20.87)	1.4 (± 3.21)	0.8 (± 1.86)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo (Part A Core) v Ozanimod 1 mg (Part A Core)
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - Comparison between the active and placebo arms is based on a stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo (Part A Core) v Ozanimod 0.5 mg (Part A Core)

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - Comparison between the active and placebo arms is based on a stratified Wilcoxon-Mann-Whitney test, stratified by presence of GdE lesions at baseline.

Secondary: Part A: Adjusted Annualized Relapse Rate (ARR) at Week 24

End point title	Part A: Adjusted Annualized Relapse Rate (ARR) at Week 24[16]

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 ITT population consisted of all randomized participants who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

At the End of Week 24

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Part A: The Adjusted Annualized Relapse Rate (ARR) at Week 24 statistical analysis was performed in the study for Part A only.

End point values	Placebo (Part A Core)	Ozanimod 0.5 mg (Part A Core)	Ozanimod 1 mg (Part A Core)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	87	83	
Units: Relapses/Year				
least squares mean (confidence interval 95%)	0.50 (0.22 to 1.15)	0.35 (0.15 to 0.82)	0.24 (0.09 to 0.61)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo (Part A Core) v Ozanimod 1 mg (Part A Core)
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0531 [17]
Method	Poisson regression model
Parameter estimate	Rate Ratio
Point estimate	0.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.01

Notes:

[17] - Adjusted for region, the number of relapses within 24 months prior to the study, and the presence of GdE lesions as baseline.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo (Part A Core) v Ozanimod 0.5 mg (Part A Core)
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2714 [18]
Method	Poisson regression model
Parameter estimate	Rate Ratio
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.34

Notes:

[18] - Adjusted for region, the number of relapses within 24 months prior to the study, and the presence of GdE lesions as baseline.

Secondary: Part A: Number of Participants With Treatment Emergent Adverse Events (TEAE) During the Placebo-Controlled Treatment Phase

End point title	Part A: Number of Participants With Treatment Emergent Adverse Events (TEAE) During the Placebo-Controlled Treatment Phase[19]

End point description:

A TEAE was defined as any event with an onset date on or after first dose date, or any ongoing event on the first dose date that worsened in severity after first dose date to the time that the participant concluded or was terminated in the study. AEs included, but were not limited to a worsening or change in nature, severity, or frequency of conditions present at the start of the study, patient deterioration due to primary illness, intercurrent illness and drug interaction. A serious AE (SAE) was defined as any untoward medical occurrence that at any dose results in death, was life threatening, required inpatient hospitalization or prolongation of existing inpatient hospitalization, was a congenital abnormality or birth defect, or resulted in significant disability/incapacity. Adverse events were classified by severity (mild, moderate and severe).

End point type	Secondary

End point timeframe:

Day 1 of first dose of study drug to the time that the participant concluded or was terminated in the study. The maximum duration of exposure in the ozanimod 0.5 mg arm was 189 days and 190 days in the ozanimod 1 mg arm.

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses were performed for the TEAE during the placebo-controlled period in 201 Part A.

End point values	Placebo (Part A Core)	Ozanimod 0.5 mg (Part A Core)	Ozanimod 1 mg (Part A Core)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	87	83	
Units: Participants				
Any TEAE	52	57	47	
Any Moderate or Severe TEAE	23	23	13	
Any Severe TEAE	1	2	1	
Any Possible, Probable or Related TEAE	11	19	15	
Any Related TEAE	1	1	0	
Any Serious TEAE|	0	3	0	
Any Related Serious TEAE	0	0	0	
Any TEAE Leading to Discontinuation of Drug	0	0	0	
Any Death Related to RPC1063	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Participants With Treatment Emergent Adverse Events During the Placebo Controlled and Blinded Extension Phase

End point title	Part A: Number of Participants With Treatment Emergent Adverse Events During the Placebo Controlled and Blinded Extension Phase

End point description:

A TEAE was defined as any adverse event with a start date on or after the date of first dose of study drug up through the first dose of study drug in the open-label extension for those who continued into the open-label extension. AEs included, but were not limited to a worsening or change in nature, severity, or frequency of conditions present at the tart of the study, patient deterioration due to primary illness, intercurrent illness and drug interaction. A serious AE (SAE) was defined as any untoward medical occurrence that at any dose results in death, was life threatening, required inpatient hospitalization or prolongation of existing inpatient hospitalization, was a congenital abnormality or birth defect, or resulted in significant disability/incapacity. Adverse events were classified by severity (mild, moderate and severe).

End point type	Secondary

End point timeframe:

Day 1 of first dose of study drug to the time that the participant concluded or was terminated in the study; maximum duration of exposure for PBO-Ozanimod 0.5 mg was 30.82 months, 37.04 months for Ozanimod 0.5 mg-0.5mg, 33.21 months for PBO-Ozanimod 1mg.

End point values	Placebo-Ozanimod 0.5 mg (Part A Extension)	Ozanimod 0.5 mg - 0.5 mg (Part A Extension)	Placebo-Ozanimod 1 mg (Part A Extension)	Ozanimod 1 mg - 1mg (Part A Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	85	42	81
Units: Participants				
Any TEAE	26	73	32	61
Any Moderate or Severe TEAE	17	42	18	35
Any Severe TEAE	2	4	1	2

Any Possible, Probable or Related TEAE	11	30	12	26
Any Related TEAE	2	3	1	3
Any Serious TEAE|	2	10	3	6
Any Related Serious TEAE	0	0	0	0
Any TEAE Leading to Discontinuation of Ozanimod	2	1	1	0
Any Death Related to Ozanimod	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Adjusted Mean Number of New or Enlarging Hyperintense T2-Weighted Brain Magnetic Resonance Imaging Lesions Per Scan Over 24 Months

End point title	Part B: Adjusted Mean Number of New or Enlarging Hyperintense T2-Weighted Brain Magnetic Resonance Imaging Lesions Per Scan Over 24 Months

End point description:

The adjusted mean 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 24 months. Adjusted mean (95% CI) over 24 months was calculated as the model-based adjusted mean (95% CI) per scan multiplied by the mean number of available MRI scans over 24 months. The ITT population included all randomized participants who received at least 1 dose of study drug. Includes participants with non-missing MRI results.

End point type	Secondary

End point timeframe:

24 month treatment period; MRI scans performed at baseline, at month 12 and 24

End point values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	336	329	327	
Units: Lesions/Scan				
least squares mean (confidence interval 95%)	3.183 (2.640 to 3.838)	2.092 (1.741 to 2.514)	1.835 (1.523 to 2.211)	

Statistical analyses

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

Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	< 0.0001 [21]
Method	Negative Binomial Regression Model
Parameter estimate	Rate Ratio
Point estimate	0.576
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.465
upper limit	0.714

Notes:

[20] - To control for type 1 error, the 3 key secondary endpoints were tested in order in a sequential, closed hierarchical testing procedure. Each comparison was tested at the alpha = 0.05 level
[21] - Adjusted for region, age at baseline, and baseline GdE lesions; included the natural log transformation of available MRI scans as an offset term.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 1 mg (Part B)
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	< 0.0001 [23]
Method	Negative binomial regression model
Parameter estimate	Rate Ratio
Point estimate	0.657
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.531
upper limit	0.813

Notes:

[22] - To control for type 1 error, the 3 key secondary endpoints were tested in order in a sequential, closed hierarchical testing procedure. Each comparison was tested at the alpha = 0.05 level
[23] - Adjusted for region, age at baseline, and baseline GdE lesions; included the natural log transformation of available MRI scans as an offset term.

Secondary: Part B: Adjusted Mean Number of Gadolinium Enhancing Brain Lesions per Scan at Month 24

End point title	Part B: Adjusted Mean Number of Gadolinium Enhancing Brain Lesions per Scan at Month 24

End point description:

The number of GdE T1-lesions per MRI scan was measured as the total number of Gd- enhancing T1-lesions on the 24-month MRI scan. The ITT population consisted of all randomized participants who received at least 1 dose of study medication. Includes participants with non-missing MRI results.

End point type	Secondary

End point timeframe:

Month 24

End point values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	336	329	237	
Units: Lesions				
least squares mean (confidence interval 95%)	0.373 (0.256 to 0.543)	0.197 (0.131 to 0.296)	0.176 (0.116 to 0.266)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 1 mg (Part B)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	< 0.0006 [25]
Method	Negative Binomial Regression Model
Parameter estimate	Rate Ratio
Point estimate	0.471
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.306
upper limit	0.725

Notes:

[24] - To control for type 1 error, the 3 key secondary endpoints were tested in order in a sequential, closed hierarchical testing procedure. Each comparison was tested at the alpha = 0.05 level.
[25] - Adjusted for region, age at baseline, and baseline GdE lesions. Included the natural log transformation of the number available MRI scans at 24 month was used as an offset term.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 0.5 mg (Part B)
Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	< 0.003 [27]
Method	Negative binomial regression model
Parameter estimate	Rate Ratio
Point estimate	0.528
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.346
upper limit	0.805

Notes:

[26] - To control for type 1 error, the 3 key secondary endpoints were tested in order in a sequential, closed hierarchical testing procedure. Each comparison was tested at the alpha = 0.05 level.
[27] - Adjusted for region, age at baseline, and baseline GdE lesions. Included the natural log transformation of the number available MRI scans at 24 month was used as an offset term.

Secondary: Part B: Time to Onset of Disability Progression Confirmed After 3 Months

End point title	Part B: Time to Onset of Disability Progression Confirmed After 3 Months

End point description:

The Expanded Disability Status Scale (EDSS) is an ordinal scale in half-point increments that quantifies disability progression in MS patients over time. It assesses seven functional (neurologic) systems and ambulation scores that are combined to determine the EDSS score ranging from 1 (normal) to 10 (death due to MS) with higher scores indicating greater disability. The 7 Functional System (FS) scales are: pyramidal, cerebellar, brainstem, sensory, bowel or bladder, visual, and cerebral. Disability progression was defined by a sustained worsening (increase) in EDSS of 1.0 points or more from baseline, confirmed after 3 months. Participants were censored if follow-up ended before a sustained progression occurred, whether due to the patient completing study, withdrawing from the study, or due to the cutoff of data collection for the analysis. The ITT population consisted of all randomized participants who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

For the duration of the entire treatment period; 24 months

End point values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	441[28]	439[29]	433[30]	
Units: days				
median (confidence interval 95%)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	

Notes:

[28] - 99999 = data was not estimable as there were insufficient disability events at 3 months

[29] - 99999 = data was not estimable as there were insufficient disability events at 3 months

[30] - 99999 = data was not estimable as there were insufficient disability events at 3 months

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 1 mg (Part B)
Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.8224 [32]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.711
upper limit	1.537

Notes:

[31] - Cox proportional hazard model with factors for treatment group

[32] - Adjusted for region (Eastern Europe vs Rest of World) age at baseline, and baseline EDSS score.

Statistical analysis title	Statistical Analysis 2

Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 0.5 mg (Part B)
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.2849 [34]
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.798
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.528
upper limit	1.206

Notes:

[33] - Cox proportional hazard model with factors for treatment group.

[34] - Adjusted for region (Eastern Europe vs Rest of World) age at baseline, and baseline EDSS score.

Secondary: Part B: Time to Onset of Disability Progression Confirmed After 6 months

End point title	Part B: Time to Onset of Disability Progression Confirmed After 6 months

End point description:

The Expanded Disability Status Scale (EDSS) is an ordinal scale in half-point increments that quantifies disability progression in MS patients over time. It assesses seven functional (neurologic) systems and ambulation scores that are combined to determine the EDSS score ranging from 1 (normal) to 10 (death due to MS) with higher scores indicating greater disability. The 7 Functional System (FS) scales are: pyramidal, cerebellar, brainstem, sensory, bowel or bladder, visual, and cerebral. Disability progression was defined by a sustained worsening (increase) in EDSS of 1.0 points or more from baseline, confirmed after 6 months. Participants were censored if follow-up ended before a sustained progression occurred, whether due to the patient completing study, withdrawing from the study, or due to the cutoff of data collection for the analysis. The ITT population consisted of all randomized participants who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

For the duration of the entire treatment period; 24 months

End point values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	441[35]	439[36]	433[37]	
Units: days				
median (confidence interval 95%)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	

Notes:

[35] - 99999 = Not Estimable as there were insufficient disability events at 6 months

[36] - 99999 = Not Estimable as there were insufficient disability events at 6 months

[37] - 99999 = Not Estimable as there were insufficient disability events at 6 months

Statistical analyses

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

Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.1353 [39]
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.435
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.893
upper limit	2.305

Notes:

[38] - Cox proportional hazard model with factors for treatment group.

[39] - Adjusted for region (Eastern Europe vs Rest of World) age at baseline, and baseline EDSS score.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 0.5 mg (Part B)
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.7154 [41]
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.098
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.664
upper limit	1.815

Notes:

[40] - Cox proportional hazard model with factors for treatment group.

[41] - Adjusted for region (Eastern Europe vs Rest of World) age at baseline, and baseline EDSS score.

Secondary: Part B: Percentage of Participants Who Were Gadolinium Enhancing Lesion-Free at Month 24

End point title	Part B: Percentage of Participants Who Were Gadolinium Enhancing Lesion-Free at Month 24

End point description:

Participants were considered lesion free at Month 24 if they did not show evidence of GdE lesions at the month 24 MRI scan. The ITT population included all randomized participants who received at least 1 dose of study drug; analysis included non-responder imputation that being as not lesion-free.

End point type	Secondary

End point timeframe:

Month 24

End point values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	441	439	433	
Units: Percentage of Participants				
number (confidence interval 95%)	56.2 (51.6 to 60.9)	63.3 (58.8 to 67.8)	65.6 (61.1 to 70.1)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 1 mg (Part B)
Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0047 [42]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Percentage
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.9
upper limit	15.8

Notes:

[42] - Stratified by region (Eastern Europe vs Rest of the World) and EDSS category per Interactive Voice Response System (IVRS).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 0.5 mg (Part B)
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 [43]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Percentage
Point estimate	7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	13.6

Notes:

[43] - Stratified by region (Eastern Europe vs Rest of the World) and EDSS category per Interactive Voice Response System (IVRS).

Secondary: Part B: Percentage of Participants Who Were New or Enlarging T2 Lesion-Free at Month 24

End point title	Part B: Percentage of Participants Who Were New or Enlarging

	T2 Lesion-Free at Month 24

End point description:

Participants were considered T2 lesion free at Month 24 if they did not show evidence of a relapse in T2 lesions at month 24. The ITT population consisted of all randomized participants who received at least 1 dose of study medication; participants who were missing the Month 24 MRI data were considered non-responders, ie, as not being lesion-free.

End point type	Secondary

End point timeframe:

Month 24

End point values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	441	439	433	
Units: Percentage of Participants				
number (confidence interval 95%)	18.4 (14.8 to 22.0)	23.5 (19.5 to 27.4)	23.8 (19.8 to 27.8)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 1 mg (Part B)
Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0466 [44]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Percentage
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	10.8

Notes:

[44] - Based on the Cochran-Mantel-Haenszel test stratified by region (Eastern Europe vs. rest of the world) and EDSS category per IVRS.

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

Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0581 [45]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Percentage
Point estimate	5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	10.5

Notes:

[45] - Based on the Cochran-Mantel-Haenszel test stratified by region (Eastern Europe vs. rest of the world) and EDSS category per IVRS.

Secondary: Part B: Percent Change in Normalized Brain Volume (Atrophy) on Brain MRI Scans from Baseline to Month 24

End point title	Part B: Percent Change in Normalized Brain Volume (Atrophy) on Brain MRI Scans from Baseline to Month 24

End point description:

Atrophy or loss in brain volume was measured by MRI scan from baseline to month 24. Observed values for the ITT Population; included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline and Month 24

End point values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	439	437	432	
Units: Percent Change in Brain Volume Loss				
median (full range (min-max))				
Baseline	1455.662 (1208.191 to 1667.703)	1452.878 (1171.858 to 1663.032)	1445.978 (1190.494 to 1660.718)	
Percent Change from Baseline to Month 24	-0.940 (-5.33 to 1.44)	-0.710 (-5.21 to 1.36)	-0.690 (-5.65 to 0.85)	

Statistical analyses

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

Number of subjects included in analysis	871
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [46]
Method	Rank Ancova

Notes:

[46] - Based on the analysis of covariance model, adjusted for region, and EDSS category per IVRS, with the dependent variable as the residual of the rank of brain volume at Baseline (Month 12 brain volume for Percent Change from Month 12 to Month 24).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 0.5 mg (Part B)
Number of subjects included in analysis	876
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [47]
Method	Rank Ancova

Notes:

[47] - Based on the analysis of covariance model, adjusted for region, and EDSS category per IVRS, with the dependent variable as the residual of the rank of brain volume at Baseline (Month 12 brain volume for Percent Change from Month 12 to Month 24).

Secondary: Part B: Change in Multiple Sclerosis Functional Composite (MSFC) Score from Baseline to Month 24 (including the Low-Contrast Letter Acuity test [LCLA] Measurement of Visual Function as a Component)

End point title	Part B: Change in Multiple Sclerosis Functional Composite (MSFC) Score from Baseline to Month 24 (including the Low-Contrast Letter Acuity test [LCLA] Measurement of Visual Function as a Component)

End point description:

The MSFC-LCLA is a battery of tests including 4 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 is a quantitative measure of upper extremity (arm and hand) function • The Symbol Digit Modalities Test is a measure of executive cognitive function that assesses processing speed, flexibility, and calculation ability • 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 Z -score. A z-score represents the number of standard deviations a patient's test result is higher (z >0) or lower (z <0) than the average test result (z = 0) of the reference population. A score of +1 indicates that, on average, an individual scored 1 standard deviation better than the reference population and a score of -1 indicates that an individual scored 1 SD worse than the reference population.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	437	435	428	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.052 (± 0.601)	0.036 (± 0.440)	-0.010 (± 0.622)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 1 mg (Part B)
Number of subjects included in analysis	865
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.248 [48]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.116

Notes:

[48] - Based on the analysis of covariance model, adjusted for region, EDSS category per IVRS and baseline MSFC Z-score

Statistical analysis title	Statistical Analysis 2
Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 0.5 mg (Part B)
Number of subjects included in analysis	872
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0123 [49]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.093
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.165

Notes:

[49] - Based on the analysis of covariance model, adjusted for region, EDSS category per IVRS, and baseline MSFC Z-score

Secondary: Part B: Mean Change in Multiple Sclerosis Quality of Life (MSQOL)-54 Score from Baseline to Month 24

End point title	Part B: Mean Change in Multiple Sclerosis Quality of Life (MSQOL)-54 Score from Baseline to Month 24

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, plus statistical analysis are reported. Each domain has a range from 0 to 100 where higher means better. The ITT population consisted of all randomized participants who received at least 1 dose of study drug. Missing data were imputed using a mixed effects regression model.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	441	439	433	
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical Health Composite Summary	-1.526 (± 12.319)	0.609 (± 12.315)	0.209 (± 12.321)	
Mental Health Composite Summary	-1.831 (± 16.422)	-1.182 (± 14.379)	-1.517 (± 15.544)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of Physical Health Composite Summary Month 24

Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 1 mg (Part B)
Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0988 [50]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.345
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.252
upper limit	2.943

Notes:

[50] - Based on the analysis of covariance model, adjusted for region, EDSS category per IVRS, and the baseline summary score of interest.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis of Physical Health Composite Summary Month 24

Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 0.5 mg

	(Part B)
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0228 [51]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.849
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.258
upper limit	3.44

Notes:

[51] - Based on the analysis of covariance model, adjusted for region, EDSS category per IVRS, and the baseline summary score of interest.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis of Mental Health Composite Summary Month 24

Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 1 mg (Part B)
Number of subjects included in analysis	874
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6997 [52]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.553
upper limit	2.313

Notes:

[52] - Based on the analysis of covariance model, adjusted for region, EDSS category per IVRS, and the baseline summary score of interest.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Analysis of Mental Health Composite Summary Month 24

Comparison groups	Interferon Beta-1a (IFN β-1a) (Part B) v Ozanimod 0.5 mg (Part B)
Number of subjects included in analysis	880
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5501 [53]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.587

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.339
upper limit	2.513

Notes:

[53] - Based on the analysis of covariance model, adjusted for region, EDSS category per IVRS, and the baseline summary score of interest.

Secondary: Part B: Number of Participants with Treatment Emergent Adverse Events (TEAEs) During Part B

End point title	Part B: Number of Participants with Treatment Emergent Adverse Events (TEAEs) During Part B

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 TEAE = an AE with a start date on or after the date of first dose of IP to the time that the participant concluded or was terminated in the study. 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 consisted of all participants who received at least 1 dose of randomized study medication.

End point type	Secondary

End point timeframe:

Day 1 of first dose of study drug to the time that the participant concluded or was terminated in the study; the overall maximum study duration of exposure to IFN = 24.46 months, 25.05 months for ozanimod 0.5 mg and 25.05 months for ozanimod 1 mg.

End point values	Interferon Beta-1a (IFN β-1a) (Part B)	Ozanimod 0.5 mg (Part B)	Ozanimod 1 mg (Part B)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	440	439	434	
Units: Participants				
number (not applicable)				
Any TEAE	365	326	324	
Any Moderate or Severe TEAE	235	169	170	
Any Severe TEAE	19	19	15	
Any Suspected TEAE	113	104	115	
Any Related TEAE	30	12	19	
Any Serious TEAE	28	31	28	
Any Suspected Serious TEAE	3	4	4	
Any Related Serious TEAE	0	1	1	
Any TEAE Leading to Stopping of Study Drug	18	14	13	
Any TEAE Leading to Study Withdrawal	20	13	13	
Any Death	0	1	1	
Any Death on Study	0	1	0	

Statistical analyses

No statistical analyses for this end point

Post-hoc: Summary of Gadolinium-Enhancing Lesion Counts by Visit in the Extension Period

End point title	Summary of Gadolinium-Enhancing Lesion Counts by Visit in the Extension Period

End point description:

Summary of Gadolinium-Enhancing Lesion Counts by Visit in the Extension Period.

End point type	Post-hoc

End point timeframe:

From Week 24 to Week 120

End point values	Placebo-Ozanimod 0.5 mg (Part A Extension)	Ozanimod 0.5 mg - 0.5 mg (Part A Extension)	Placebo-Ozanimod 1 mg (Part A Extension)	Ozanimod 1 mg - 1mg (Part A Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41[54]	85[55]	42[56]	81[57]
Units: Lesions				
geometric mean (standard error)				
Week 24	4.5 (± 13.02)	0.4 (± 1.28)	1.9 (± 5.93)	0.2 (± 0.60)
Week 72	0.4 (± 1.95)	0.4 (± 1.60)	0.1 (± 0.28)	0.2 (± 0.56)
Week 120	0.1 (± 0.46)	0.4 (± 1.49)	0.1 (± 0.37)	0.2 (± 0.51)

Notes:

[54] - Week 72 = 38
Week 120 N = 37
[55] - Week 72 N = 76
Week 120 N = 72
[56] - Week 72 N = 37
Week 120 N = 36
[57] - Week 72 N = 79
Week 120 N = 74

Statistical analyses

No statistical analyses for this end point

Post-hoc: The Total Number of New or Enlarging Hyperintense T2-Weighted Brain MRI Lesions In the Blinded Extension Period

End point title	The Total Number of New or Enlarging Hyperintense T2-Weighted Brain MRI Lesions In the Blinded Extension Period

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 on MRI

End point type	Post-hoc

End point timeframe:

From Week 0 to Week 24 of Part A of the 201A Core Period and Year 1 and 2 of the Extension Period

End point values	Placebo-Ozanimod 0.5 mg (Part A Extension)	Ozanimod 0.5 mg - 0.5 mg (Part A Extension)	Placebo-Ozanimod 1 mg (Part A Extension)	Ozanimod 1 mg - 1mg (Part A Extension)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41[58]	85[59]	42[60]	81[61]
Units: lesions				
geometric mean (standard error)				
ROC01-201A Core (Weeks 0 to 24)	10.8 (± 3.58)	1.4 (± 0.35)	7.3 (± 3.07)	0.9 (± 0.21)
Year 1 In Extension Study	4.3 (± 1.99)	2.8 (± 0.72)	1.5 (± 0.39)	1.9 (± 0.84)
Year 2 In Extension Study	3.2 (± 1.31)	2.3 (± 0.61)	1.9 (± 0.48)	0.7 (± 0.16)

Notes:

[58] - Year 1 N = 38
Year 2 N = 37

[59] - Year 1 N = 76
Year 2 N = 71

[60] - Year 1 N = 37
Year 2 N = 36

[61] - Year 1 N = 79
Year 2 N = 74

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

From Day 1 of study drug to the date that the participant concluded or was terminated in the study. AEs are reported for Part A placebo-controlled and extension periods followed by Part B for 2 years.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Placebo (Part A Core)

Reporting group description:

Participants received placebo capsules (identical in appearance to ozanimod) PO daily during the placebo-controlled phase (Weeks 0-24).

Reporting group title	Ozanimod 0.5 mg (Part A Core)

Reporting group description:

Participants received ozanimod 0.5 mg capsules PO daily during the placebo-controlled phase (Weeks 0 to 24).

Reporting group title	Ozanimod 1.0 mg (Part A Core)

Reporting group description:

Participants received ozanimod 1 mg capsules PO daily during the placebo-controlled phase (Weeks 0 to 24).

Reporting group title	Ozanimod 0.5 mg (Part A Extension)

Reporting group description:

Participants received ozanimod 0.5 mg capsules PO daily during the blinded extension phase (Weeks 25 to 96).

Reporting group title	Ozanimod 1.0 mg (Part A Extension)

Reporting group description:

Participants received ozanimod 1 mg capsules PO daily during the blinded extension phase (Weeks 25 to 96).

Reporting group title	Interferon ß-1a 30 µg (Part B)

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 daily for 24 months.

Reporting group title	Ozanimod 0.5 mg (Part B)

Reporting group description:

Participants received ozanimod 0.5 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to Interferon) weekly for 24 months.

Reporting group title	Ozanimod 1.0 mg (Part B)

Reporting group description:

Participants received ozanimod 1 mg oral capsules daily and an intramuscular placebo injection (identical in appearance to Interferon) weekly for 24 months.

Serious adverse events	Placebo (Part A Core)	Ozanimod 0.5 mg (Part A Core)	Ozanimod 1.0 mg (Part A Core)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 88 (0.00%)	3 / 87 (3.45%)	0 / 83 (0.00%)
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)			
Breast Cancer			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Lymphocytic Leukaemia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Breast Carcinoma			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratoacanthoma			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Melanoma In Situ			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medulloblastoma			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Fibroma			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pregnancy, puerperium and perinatal conditions			
Foetal Growth Restriction			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Placental Polyp			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vanishing Twin Syndrome			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Cyst			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drowning			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast Cyst			

subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Polyp			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysfunctional Uterine Bleeding			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menometrorrhagia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Cyst			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Cervical Squamous Metaplasia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	0 / 83 (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 Haemorrhage			

subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Polyp			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somatoform Disorder			
subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	0 / 83 (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
Suicide Attempt			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	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 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carbon Monoxide Poisoning			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle Fracture			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Comminuted Fracture			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral Injury			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Overdose			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw Fracture			

subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint Injury			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament Sprain			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Limb Fracture			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Fracture			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Tachycardia			

subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular Tachycardia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Acoustic Neuritis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autonomic Nervous System Imbalance			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cauda Equina Syndrome			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central Nervous System Lesion			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Haemorrhage			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Infarction			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Radiculopathy			

subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre Syndrome			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial Aneurysm			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Radiculopathy			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Sclerosis Relapse			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			

subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic Neuritis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	0 / 83 (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
Sciatica			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech Disorder			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Keratoconus			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal Pain			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Wall Haematoma			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable Bowel Syndrome			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Polyp			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical Hernia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis Chronic			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperplastic Cholecystopathy			

subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin Ulcer			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stasis Dermatitis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus Urinary			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Kidney Disease			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Colic			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral Stenosis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Goitre			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Disorder			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteitis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudarthrosis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid Arthritis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute Hepatitis B			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Appendicitis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Sinusitis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis Infectious			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ozanimod 0.5 mg	Ozanimod 1.0 mg	Interferon ß-1a 30

	(Part A Extension)	(Part A Extension)	µg (Part B)
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 126 (7.94%)	9 / 123 (7.32%)	28 / 440 (6.36%)
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)			
Breast Cancer			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Lymphocytic Leukaemia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Breast Carcinoma			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratoacanthoma			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Melanoma In Situ			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medulloblastoma			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Fibroma			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Foetal Growth Restriction			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Placental Polyp			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vanishing Twin Syndrome			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Cyst			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drowning			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast Cyst			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Polyp			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysfunctional Uterine Bleeding			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menometrorrhagia			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	0 / 440 (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
Metrorrhagia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Cyst			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Cervical Squamous Metaplasia			

subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Haemorrhage			
subjects affected / exposed	0 / 126 (0.00%)	1 / 123 (0.81%)	0 / 440 (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 Polyp			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 126 (0.00%)	1 / 123 (0.81%)	0 / 440 (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
Somatoform Disorder			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carbon Monoxide Poisoning			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle Fracture			
subjects affected / exposed	0 / 126 (0.00%)	1 / 123 (0.81%)	0 / 440 (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
Comminuted Fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral Injury			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	0 / 440 (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
Intentional Overdose			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Jaw Fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint Injury			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament Sprain			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Limb Fracture			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Tachycardia			

subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular Tachycardia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Acoustic Neuritis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autonomic Nervous System Imbalance			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cauda Equina Syndrome			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	0 / 440 (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
Central Nervous System Lesion			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Haemorrhage			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Infarction			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Radiculopathy			

subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre Syndrome			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 126 (0.00%)	1 / 123 (0.81%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial Aneurysm			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	0 / 440 (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
Lumbar Radiculopathy			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Sclerosis Relapse			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			

subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic Neuritis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech Disorder			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 126 (0.00%)	1 / 123 (0.81%)	0 / 440 (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
Eye disorders			
Keratoconus			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal Pain			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Wall Haematoma			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable Bowel Syndrome			
subjects affected / exposed	0 / 126 (0.00%)	1 / 123 (0.81%)	0 / 440 (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
Large Intestine Polyp			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical Hernia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis Chronic			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperplastic Cholecystopathy			

subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin Ulcer			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stasis Dermatitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 123 (0.81%)	0 / 440 (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
Urticaria			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus Urinary			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Kidney Disease			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Colic			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral Stenosis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 123 (0.81%)	0 / 440 (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
Endocrine disorders			

Goitre			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
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 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
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 Protrusion			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudarthrosis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid Arthritis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 123 (0.81%)	0 / 440 (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			
Acute Hepatitis B			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Appendicitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	2 / 440 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Sinusitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis Infectious			
subjects affected / exposed	1 / 126 (0.79%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	1 / 440 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	0 / 440 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ozanimod 0.5 mg	Ozanimod 1.0 mg	

	(Part B)	(Part B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 439 (7.06%)	28 / 434 (6.45%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Lymphocytic Leukaemia			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive Breast Carcinoma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant Melanoma In Situ			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medulloblastoma			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Fibroma			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Foetal Growth Restriction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placental Polyp			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vanishing Twin Syndrome			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cyst			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowning			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast Cyst			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Polyp			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysfunctional Uterine Bleeding			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menometrorrhagia			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Cyst			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Cervical Squamous Metaplasia			

subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Haemorrhage			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Polyp			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somatoform Disorder			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbon Monoxide Poisoning			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle Fracture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted Fracture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral Injury			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional Overdose			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Jaw Fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Injury			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament Sprain			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Limb Fracture			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic Fracture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Tachycardia			

subjects affected / exposed	2 / 439 (0.46%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Acoustic Neuritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic Nervous System Imbalance			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda Equina Syndrome			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central Nervous System Lesion			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haemorrhage			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Radiculopathy			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre Syndrome			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial Aneurysm			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Radiculopathy			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Sclerosis Relapse			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic Neuritis			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech Disorder			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Keratoconus			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal Pain			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Wall Haematoma			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable Bowel Syndrome			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Polyp			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Chronic			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperplastic Cholecystopathy			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin Ulcer			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stasis Dermatitis			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus Urinary			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Kidney Disease			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal Colic			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral Stenosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Goitre			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Disorder			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudarthrosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid Arthritis			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute Hepatitis B			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Appendicitis			
subjects affected / exposed	1 / 439 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Sinusitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis Infectious			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo (Part A Core)	Ozanimod 0.5 mg (Part A Core)	Ozanimod 1.0 mg (Part A Core)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 88 (27.27%)	24 / 87 (27.59%)	10 / 83 (12.05%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 88 (0.00%)	3 / 87 (3.45%)	4 / 83 (4.82%)
occurrences (all)	0	4	4
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 88 (0.00%)	2 / 87 (2.30%)	5 / 83 (6.02%)
occurrences (all)	0	2	5
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 88 (1.14%)	1 / 87 (1.15%)	2 / 83 (2.41%)
occurrences (all)	1	1	2
Orthostatic Hypotension			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 88 (9.09%)	5 / 87 (5.75%)	3 / 83 (3.61%)
occurrences (all)	9	11	4
General disorders and administration site conditions			
Influenza Like Illness			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	9 / 88 (10.23%)	5 / 87 (5.75%)	2 / 83 (2.41%)
occurrences (all)	9	5	2
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	12 / 88 (13.64%)	11 / 87 (12.64%)	5 / 83 (6.02%)
occurrences (all)	15	11	6
Pharyngitis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 87 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 88 (3.41%)	4 / 87 (4.60%)	3 / 83 (3.61%)
occurrences (all)	3	5	4
Urinary Tract Infection			
subjects affected / exposed	2 / 88 (2.27%)	6 / 87 (6.90%)	2 / 83 (2.41%)
occurrences (all)	3	6	2

Non-serious adverse events	Ozanimod 0.5 mg (Part A Extension)	Ozanimod 1.0 mg (Part A Extension)	Interferon ß-1a 30 µg (Part B)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 126 (41.27%)	43 / 123 (34.96%)	275 / 440 (62.50%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	10 / 126 (7.94%)	12 / 123 (9.76%)	20 / 440 (4.55%)
occurrences (all)	17	17	28
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	11 / 126 (8.73%)	8 / 123 (6.50%)	9 / 440 (2.05%)
occurrences (all)	16	10	10
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 126 (6.35%)	2 / 123 (1.63%)	14 / 440 (3.18%)
occurrences (all)	8	2	14
Orthostatic Hypotension			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	27 / 440 (6.14%)
occurrences (all)	0	0	30
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 126 (5.56%)	9 / 123 (7.32%)	53 / 440 (12.05%)
occurrences (all)	14	38	138
General disorders and administration site conditions			

Influenza Like Illness			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	215 / 440 (48.86%)
occurrences (all)	0	0	485
Pyrexia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	27 / 440 (6.14%)
occurrences (all)	0	0	279
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	5 / 126 (3.97%)	7 / 123 (5.69%)	0 / 440 (0.00%)
occurrences (all)	5	12	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	17 / 126 (13.49%)	17 / 123 (13.82%)	48 / 440 (10.91%)
occurrences (all)	37	28	77
Pharyngitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 123 (0.00%)	15 / 440 (3.41%)
occurrences (all)	0	0	16
Upper Respiratory Tract Infection			
subjects affected / exposed	20 / 126 (15.87%)	11 / 123 (8.94%)	37 / 440 (8.41%)
occurrences (all)	25	15	47
Urinary Tract Infection			
subjects affected / exposed	7 / 126 (5.56%)	4 / 123 (3.25%)	17 / 440 (3.86%)
occurrences (all)	11	4	21

Non-serious adverse events	Ozanimod 0.5 mg (Part B)	Ozanimod 1.0 mg (Part B)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	185 / 439 (42.14%)	199 / 434 (45.85%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	29 / 439 (6.61%)	26 / 434 (5.99%)	
occurrences (all)	37	35	
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	16 / 439 (3.64%)	25 / 434 (5.76%)	
occurrences (all)	20	28	
Vascular disorders			

Hypertension			
subjects affected / exposed	20 / 439 (4.56%)	24 / 434 (5.53%)	
occurrences (all)	21	24	
Orthostatic Hypotension			
subjects affected / exposed	27 / 439 (6.15%)	30 / 434 (6.91%)	
occurrences (all)	29	33	
Nervous system disorders			
Headache			
subjects affected / exposed	55 / 439 (12.53%)	44 / 434 (10.14%)	
occurrences (all)	134	187	
General disorders and administration site conditions			
Influenza Like Illness			
subjects affected / exposed	26 / 439 (5.92%)	27 / 434 (6.22%)	
occurrences (all)	38	41	
Pyrexia			
subjects affected / exposed	12 / 439 (2.73%)	10 / 434 (2.30%)	
occurrences (all)	12	11	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 439 (0.00%)	0 / 434 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	59 / 439 (13.44%)	68 / 434 (15.67%)	
occurrences (all)	101	100	
Pharyngitis			
subjects affected / exposed	24 / 439 (5.47%)	17 / 434 (3.92%)	
occurrences (all)	30	23	
Upper Respiratory Tract Infection			
subjects affected / exposed	36 / 439 (8.20%)	34 / 434 (7.83%)	
occurrences (all)	47	42	
Urinary Tract Infection			
subjects affected / exposed	22 / 439 (5.01%)	19 / 434 (4.38%)	
occurrences (all)	30	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2012	1. Modification of the primary objective in Part A from cumulative number of new GdE lesions to cumulative total number of GdE lesions. 2. Addition of a secondary objective in Part A to assess proportion of patients who are free of GdE lesions at Week 24. 3. Modification to treatment duration in Part B to 24 months for all patients. 4. Modification to inclusion/exclusion criteria to remove the exclusion of diagnosis with secondary progressive MS, and to require that patients must discontinue nonlymphocyte-depleting disease-modifying MS agents from signing of the informed consent until randomization. 5. Corresponding changes to study endpoints to accommodate modifications to study objectives in Part A. 6. Change in PK sampling schedule. 7. Addition of QuantiFERON Gold test as alternative to purified protein derivative test for TB screening. 8. Clarification of timing of procedures for Part A patients who elect to enter the blinded extension period after the Week 24 visit. 9. Clarification of unblinding procedure and timing of treatment for relapse. 10. Clarifications to the inclusion/exclusion criteria, study design, study procedures (throughout), Schedule of Assessment and corresponding footnotes, handling missed doses, matching placebo for IFN β-1, allowed/prohibited medications, clinical laboratory procedures, and notifications. Many of the remaining changes were related to consistency within the protocol, addition of clinical laboratory and corresponding contact details, project biostatistician personnel change, correction of typographical errors in the protocol and formatting throughout.
31 July 2013	1. Addition of exploratory endpoint to Part B: "the number of GdE brain MRI lesions at 24 months". 2. Duration of the blinded extension of Part A was increased to at least 48 weeks for all patients (with total duration of Part A of at least 72 weeks, 24 weeks placebo-controlled period and at least 48 weeks blinded extension). 3. Clarifications that for patients continuing to the blinded extension, MRI scans would be performed annually after the Week 24 visit (at approximately Week 72) and/or at the End of-Study Visit. 4. Increase in sample size in Part B to 1200 patients (400 per arm) and modification of sample size justification accordingly. 5. Addition of section on "Considerations for Patients with Comorbid Conditions". 6. Modification to withdrawal criteria and discontinuation of study medication. 7. Modifications to inclusion/exclusion criteria: Inclusion criterion no. 8 – clarification of sexual abstinence, Inclusion criterion no. 9 – clarification regarding proof of immunization for varicella zoster virus, Exclusion criterion no. 7 – specification of excluded cardiac conditions, Exclusion criterion no. 9 – specification of diabetes mellitus history, Addition of exclusion criterion no. 25 on excluded disease modifying therapies, Removal of exclusion criterion regarding B12 deficiency. 8. Modification to statistical methods including Clarification when the interim analysis of Part A would be done, and clarification of the Part B primary analysis per request of FDA. 9. Clarification that dermatological (skin) examination would be done by the investigator, not the dermatologist. 10. Other changes included clarifications to inclusion/exclusion criteria, study design, study procedures (throughout), Schedule of Assessment and corresponding footnotes, number of participating sites in Part A and B, study drug accountability, allowed and prohibited medications, and procedures in case of pregnancy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26879276