



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 standard deviation | 36.5 ± 8.75 | 37.2 ± 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

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

| | |
|-----------------|--------------------------------------------------------------------------------|
| End point title | Change from Baseline in Expanded Disability Status Scale (EDSS) ^[5] |
|-----------------|--------------------------------------------------------------------------------|

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:

[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 | 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: 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 ^[6] |
|-----------------|----------------------------------------------------------------------------------------------------------------|

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:

[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 | 439 | 436 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 17.5 | 7.5 | | |

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) ^[7] |
|-----------------|-----------------------------------------------------------------------------------------------------------------|

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 (cm³). 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:

[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 | 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 ^[8] |
|-----------------|----------------------------------------------------------------------------------------------------------------|

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 $\geq 0.4\%$ 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:

[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 | 437 | 435 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 5.2 | 2.3 | | |

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 ^[9] |
|-----------------|-------------------------------------------------------------------------------------------|

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:

[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 | 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 Gadolinium-enhancing (Gd+) T1 lesions Measured by MRI

| | |
|-----------------|---------------------------------------------------------------------------------|
| End point title | Number of Gadolinium-enhancing (Gd+) T1 lesions Measured by MRI ^[10] |
|-----------------|---------------------------------------------------------------------------------|

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:

[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 | 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 ^[11] |
|-----------------|----------------------------------------------------------------------------------|

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:

[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: 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: 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) ^[12] |
|-----------------|-------------------------------------------------------------------------------------------------------|

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:

[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 | 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 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) ^[13] |
|-----------------|--------------------------------------------------------------------------------------------------------------|

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:

[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 | 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: 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 ^[14] |
|-----------------|--------------------------------------------------------------------------------------------------------------------|

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:

[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 | 153 | 140 | | |

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) ^[15] |
|-----------------|-----------------------------------------------------------------------------------|

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:

[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 | 411 | 410 | | |

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) ^[16] |
|-----------------|-------------------------------------------------------------------------------------------------|

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:

[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 | 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: Heart Rate

| | |
|-----------------|----------------------------------------------------------------------------------------------------|
| End point title | Actual Values of 12-lead ECG Measurements up to End of Study Treatment: Heart Rate ^[17] |
|-----------------|----------------------------------------------------------------------------------------------------|

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:

[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 | 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: 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 |
|-----------------|------------------------------------------------------------|

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) | Terflunomide 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: 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 ^[27] |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|

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:

[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 | 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 $\geq 12\%$ in FEV1 or FVC from baseline to EOT

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Subjects with a Decrease of ≥ 200 mL or $\geq 12\%$ in FEV1 or FVC from baseline to EOT ^[28] |
|-----------------|------------------------------------------------------------------------------------------------------------------------|

End point description:

Number of subjects with a decrease of ≥ 200 mL or $\geq 12\%$ 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:

[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 | 0 ^[29] | 0 ^[30] | | |
| Units: Participants | | | | |

Notes:

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

[30] - 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 Treatment (EOT)

| | |
|-----------------|----------------------------------------------------------------------------------------------|
| End point title | Change in FEV1 and FVC (% predicted) from baseline to End of Treatment (EOT) ^[31] |
|-----------------|----------------------------------------------------------------------------------------------|

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:

[31] - 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: 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 | |

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

| | | | |
|---------------------------------------------------|-----------------|-----------------|--|
| 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 | |

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|-------------------------------------------------|-----------------|-----------------|--|
| 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 | | | |

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|-------------------------------------------------|-----------------|-----------------|
| 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 | |
| Hypertransaminaemia | | | |
| 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 occurrences (all) | 37 / 439 (8.43%) 40 | 44 / 438 (10.05%) 48 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 22 / 439 (5.01%) 25 | 17 / 438 (3.88%) 21 | |
| Headache subjects affected / exposed occurrences (all) | 57 / 439 (12.98%) 70 | 64 / 438 (14.61%) 96 | |
| Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) | 18 / 439 (4.10%) 25 | 23 / 438 (5.25%) 28 | |
| Lymphopenia subjects affected / exposed occurrences (all) | 66 / 439 (15.03%) 86 | 64 / 438 (14.61%) 82 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 24 / 439 (5.47%) 27 | 30 / 438 (6.85%) 37 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 22 / 439 (5.01%) 26 | 15 / 438 (3.42%) 18 | |
| Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) | 45 / 439 (10.25%) 59 | 30 / 438 (6.85%) 36 | |
| Arthralgia subjects affected / exposed occurrences (all) | 31 / 439 (7.06%) 37 | 38 / 438 (8.68%) 44 | |
| Infections and infestations Covid-19 subjects affected / exposed occurrences (all) | 115 / 439 (26.20%) 133 | 108 / 438 (24.66%) 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.COVS.2); (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: