Clinical trial results:
Multicenter, non-comparative extension to study AC-058B301, to investigate the long-term safety, tolerability, and control of disease of ponesimod 20 mg in subjects with relapsing multiple sclerosis

Summary

EudraCT number	2016-004719-10
Trial protocol	ES SE PL CZ BG LV HU LT PT HR GB FI GR RO
Global end of trial date	15 January 2024

Results information

Result version number	v1 (current)
This version publication date	30 January 2025
First version publication date	30 January 2025

Trial information

Trial identification

Sponsor protocol code	AC-058B303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03232073
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.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	14 March 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of trial is to describe the long-term (LT) safety and tolerability of ponesimod 20 milligrams (mg) in subjects with relapsing multiple sclerosis (RMS), to describe the effects of reinitiation of ponesimod treatment after interruption in subjects with RMS, to describe the long-term (LT) disease control in subjects with RMS receiving ponesimod 20 mg, and to describe the effect of a switch from teriflunomide to ponesimod 20 mg on disease control in subjects with RMS.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 July 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Bulgaria: 32
Country: Number of subjects enrolled	Croatia: 29
Country: Number of subjects enrolled	Czechia: 83
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Lithuania: 8
Country: Number of subjects enrolled	Poland: 122
Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Spain: 56
Country: Number of subjects enrolled	Sweden: 9

Country: Number of subjects enrolled	Türkiye: 1
Country: Number of subjects enrolled	Bosnia and Herzegovina: 2
Country: Number of subjects enrolled	Ukraine: 100
Country: Number of subjects enrolled	Belarus: 38
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Georgia: 30
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	Russian Federation: 191
Country: Number of subjects enrolled	Serbia: 28
Worldwide total number of subjects	877
EEA total number of subjects	427

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)	877
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Total of 877 subjects entered this extension study from the core study (NCT02425644) and all received at least one dose of ponesimod 20 milligrams (mg) treatment.

Pre-assignment

Screening details:

Efficacy data: reporting extension set (ES) in combined analysis period (all data from randomisation in core study till extension end of study [EOS] for those who entered ES). Safety data: reporting ES in extension analysis period (all data collected on/after date of 1st intake of ponesimod till last treatment date in extension study+15 days).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ponesimod 20 mg (Core and Extension Study)

Arm description:

Subjects with multiple sclerosis (MS) who were treated with ponesimod 20 milligrams (mg) in the core study (2012-000540-10), and entered into this extension study, received a 14-day gradual up-titrated treatment (from 2 mg to 10 mg) of ponesimod tablet orally once daily from Days 1 to 14. Subjects received a daily maintenance dose of ponesimod 20 mg tablet orally once daily from Day 15 up to Week 240 or till ponesimod became commercially available in a subject's country. Subjects located in Ukraine had an extended treatment duration up to 288 weeks in the extension study due to the regional crisis.

Arm type	Experimental
Investigational medicinal product name	Ponesimod
Investigational medicinal product code	
Other name	JNJ-67896153, ACT-128800
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received ponesimod 20 mg treatment.

Arm title	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)

Arm description:

Subjects with multiple sclerosis (MS) who were treated with teriflunomide 14 mg in the core study (2012-000540-10), and entered into this extension study, received a 14-day gradual up-titrated treatment (from 2 mg to 10 mg) of ponesimod tablet orally once daily from Days 1 to 14. Subjects received a daily maintenance dose of ponesimod 20 mg tablet orally once daily from Day 15 up to Week 240 or till ponesimod became commercially available in a subject's country. Subjects located in Ukraine had an extended treatment duration up to 288 weeks in the extension study due to the regional crisis.

Arm type	Experimental
Investigational medicinal product name	Ponesimod
Investigational medicinal product code	
Other name	JNJ-67896153, ACT-128800
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received ponesimod 20 mg treatment.

Number of subjects in period 1	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)
Started	439	438
Completed	352	371
Not completed	87	67
Adverse event, serious fatal	1	-
Physician decision	9	2
Consent withdrawn by subject	54	39
Adverse event, non-fatal	7	12
Lost to follow-up	6	6
Lack of efficacy	10	8

Baseline characteristics

Reporting groups	
Reporting group title	Ponesimod 20 mg (Core and Extension Study)
Reporting group description:	
Subjects with multiple sclerosis (MS) who were treated with ponesimod 20 milligrams (mg) in the core study (2012-000540-10), and entered into this extension study, received a 14-day gradual up-titrated treatment (from 2 mg to 10 mg) of ponesimod tablet orally once daily from Days 1 to 14. Subjects received a daily maintenance dose of ponesimod 20 mg tablet orally once daily from Day 15 up to Week 240 or till ponesimod became commercially available in a subject's country. Subjects located in Ukraine had an extended treatment duration up to 288 weeks in the extension study due to the regional crisis.	
Reporting group title	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)
Reporting group description:	
Subjects with multiple sclerosis (MS) who were treated with teriflunomide 14 mg in the core study (2012-000540-10), and entered into this extension study, received a 14-day gradual up-titrated treatment (from 2 mg to 10 mg) of ponesimod tablet orally once daily from Days 1 to 14. Subjects received a daily maintenance dose of ponesimod 20 mg tablet orally once daily from Day 15 up to Week 240 or till ponesimod became commercially available in a subject's country. Subjects located in Ukraine had an extended treatment duration up to 288 weeks in the extension study due to the regional crisis.	

Reporting group values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)	Total
Number of subjects	439	438	877
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	36.5	37.2	
standard deviation	± 8.75	± 8.75	-
Gender categorical Units: Subjects			
Male	153	148	301
Female	286	290	576
Age Categorical Units: Subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	439	438	877
From 65 to 84 years	0	0	0
85 years and over	0	0	0

End points

End points reporting groups

Reporting group title	Ponesimod 20 mg (Core and Extension Study)

Reporting group description:

Subjects with multiple sclerosis (MS) who were treated with ponesimod 20 milligrams (mg) in the core study (2012-000540-10), and entered into this extension study, received a 14-day gradual up-titrated treatment (from 2 mg to 10 mg) of ponesimod tablet orally once daily from Days 1 to 14. Subjects received a daily maintenance dose of ponesimod 20 mg tablet orally once daily from Day 15 up to Week 240 or till ponesimod became commercially available in a subject's country. Subjects located in Ukraine had an extended treatment duration up to 288 weeks in the extension study due to the regional crisis.

Reporting group title	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)

Reporting group description:

Subjects with multiple sclerosis (MS) who were treated with teriflunomide 14 mg in the core study (2012-000540-10), and entered into this extension study, received a 14-day gradual up-titrated treatment (from 2 mg to 10 mg) of ponesimod tablet orally once daily from Days 1 to 14. Subjects received a daily maintenance dose of ponesimod 20 mg tablet orally once daily from Day 15 up to Week 240 or till ponesimod became commercially available in a subject's country. Subjects located in Ukraine had an extended treatment duration up to 288 weeks in the extension study due to the regional crisis.

Primary: Time From Core Study Randomisation to First Confirmed Relapse

End point title	Time From Core Study Randomisation to First Confirmed Relapse[1]

End point description:

Time to first confirmed relapse: date of first confirmed relapse (core or extension study) minus date of randomisation in core study+1 day. Relapse: new, worsening, or recurrent neurological symptoms that occurred at least 30 days after the onset of a preceding relapse, that lasted at least 24 hours,in absence of fever/infection. Confirmed relapse: when patient's symptoms worsen by increase in EDSS or FS scores, consistent to previous clinically stable assessments. Specific criteria for confirmed relapse: increase of 0.5 points on EDSS;(unless EDSS=0, then increase of 1.0-point); increase of 1.0 point in at least two FS scores; or 2.0-point increase in one FS score (excluding bladder/bowel/cerebral).Rating individual FS scores is used to rate EDSS (ordinal clinical rating scale ranging:0[normal]-10[death due to MS]) along with observations/ information concerning gait and use of assistance. Extension set was used. Here, '99999' refers to data not estimable due to low number of events.

End point type	Primary

End point timeframe:

From randomisation in the core study up to the end of study (EOS) in the extension study. The actual time varied for each subjects and could be up to 98.5 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	438		
Units: weeks				
median (inter-quartile range (Q1-Q3))	402.71 (82.29 to 99999)	99999 (53.57 to 99999)		

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Confirmed Relapse Rate (ARR)

End point title	Annualized Confirmed Relapse Rate (ARR)

End point description:

ARR: number of confirmed relapses per patient-year. Relapse: new, worsening, or recurrent neurological symptoms that occurred at least 30 days after the onset of a preceding relapse, and that lasted at least 24 hours,in absence of fever or infection. Confirmed relapse: when patient's symptoms worsen by increase in Expanded Disability Status Scale (EDSS) or Functional Systems (FS) scores, consistent to previous clinically stable assessments. Specific criteria for confirmed relapse: increase of 0.5 points on EDSS;(unless EDSS=0, then increase of 1.0-point); increase of 1.0 point in at least two FS scores; or 2.0-point increase in one FS score (excluding bladder/bowel/cerebral).Rating individual FS scores is used to rate EDSS (ordinal clinical rating scale ranging:0[normal]-10[death due to MS]) along with observations/ information concerning gait and use of assistance. Extension set: all subjects who signed informed consent to enter extension study and received one dose of ponesimod.

End point type	Primary

End point timeframe:

From randomisation in the core study up to the end of study (EOS) in the extension study. The actual time varied for each subject and could be up to 98.5 months

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	438		
Units: relapses per year				
arithmetic mean (confidence interval 95%)	0.143 (0.123 to 0.167)	0.184 (0.158 to 0.213)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The Analysis type is Exploratory.

Comparison groups	Ponesimod 20 mg (Core and Extension Study) v Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)

Number of subjects included in analysis	877
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment effect (rate ratio)
Point estimate	0.779
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.629
upper limit	0.965

Primary: Time to First 12-week Confirmed Disability Accumulation (CDA)

End point title	Time to First 12-week Confirmed Disability Accumulation

End point description:

Time to first 12-week CDA is defined as start date of the first 12-week CDA minus date of randomisation in the core study+1 day. A 12-week CDA is defined as a 12-week sustained increase from the core baseline EDSS score, which is confirmed at a scheduled visit after 12-weeks. CDA is defined as: (a) Sustained increase of at least 1.5 in EDSS for subjects with a core baseline EDSS score of 0; (b) Sustained increase of at least 1.0 in EDSS for subjects with a core baseline EDSS score of 1.0 to 5.0; (c) Sustained increase of at least 0.5 in EDSS for subjects with a core baseline EDSS score >=5.5, confirmed after 12 weeks. EDSS is an ordinal clinical rating scale ranged 0 (normal neurological examination) to 10 (death due to MS). Core baseline for efficacy: last non-missing value recorded before or on randomisation in the core study for each endpoint and subject individually. Extension set was used. Here, '99999' refers to data not estimable due to low number of events.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of study (EOS) in the extension study. The actual time varied for each subject and could be up to 98.5 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	438		
Units: weeks				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (254.86 to 99999)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to First 24-week Confirmed Disability Accumulation (CDA)

End point title	Time to First 24-week Confirmed Disability Accumulation

End point description:

Time to first 24-week CDA is defined as start date of the first 24-week CDA minus date of randomisation in the core study+1 day. A 24-week CDA is defined as a 24-week sustained increase from the core baseline EDSS score, which is confirmed at a scheduled visit after 24-weeks. CDA is defined as: (a) Sustained increase of at least 1.5 in EDSS for subjects with a core baseline EDSS score of 0; (b) Sustained increase of at least 1.0 in EDSS for subjects with a core baseline EDSS score of 1.0 to 5.0; (c) Sustained increase of at least 0.5 in EDSS for subjects with a core baseline EDSS score >=5.5, confirmed after 24 weeks. EDSS is an ordinal clinical rating scale ranged 0 (normal neurological examination) to 10 (death due to MS). Core baseline for efficacy: last non-missing value recorded before or on randomisation in the core study for each endpoint and subject individually. Extension set was used. Here, '99999' refers to data not estimable due to low number of events.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of study (EOS) in the extension study. The actual time varied for each subject and could be up to 98.5 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	438		
Units: weeks				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (313.29 to 99999)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Absence of Relapses

End point title	Percentage of Subjects with Absence of Relapses[4]

End point description:

Relapse: new, worsening, or recurrent neurological symptoms that occurred at least 30 days after the onset of a preceding relapse, and that lasted at least 24 hours, in absence of fever or infection. Confirmed relapse is identified when a patient's symptoms worsen as indicated by an increase in their EDSS or FS scores, consistent with previous clinically stable assessments. Specific criteria for a confirmed relapse include: An increase of 0.5 points on EDSS; (unless EDSS=0, then requires an increase of 1.0-point); An increase of at least 1.0 point in at least two FS scores; or a 2.0-point increase in one FS score (excluding bladder/bowel and cerebral). Rating individual FS scores is used to rate EDSS along with observations and information concerning gait and use of assistance. EDSS is ordinal clinical rating scale ranging:0(normal)-10(death due to MS). Extension set: all subjects who signed informed consent to enter extension study and received one dose of ponesimod.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of study (EOS) in the extension study. The actual time varied for each subject and could be up to 98.5 months

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	438		
Units: Percentage of Subjects				
number (not applicable)	56.7	51.6		

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change from Baseline in Brain Volume (PCBV) Measured by Magnetic Resonance Imaging (MRI)

End point title	Percent Change from Baseline in Brain Volume (PCBV) Measured by Magnetic Resonance Imaging (MRI)[5]

End point description:

Percent change from baseline in brain volume (PCBV) measured by MRI were reported. Normalized Brain Volume at core baseline was measured in cubic centimeter (cm^3). Core baseline for efficacy is defined as the last non-missing value recorded before or on randomisation in the core study for each outcome measure and each subject individually. In this endpoint, results were presented for extension end of treatment visit. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of treatment (EOT) in the extension study. The actual time varied for each subject and could be up to 94.8 months

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	193		
Units: Percent Change				
arithmetic mean (standard deviation)	-2.52 (± 2.179)	-2.72 (± 2.024)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With No Evidence of Disease (NEDA-4) Status Until Extension End of Study

End point title	Percentage of Subjects With No Evidence of Disease (NEDA-4) Status Until Extension End of Study[6]

End point description:

NEDA-4 up to EOS is defined by absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, 12-week CDA until EOS, and absence of annual brain volume decrease >=0.4% from core baseline up to extension EOS. If at least one of the criteria was not fulfilled or the subject discontinued treatment prematurely, the subject was not considered to have achieved NEDA-4. Confirmed relapse: when patient's symptoms worsen by an increase in their EDSS/FS scores, consistent with previous clinically stable assessments. Rating individual FS scores is used to rate EDSS (ordinal clinical rating scale ranging 0:normal-10:death due to MS) along with observations, information concerning gait and use of assistance. Core baseline for efficacy: last non-missing value recorded before or on randomisation in core study for each outcome measure and subject individually. Extension set was used. Here, 'N' is number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of study (EOS) in the extension study. The actual time varied for each subject and could be up to 98.5 months

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	435		
Units: Percentage of Subjects				
number (not applicable)	5.2	2.3		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With No Evidence of Disease (NEDA-3) Status Until Extension End of Study

End point title	Percentage of Subjects With No Evidence of Disease (NEDA-3) Status Until Extension End of Study[7]

End point description:

NEDA-3 up to extension EOS is defined by the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, and 12-week CDA. If at least one of the criteria was not fulfilled or the subject discontinued treatment prematurely, the subject was not considered to have achieved NEDA-3. Confirmed relapse: when patient's symptoms worsen as indicated by an increase in their EDSS/FS scores, consistent with previous clinically stable assessments. Rating individual FS scores is used to rate EDSS along with observations and information
concerning gait and use of assistance. EDSS is ordinal clinical rating scale ranging:0(normal)-10(death due to MS). Core baseline for efficacy is the last non-missing value recorded before or on randomisation in core study for each outcome measure and each subject individually. Extension set was used. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of study (EOS) in the extension study. The actual time varied for each subject and could be up to 98.5 months

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	436		
Units: Percentage of Subjects				
number (not applicable)	17.5	7.5		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Expanded Disability Status Scale (EDSS)

End point title	Change from Baseline in Expanded Disability Status Scale (EDSS)[8]

End point description:

EDSS is ordinal clinical rating scale based on standard neurological examination for assessing neurological disability and impairment in MS. Seven FS scores were rated on a scale ranged from 0 to 5 or 6 to assess visual, brain, stem, pyramidal, cerebellar, sensory, bowel and bladder, and cerebral functions while ambulation was scored on scale ranged from 0 to 12 to assess walking distance and assistance. Individual FS scores were then used in conjugation with ambulation score to obtain EDSS score which ranged from 0 (normal) to 10 (death due to MS) in 0.5 unit increments that represented higher levels of disability. Core baseline for efficacy is defined as the last non-missing value recorded before or on randomisation in the core study for each endpoint and each subject individually. Extension set was used. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of study (EOS) in the extension study. The actual time varied for each subject and could be up to 98.5 months

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	364		
Units: Score on a scale				
arithmetic mean (standard deviation)	0.16 (± 1.008)	0.34 (± 1.105)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Gadolinium-enhancing (Gd+) T1 lesions Measured by MRI

End point title	Number of Gadolinium-enhancing (Gd+) T1 lesions Measured by MRI[9]

End point description:

Number of Gd+ T1 lesions measured by MRI were reported. Core baseline for efficacy is defined as the last non-missing value recorded before or on randomisation in the core study for each endpoint and each subject individually. In this endpoint, results were presented for extension end of treatment visit based on a negative-binomial regression model. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of treatment (EOT) in the extension study. The actual time varied for each subject and could be up to 94.8 months

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	347		
Units: Gd+ T1 lesions				
arithmetic mean (confidence interval 95%)	0.211 (0.131 to 0.341)	0.395 (0.250 to 0.622)		

Statistical analyses

No statistical analyses for this end point

Primary: Cumulative Number of New or Enlarging T2 Lesions Measured by MRI

End point title	Cumulative Number of New or Enlarging T2 Lesions Measured by MRI[10]

End point description:

Cumulative number of new or enlarging T2 lesions measured by MRI were reported. Average number of lesions per year were reported. Results are based on a negative-binomial regression model. Core baseline for efficacy is defined as the last non-missing value recorded before or on randomisation in the core study for each outcome measure and each subject individually. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of study (EOS) in the extension study. The actual time varied for each subject and could be up to 98.5 months

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were

planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	435		
Units: Lesions per year				
arithmetic mean (confidence interval 95%)	1.352 (1.152 to 1.586)	1.951 (1.664 to 2.287)		

Statistical analyses

No statistical analyses for this end point

Primary: Cumulative Number of Combined Unique Active Lesions (CUAL) Measured by MRI

End point title	Cumulative Number of Combined Unique Active Lesions (CUAL) Measured by MRI[11]

End point description:

CUALs was calculated as sum of new T1 Gd+ lesions and new or enlarging T2 lesions (without double-counting of lesions) from baseline up to extension EOS based on the Magnetic resonance imaging (MRI). Average number of lesions per-patient year were reported. Results are based on a negative-binomial regression model. Core baseline for efficacy is defined as the last non-missing value recorded before or on randomisation in the core study for each outcome measure and each subject individually. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of study (EOS) in the extension study. The actual time varied for each subject and could be up to 98.5 months

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	435		
Units: CUAL per patient-year				
arithmetic mean (confidence interval 95%)	1.352 (1.153 to 1.586)	1.954 (1.667 to 2.291)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Absence of MRI lesions (Gd+ T1 lesions, new or enlarging T2 lesions)

End point title	Number of Subjects with Absence of MRI lesions (Gd+ T1 lesions, new or enlarging T2 lesions)[12]

End point description:

Number of subjects with absence of MRI lesions (Gd+ T1 lesions, new or enlarging T2 lesions) were reported. Core baseline for efficacy is defined as the last non-missing value recorded before or on randomisation in the core study for each outcome measure and each subject individually. In this endpoint, results were presented for extension end of treatment visit. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint. Here, 'n' (number analysed) is defined as subjects analysed at specified categories.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of treatment (EOT) in the extension study. The actual time varied for each subject and could be up to 94.8 months

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	435		
Units: Subjects				
Gd+ T1 lesions (n= 439, 435)	293	236		
T2 lesions (n= 438, 435)	152	101		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Volume of MRI Lesions (T2 Lesions and T1 Hypointense Lesions)

End point title	Change from Baseline in Volume of MRI Lesions (T2 Lesions and T1 Hypointense Lesions)[13]

End point description:

Change from baseline in volume of MRI lesions (T2 lesions, T1 hypointense lesions) were reported. Core baseline for efficacy is defined as the last non-missing value recorded before or on randomisation in the core study for each outcome measure and each subject individually. In this endpoint, results were presented for extension end of treatment visit. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint. Here, 'n' (number analysed) is defined as subjects analysed at specified categories.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of treatment (EOT) in the extension study. The actual

time varied for each subject and could be up to 94.8 months

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	348		
Units: cubic millimetres (mm^3)				
arithmetic mean (standard deviation)				
T2 Lesions (n=347, 348)	-435.7 (± 2822.71)	91.5 (± 3647.08)		
T1 Hypointense Lesions (n=346, 345)	165.6 (± 1427.30)	309.4 (± 1712.36)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs)[14]

End point description:

Number of subjects with TEAEs were reported. An AE is any untoward medical event that occurs in a subjects being administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. TEAEs are defined as AEs occurring from start of treatment up to end of treatment date + 15 days. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod.

End point type	Primary

End point timeframe:

From the start of study treatment in the extension study up to the end of study treatment + 15 days in the extension study. The actual time varied for each subject and could be up to 71.8 months + 15 days

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	438		
Units: Subjects	411	410		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment-emergent New Morphological Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects with Treatment-emergent New Morphological Electrocardiogram (ECG) Abnormalities[15]

End point description:

Number of subjects with treatment-emergent new morphological ECG abnormalities were reported. Treatment-emergent new morphological ECG abnormalities are defined as those ECG abnormalities occurring from start of treatment up to treatment end date + 15 days. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod.

End point type	Primary

End point timeframe:

From the start of study treatment in the extension study up to the end of study treatment + 15 days in the extension study. The actual time varied for each subject and could be up to 71.8 months + 15 days

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	438		
Units: Subjects	153	140		

Statistical analyses

No statistical analyses for this end point

Primary: Actual Values of 12-lead ECG Measurements up to End of Study Treatment: Heart Rate

End point title	Actual Values of 12-lead ECG Measurements up to End of Study Treatment: Heart Rate[16]

End point description:

Actual values of 12-lead ECG measurements: heart rate were reported. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From the start of study treatment in the extension study up to the end of study treatment in the extension study. The actual time varied for each subject and could be up to 71.8 months

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	361		
Units: Beats per minute (bpm)				
arithmetic mean (standard deviation)	67.4 (± 9.64)	67.6 (± 9.33)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Gd+ Lesions at Baseline Evolving to Persistent Black Holes (PBHs)

End point title	Percentage of Gd+ Lesions at Baseline Evolving to Persistent Black Holes (PBHs)[17]

End point description:

Percentage of Gd+ lesions at baseline evolving to PBHs were reported. Core baseline for efficacy is defined as the last non-missing value recorded before or on randomisation in the core study for each outcome measure and each subject individually. In this endpoint, results were presented for extension end of treatment visit. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From baseline in the core study up to the end of treatment (EOT) in the extension study. The actual time varied for each subjects and could be up to 94.8 months

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	350	346		
Units: Percentage of lesions				
number (not applicable)	22.3	25.1		

Statistical analyses

No statistical analyses for this end point

Primary: Actual Values of 12-lead ECG Measurements up to End of Study Treatment: PR, QRS, QT, QTcB, QTcF

End point title	Actual Values of 12-lead ECG Measurements up to End of Study

	Treatment: PR, QRS, QT, QTcB, QTcF[18]

End point description:

Actual values of 12-lead ECG measurements up to end of study: PR, QRS, QT, QTcB, QTcF were reported. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From the start of study treatment in the extension study up to the end of study treatment in the extension study. The actual time varied for each subject and could be up to 71.8 months

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	361		
Units: millisecond (ms)				
arithmetic mean (standard deviation)				
PR Interval	150.0 (± 20.41)	153.3 (± 20.27)		
QRS Duration	92.1 (± 9.22)	93.3 (± 10.63)		
QT Interval	392.5 (± 27.26)	391.0 (± 25.67)		
QTcB Interval	414.8 (± 19.20)	413.8 (± 19.66)		
QTcF Interval	406.9 (± 17.78)	405.7 (± 17.78)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Heart Rate (HR) up to End of Study Treatment

End point title	Change from Baseline in Heart Rate (HR) up to End of Study Treatment[19]

End point description:

Change from baseline in heart rate (HR) were reported. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From the start of study treatment in the extension study up to the end of study treatment in the extension study. The actual time varied for each subject and could be up to 71.8 months

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	361		
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)	-1.7 (± 10.00)	-1.5 (± 9.17)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in PR, QRS, QT, QTcB, QTcF up to End of Study Treatment

End point title	Change from Baseline in PR, QRS, QT, QTcB, QTcF up to End of Study Treatment[20]

End point description:

Change from baseline in PR, QRS, QT, QTcB, QTcF were reported. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From the start of study treatment in the extension study up to the end of study treatment in the extension study. The actual time varied for each subject and could be up to 71.8 months

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	361		
Units: millisecond (ms)				
arithmetic mean (standard deviation)				
PR Interval	0.5 (± 14.09)	2.0 (± 14.37)		
QRS Duration	-0.4 (± 6.79)	2.9 (± 6.88)		
QT Interval	7.8 (± 25.68)	8.9 (± 21.66)		
QTcB Interval	2.9 (± 16.75)	5.2 (± 17.07)		
QTcF Interval	4.6 (± 15.28)	6.5 (± 14.18)		

Statistical analyses

No statistical analyses for this end point

Primary: Absolute Values in Forced Expiratory Volume in 1 Second (FEV1) and Forced Vital Capacity (FVC) Values

End point title	Absolute Values in Forced Expiratory Volume in 1 Second (FEV1) and Forced Vital Capacity (FVC) Values[21]

End point description:

Absolute values in FEV1 and FVC were reported. FEV1: the maximal volume of air exhaled from the lungs in 1 second of a forced expiration from a position of full inspiration as measured by spirometer. FVC: the volume of air (in liters) that can be forcibly blown out after full inspiration in the upright position. Extension baseline for safety is the last valid non-missing assessment that is taken on or after EOT visit in the core study, and prior to first study drug intake in the extension study. Results are presented for extension end of treatment visit. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From extension study baseline up to the end of study treatment in the extension study. The actual time varied for each subject and could be up to 71.8 months

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315	327		
Units: Percent predicted FEV1 and FVC				
arithmetic mean (standard deviation)				
FEV1	3.01 (± 0.768)	3.08 (± 0.797)		
FVC	-3.96 (± 0.965)	4.04 (± 1.031)		

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change in FEV1 and FVC From Baseline (%)

End point title	Percent Change in FEV1 and FVC From Baseline (%)[22]

End point description:

Percent Change in FEV1 and FVC From Baseline (%) were reported. FEV1: the maximal volume of air exhaled from the lungs in 1 second of a forced expiration from a position of full inspiration as measured by spirometer. FVC: the volume of air (in liters) that can be forcibly blown out after full inspiration in the upright position. Extension baseline for safety is the last valid non-missing assessment that is taken on or after EOT visit in the core study, and prior to first study drug intake in the extension study. Results are presented for extension end of treatment visit. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From extension study baseline up to the end of study treatment in the extension study. The actual time varied for each subject and could be up to 71.8 months

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315	327		
Units: Percent change				
arithmetic mean (standard deviation)				
FEV1	-7.96 (± 13.356)	-6.75 (± 12.323)		
FVC	-5.09 (± 11.793)	-3.93 (± 12.141)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-emergent Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-emergent Serious Adverse Events (SAEs)[23]

End point description:

Number of subjects with treatment-emergent SAEs were reported. A SAE was defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, leads to a congenital anomaly/birth defect in the offspring of a subject, or was an important medical event. Treatment-emergent SAEs are defined as SAEs occurring from start of treatment up to treatment end date + 15 days. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod.

End point type	Primary

End point timeframe:

From the start of study treatment in the extension study up to the end of study treatment + 15 days in the extension study. The actual time varied for each subject and could be up to 71.8 months + 15 days

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	438		
Units: Subjects	56	57		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment-emergent Adverse Events of Special Interest (AESIs)

End point title	Number of Subjects with Treatment-emergent Adverse Events of Special Interest (AESIs)[24]

End point description:

Number of subjects with treatment-emergent AESIs were reported. AESIs included bradyarrhythmia occurred post-first dose, macular edema, bronchoconstriction, severe liver injury, serious opportunistic infections including progressive multifocal leukoencephalopathy (PML), skin cancer, non-skin malignancy, convulsions, unexpected neurological or psychiatric symptoms/signs (posterior reversible encephalopathy syndrome [PRES], acute disseminated encephalomyelitis [ADEM], and atypical MS relapses). Treatment-emergent AESIs are defined as AESIs occurring from start of treatment up to treatment end date + 15 days. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod.

End point type	Primary

End point timeframe:

From the start of study treatment in the extension study up to the end of study treatment + 15 days in the extension study. The actual time varied for each subject and could be up to 71.8 months + 15 days

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	438		
Units: Subjects				
Bradyarrhythmia occurring post-first dose	11	13		
Severe liver injury	5	5		
Bronchoconstriction	31	25		
Macular edema	4	6		
Serious opportunistic infections including PML	2	1		
Skin cancer	4	3		
Non-skin malignancy	4	3		
Unexpected neurological/psychiatric symptom/sign	1	2		
Convulsions	2	3		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Adverse Events Leading to Premature Discontinuation of Study Treatment

End point title	Number of Subjects with Adverse Events Leading to Premature Discontinuation of Study Treatment[25]

End point description:

Number of subjects with AE leading to premature discontinuation of study treatment were reported. An AE is any untoward medical event that occurs in a subjects being administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod.

End point type	Primary

End point timeframe:

From the start of study treatment in the extension study up to the end of study treatment + 15 days in the extension study. The actual time varied for each subject and could be up to 71.8 months + 15 days

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	438		
Units: Subjects	34	41		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment-emergent Decrease From Baseline >20% and >30% in FEV1 or FVC

End point title	Number of Subjects with Treatment-emergent Decrease From Baseline >20% and >30% in FEV1 or FVC[26]

End point description:

Number of subjects with treatment-emergent decrease from baseline >20% and >30% in FEV1 or FVC were reported. Treatment-emergent is defined as events occurring from start of treatment up to treatment end date + 15 days (that is, findings not present at any assessment prior to first treatment in the extension study). Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From the start of study treatment in the extension study up to the end of study treatment + 15 days in the extension study. The actual time varied for each subject and could be up to 71.8 months + 15 days

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were

planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	424	423		
Units: Subjects				
FEV1: >20 %	80	82		
FEV1: >30 %	18	21		
FVC: >20 %	54	60		
FVC: >30 %	19	15		

Statistical analyses

No statistical analyses for this end point

Primary: Change in FEV1 and FVC (% predicted) from baseline to End of Treatment (EOT)

End point title	Change in FEV1 and FVC (% predicted) from baseline to End of Treatment (EOT) [27]

End point description:

Change in FEV1 and FVC (% predicted) from baseline to EOT were predicted. Extension baseline for safety is the last valid non-missing assessment that is taken on or after EOT visit in the core study, and prior to first study drug intake in the extension study. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From extension study baseline up to the end of study treatment in the extension study. The actual time varied for each subject and could be up to 71.8 months

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315	327		
Units: Percentage predicted change				
arithmetic mean (standard deviation)				
FEV1	-7.14 (± 13.315)	-5.43 (± 11.839)		
FVC	-4.70 (± 13.129)	-3.19 (± 13.081)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment-emergent Decrease of >20% Points in Percent Predicted FEV1 and FVC from Baseline

End point title	Number of Subjects with Treatment-emergent Decrease of >20% Points in Percent Predicted FEV1 and FVC from Baseline[28]

End point description:

Number of subjects with treatment-emergent decrease of >20% points in percent predicted FEV1 and FVC from baseline were reported. Treatment-emergent is defined as events occurring from start of treatment up to treatment end date + 15 days (that is, findings not present at any assessment prior to first treatment in the extension study). Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From the start of study treatment in the extension study up to the end of study treatment + 15 days in the extension study. The actual time varied for each subject and could be up to 71.8 months + 15 days

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	423		
Units: Subjects				
FEV1: >20 %	70	68		
FVC: >20 %	59	57		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with a Decrease of >=200 mL or >=12% in FEV1 or FVC from baseline to EOT

End point title	Number of Subjects with a Decrease of >=200 mL or >=12% in FEV1 or FVC from baseline to EOT[29]

End point description:

Number of subjects with a decrease of >=200 mL or >=12% in FEV1 or FVC from baseline to EOT were planned to be reported. Extension baseline for safety is the last valid non-missing assessment that is

taken on or after EOT visit in the core study, and prior to first study drug intake in the extension study. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. This endpoint is not relevant as a substantial proportion of patients continued onto post-treatment disease-modifying therapy (DMT), hence it cannot provide an assessment of reversibility.

End point type	Primary

End point timeframe:

From extension study baseline up to the end of study treatment in the extension study. The actual time varied for each subject and could be up to 71.8 months

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[30]	0[31]		
Units: Participants				

Notes:

[30] - The reason has been already provided above in endpoint description.

[31] - The reason has been already provided above in endpoint description.

Statistical analyses

No statistical analyses for this end point

Primary: Change in FEV1 and FVC (% predicted) from baseline to End of Study (EOS)

End point title	Change in FEV1 and FVC (% predicted) from baseline to End of Study (EOS) [32]

End point description:

Change in FEV1 and FVC (% predicted) from baseline to EOS were predicted. Extension baseline for safety is the last valid non-missing assessment that is taken on or after EOT visit in the core study, and prior to first study drug intake in the extension study. Extension set included all subjects who signed informed consent to enter extension study and received one dose of ponesimod. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From extension study baseline up to the end of study in the extension study. The actual time varied for each subject and could be up to 73.2 months

Notes:

[32] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	299		
Units: Percentage predicted change				

arithmetic mean (standard deviation)				
FEV1	-5.95 (± 12.854)	-4.08 (± 14.365)		
FVC	-4.48 (± 13.727)	-1.98 (± 15.747)		

Statistical analyses

No statistical analyses for this end point

Primary: Absolute Change in Lung Diffusion Capacity as Assessed by Diffusing Capacity for the Lungs Measured Using Carbon Monoxide (DL[CO]) From Baseline

End point title	Absolute Change in Lung Diffusion Capacity as Assessed by Diffusing Capacity for the Lungs Measured Using Carbon Monoxide (DL[CO]) From Baseline [33]

End point description:

Absolute change in lung diffusion capacity as assessed by DL[CO] from baseline were reported. Extension baseline for safety is the last valid non-missing assessment that is taken on or after EOT visit in the core study, and prior to first study drug intake in the extension study. The DLCO sub-study extension set includes all subjects in the extension set who have consented to participate in the DLCO sub-study during the extension study. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From extension study baseline up to the end of study in the extension study. The actual time varied for each subject and could be up to 73.2 months

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	53		
Units: Millimoles/minute/kilopascal				
arithmetic mean (standard deviation)	0.7 (± 3.44)	0.1 (± 4.17)		

Statistical analyses

No statistical analyses for this end point

Primary: Change in DL[CO] (% predicted) from Baseline to EOT

End point title	Change in DL[CO] (% predicted) from Baseline to EOT [34]

End point description:

Change in DL[CO] (% predicted) from baseline to EOT were predicted. Extension baseline for safety is the last valid non-missing assessment that is taken on or after EOT visit in the core study, and prior to first study drug intake in the extension study. The DLCO sub-study extension set includes all subjects in the extension set who have consented to participate in the DLCO sub-study during the extension study.

Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From extension study baseline up to the end of study treatment in the extension study. The actual time varied for each subject and could be up to 71.8 months

Notes:

[34] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	41		
Units: Percentage predicted DL[CO]				
arithmetic mean (standard deviation)	5.7 (± 32.20)	-9.4 (± 7.82)		

Statistical analyses

No statistical analyses for this end point

Primary: Change in DL[CO] (% predicted) from Baseline to EOS

End point title	Change in DL[CO] (% predicted) from Baseline to EOS [35]

End point description:

Change in DL[CO] (% predicted) from baseline to EOS were predicted. Extension baseline for safety is the last valid non-missing assessment that is taken on or after EOT visit in the core study, and prior to first study drug intake in the extension study. The DLCO sub-study extension set includes all subjects in the extension set who have consented to participate in the DLCO sub-study during the extension study.
Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

From extension study baseline up to the end of study in the extension study. The actual time varied for each subject and could be up to 73.2 months

Notes:

[35] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only statistical analysis were planned for this endpoint. No inferential statistics were planned.

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	35		
Units: Percentage predicted DL[CO]				
arithmetic mean (standard deviation)	9.3 (± 39.38)	2.2 (± 49.50)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Actual Values of 12-lead ECG Measurements on Day of First Re-initiation (Day 1) of Study Drug: Heart Rate

End point title	Actual Values of 12-lead ECG Measurements on Day of First Re-initiation (Day 1) of Study Drug: Heart Rate

End point description:

Actual values of 12-lead ECG measurements on day of first Re-initiation (Day 1) of study drug: heart rate were reported. Population analysis included numbers of subjects based on sub-set of extension set who had a re-initiation. Here, 'n' (number analyzed) is defined as subjects analysed at specified timepoints.

End point type	Other pre-specified

End point timeframe:

Extension analysis period: Predose, 1, 2, 3, 4 hours post dose on Day 1 of re-initiation (re-initiation could occur on any day during the treatment period when drug was interrupted for at least 3 consecutive days [up to 71.8 months])

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	40		
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
Predose (n=30, 40)	68.1 (± 8.73)	71.0 (± 9.21)		
1 hour Post-dose (n=24, 34)	66.5 (± 10.53)	69.0 (± 10.13)		
2 hours Post-dose (n=24, 31)	64.3 (± 9.91)	65.1 (± 8.68)		
3 hours Post-dose (n=24, 31)	64.6 (± 9.33)	67.8 (± 10.71)		
4 hours Post-dose (n=24, 31)	66.0 (± 9.73)	67.6 (± 10.01)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Actual Values of 12-lead ECG Measurements on Day of First Re-initiation (Day 1) of Study Drug: PR, QRS, QT, QTcB, QTcF

End point title	Actual Values of 12-lead ECG Measurements on Day of First Re-initiation (Day 1) of Study Drug: PR, QRS, QT, QTcB, QTcF

End point description:

Actual values of 12-lead ECG measurements on day of first Re-initiation (Day 1) of study drug: PR, QRS, QT, QTcB, QTcF were reported. Population analysis included numbers of subjects based on sub-set of extension set who had a re-initiation. Here, 'n' (number analyzed) is defined as subjects analysed at specified timepoints.

End point type	Other pre-specified

End point timeframe:

Extension analysis period: Predose, 1, 2, 3, 4 hours post dose on Day 1 of re-initiation (re-initiation could occur on any day during the treatment period when drug was interrupted for at least 3 consecutive days [up to 71.8 months])

End point values	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	40		
Units: millisecond (ms)				
arithmetic mean (standard deviation)				
PR Interval: Predose (n=30, 40)	152.8 (± 17.66)	149.8 (± 19.13)		
PR Interval: 1 hour Post-dose (n=24, 34)	150.5 (± 17.25)	152.6 (± 22.66)		
PR Interval: 2 hours Post-dose (n=24, 31)	150.1 (± 16.60)	153.6 (± 23.51)		
PR Interval: 3 hours Post-dose (n=24, 31)	152.3 (± 17.73)	154.5 (± 21.91)		
PR Interval: 4 hours Post-dose (n=24, 31)	150.7 (± 17.82)	151.8 (± 19.68)		
QRS Duration: Predose (n=30, 40)	94.6 (± 11.06)	91.5 (± 7.03)		
QRS Duration: 1 hour Post-dose (n=24, 34)	95.2 (± 11.42)	93.2 (± 8.72)		
QRS Duration: 2 hours Post-dose (n=24, 31)	93.9 (± 11.71)	92.7 (± 7.57)		
QRS Duration: 3 hours Post-dose (n=24, 31)	94.5 (± 11.60)	94.5 (± 7.80)		
QRS Duration: 4 hours Post-dose (n=24, 31)	94.7 (± 10.48)	92.5 (± 7.35)		
QT Interval: Predose (n=30, 40)	391.5 (± 24.80)	378.8 (± 23.61)		
QT Interval: 1 hour Post-dose (n=24, 34)	396.7 (± 28.76)	380.9 (± 21.78)		
QT Interval: 2 hours Post-dose (n=24, 31)	402.0 (± 29.00)	386.0 (± 19.62)		
QT Interval: 3 hours Post-dose (n=24, 31)	400.2 (± 27.78)	386.9 (± 21.38)		
QT Interval: 4 hours Post-dose (n=24, 31)	400.0 (± 27.49)	383.9 (± 23.14)		
QTcB: Predose (n=30, 40)	416.2 (± 19.05)	411.4 (± 20.85)		
QTcB Interval: 1 hour Post-dose (n=24, 34)	416.0 (± 24.11)	407.6 (± 22.96)		
QTcB Interval: 2 hours Post-dose (n=24, 31)	414.8 (± 22.83)	401.7 (± 20.88)		
QTcB Interval: 3 hours Post-dose (n=24, 31)	414.2 (± 23.30)	410.1 (± 22.33)		

QTcB Interval: 4 hours Post-dose (n=24, 31)	418.0 (± 20.30)	406.6 (± 22.33)		
QTcF: Predose (n=30, 40)	407.4 (± 17.09)	400.0 (± 18.69)		
QTcF Interval: 1 hour Post-dose (n=24, 34)	409.2 (± 20.58)	398.1 (± 18.22)		
QTcF Interval: 2 hours Post-dose (n=24, 31)	410.1 (± 20.41)	396.2 (± 16.61)		
QTcF Interval: 3 hours Post-dose (n=24, 31)	409.0 (± 20.97)	402.0 (± 16.82)		
QTcF Interval: 4 hours Post-dose (n=24, 31)	411.5 (± 18.36)	398.5 (± 18.27)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious and Other AEs:From treatment start in extension study to EOT+15 days in extension study. Actual time varied till 71.8 months+15 days; All-cause mortality:From extension study baseline to EOS in extension study. Actual time varied till 73.2 months

Adverse event reporting additional description:

The extension set included all subjects who signed an informed consent to enter the extension study and who received at least one dose of ponesimod study medication in the extension study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Ponesimod 20 mg (Core and Extension Study)

Reporting group description:

Subjects with multiple sclerosis (MS) who were treated with ponesimod 20 milligrams (mg) in the core study (2012-000540-10), and entered into this extension study, received a 14-day gradual up-titrated treatment (from 2 mg to 10 mg) of ponesimod tablet orally once daily from Days 1 to 14. Subjects received a daily maintenance dose of ponesimod 20 mg tablet orally once daily from Day 15 up to Week 240 or till ponesimod became commercially available in a subject's country. Subjects located in Ukraine had an extended treatment duration up to 288 weeks in the extension study due to the regional crisis.

Reporting group title	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)

Reporting group description:

Subjects with multiple sclerosis (MS) who were treated with teriflunomide 14 mg in the core study (2012-000540-10), and entered into this extension study, received a 14-day gradual up-titrated treatment (from 2 mg to 10 mg) of ponesimod tablet orally once daily from Days 1 to 14. Subjects received a daily maintenance dose of ponesimod 20 mg tablet orally once daily from Day 15 up to Week 240 or till ponesimod became commercially available in a subject's country. Subjects located in Ukraine had an extended treatment duration up to 288 weeks in the extension study due to the regional crisis.

Serious adverse events	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)	
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 439 (12.76%)	57 / 438 (13.01%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	1 / 439 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal Cell Carcinoma			

subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive Breast Carcinoma			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
subjects affected / exposed	1 / 439 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melanocytic Naevus			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant Melanoma			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary Renal Cell Carcinoma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Iliac Artery Embolism			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous Thrombosis Limb			

subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral Artery Thrombosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose Vein			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abdominoplasty			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion Induced			
subjects affected / exposed	2 / 439 (0.46%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Conisation			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uvulopalatopharyngoplasty			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Dilation and Curettage			
subjects affected / exposed	1 / 439 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Botulinum Toxin Injection			

subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterosalpingo-Oophorectomy			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia Repair			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal Fixation of Fracture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastectomy			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteotomy			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Operation			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Unintended Pregnancy			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion Spontaneous			

subjects affected / exposed	1 / 439 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Papillitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine with Aura			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine Polyp			
subjects affected / exposed	2 / 439 (0.46%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Cyst			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heavy Menstrual Bleeding			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Dysplasia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Chronic			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal Septum Deviation			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Disorder Due to A General Medical Condition			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood Disorder Due to A General Medical Condition			

subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic Disorder			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device Dislocation			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Tendon Rupture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist Fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Limb Fracture			
subjects affected / exposed	0 / 439 (0.00%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to Various Agents			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ankle Fracture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (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%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated Incisional Hernia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament Injury			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament Sprain			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus Injury			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Wound Complication			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon Injury			

subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Node Dysfunction			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	0 / 439 (0.00%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hemianopia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysaesthesia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Amnesia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Sclerosis Relapse			
subjects affected / exposed	1 / 439 (0.23%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial Seizures with Secondary Generalisation			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sacral Radiculopathy			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 439 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uhthoff's Phenomenon			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo CNS Origin			

subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (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			
Thrombocytopenia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision Blurred			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular Oedema			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Chronic Gastritis			

subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Functional Gastrointestinal Disorder			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical Hernia			
subjects affected / exposed	0 / 439 (0.00%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Fissure			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			

subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic Cytolysis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Chronic			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 439 (0.00%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Tubulointerstitial Nephritis			
subjects affected / exposed	2 / 439 (0.46%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus Urinary			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Colic			
subjects affected / exposed	2 / 439 (0.46%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Disorder			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Ankylosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Contracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Pain			
subjects affected / exposed	0 / 439 (0.00%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Instability			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriatic Arthropathy			

subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Large Intestine Infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis Viral			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 Pneumonia			
subjects affected / exposed	1 / 439 (0.23%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	3 / 439 (0.68%)	3 / 438 (0.68%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complicated Appendicitis			
subjects affected / exposed	2 / 439 (0.46%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	2 / 439 (0.46%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 439 (0.23%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected Covid-19			

subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Abscess			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Syncytial Virus Infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Chronic			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Urinary Tract Infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 438 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Infection			

subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 439 (0.00%)	2 / 438 (0.46%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 438 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ponesimod 20 mg (Core and Extension Study)	Teriflunomide 14 mg (Core) Then Ponesimod 20 mg (Extension)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	339 / 439 (77.22%)	328 / 438 (74.89%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	73 / 439 (16.63%)	98 / 438 (22.37%)	
occurrences (all)	120	183	
Aspartate Aminotransferase Increased			
subjects affected / exposed	17 / 439 (3.87%)	26 / 438 (5.94%)	
occurrences (all)	24	34	
Lymphocyte Count Decreased			
subjects affected / exposed	30 / 439 (6.83%)	30 / 438 (6.85%)	
occurrences (all)	41	43	
Vascular disorders			

Hypertension			
subjects affected / exposed	37 / 439 (8.43%)	44 / 438 (10.05%)	
occurrences (all)	40	48	
Nervous system disorders			
Dizziness			
subjects affected / exposed	22 / 439 (5.01%)	17 / 438 (3.88%)	
occurrences (all)	25	21	
Headache			
subjects affected / exposed	57 / 439 (12.98%)	64 / 438 (14.61%)	
occurrences (all)	70	96	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	18 / 439 (4.10%)	23 / 438 (5.25%)	
occurrences (all)	25	28	
Lymphopenia			
subjects affected / exposed	66 / 439 (15.03%)	64 / 438 (14.61%)	
occurrences (all)	86	82	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	24 / 439 (5.47%)	30 / 438 (6.85%)	
occurrences (all)	27	37	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	22 / 439 (5.01%)	15 / 438 (3.42%)	
occurrences (all)	26	18	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	45 / 439 (10.25%)	30 / 438 (6.85%)	
occurrences (all)	59	36	
Arthralgia			
subjects affected / exposed	31 / 439 (7.06%)	38 / 438 (8.68%)	
occurrences (all)	37	44	
Infections and infestations			
Covid-19			
subjects affected / exposed	115 / 439 (26.20%)	108 / 438 (24.66%)	
occurrences (all)	133	126	
Urinary Tract Infection			

subjects affected / exposed	36 / 439 (8.20%)	33 / 438 (7.53%)	
occurrences (all)	51	43	
Upper Respiratory Tract Infection			
subjects affected / exposed	47 / 439 (10.71%)	51 / 438 (11.64%)	
occurrences (all)	70	73	
Respiratory Tract Infection			
subjects affected / exposed	23 / 439 (5.24%)	15 / 438 (3.42%)	
occurrences (all)	25	20	
Nasopharyngitis			
subjects affected / exposed	82 / 439 (18.68%)	74 / 438 (16.89%)	
occurrences (all)	140	126	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2018	The main reason for this amendment was to modify the pulmonary treatment discontinuation criteria based on changes in pulmonary function variables during the study treatment.
14 May 2020	The main reasons for this amendment were: (a) To allow the analysis of biomarkers in the serum sample taken at Visit 1 (Enrollment); (b) To amend the guidance for re-initiation of study treatment in the event of study treatment interruption in order to allow patients without the identified cardiovascular risk factors to re-initiate study drug at home; (c) The efficacy assessor role is no longer defined as "independent" and, depending on site setting, can now be assumed by the primary investigator / treating neurologist; (d) To provide guidance regarding conduct of the study during the coronavirus disease (COVID)-19 (coronavirus) pandemic.
19 October 2020	The main reasons for this amendment were: (a) To inform study sites that the Independent Data Monitoring Committee (IDMC) will be disbanded after the clinical database closure of the last ponesimod double-blind study, in line with the disbandment date agreed per the IDMC Charter; (b) To provide further guidance on study conduct if/when ponesimod becomes commercially available during the study and patients are switched from study treatment to commercially available ponesimod; (c) To align the safety reporting procedures with Janssen Safety processes and standards following the integration of Actelion Safety into Janssen Safety.
20 July 2021	The main reasons for this amendment were: (a) To introduce vaccination sub-study for a sub-set of subjects to investigate the immune response induced by the Janssen COVID-19 vaccine (Ad26.COV2.S); (b) Inclusion of additional serum samples for all subjects at all scheduled visits for immunogenicity evaluations; for example, to measure anti-severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antibody levels induced by vaccination with any COVID-19 vaccination or after recovery from COVID 19; (c) Addition of clarifications regarding conduct of the study during the COVID-19 pandemic and the administration of non-live and live vaccinations; (d) To make updates with regard to teriflunomide testing per the Aubagio prescribing information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to limited availability of COVID-19 vaccine-naïve MS patients, the COVID-19 vaccination sub-study was cancelled and removed from the protocol after implementation of amendment 5.

Notes: