# Clinical trial results:
# Multicenter, Randomized, Double-Blind, Parallel-Group, Active-Controlled, Superiority Study to Compare the Efficacy and Safety of Ponesimod to Teriflunomide in Subjects With Relapsing Multiple Sclerosis

## Summary

| | |
|---|---|
| EudraCT number | 2012-000540-10 |
| Trial protocol | DE FR PL LV SE CZ LT HU FI PT ES HR GR |
| Global end of trial date | 16 May 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 29 May 2020 |
| First version publication date | 29 May 2020 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | AC-058B301 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02425644 |
| 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 | 16 May 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 16 May 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study is to determine whether ponesimod is more efficacious than teriflunomide in terms of reducing relapses in subjects with relapsing multiple sclerosis (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. Safety was evaluated based on the following assessments: Adverse events (AEs), clinical laboratory tests (hematology, serum chemistry, virus serology, serum, and urine pregnancy tests, urinalysis), 12-lead Electrocardiogram (ECG), blood pressure, pulse rate, body temperature, spirometry, diffusing capacity of the lungs measured using carbon monoxide (DLCO) tests (from the substudy), chest X-ray, tuberculosis test (QuantiFERON-TB-Gold), ophthalmologic assessments including ophthalmological exam and optical coherence tomography (OCT), weight, height, physical examination, dermatological examination, locally reviewed magnetic resonance imaging (MRI) for safety (non-multiple sclerosis [MS] central nervous system [CNS] pathology), and the Columbia-Suicide Severity Rating Scale (electronic self-rated version) (eC-SSRS) questionnaire.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 27 April 2015 |
| 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 | Bulgaria: 45 |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 3 |
| Country: Number of subjects enrolled | Belarus: 45 |
| Country: Number of subjects enrolled | Canada: 17 |
| Country: Number of subjects enrolled | Czech Republic: 101 |
| Country: Number of subjects enrolled | Germany: 16 |
| Country: Number of subjects enrolled | Spain: 73 |
| Country: Number of subjects enrolled | Finland: 7 |
| Country: Number of subjects enrolled | France: 16 |
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Country: Number of subjects enrolled | Georgia: 41 |
| Country: Number of subjects enrolled | Greece: 15 |
| Country: Number of subjects enrolled | Croatia: 34 |
| Country: Number of subjects enrolled | Hungary: 19 |

| | |
|---|---|
| Country: Number of subjects enrolled | Israel: 13 |
| Country: Number of subjects enrolled | Italy: 14 |
| Country: Number of subjects enrolled | Lithuania: 11 |
| Country: Number of subjects enrolled | Latvia: 15 |
| Country: Number of subjects enrolled | Mexico: 17 |
| Country: Number of subjects enrolled | Poland: 151 |
| Country: Number of subjects enrolled | Portugal: 20 |
| Country: Number of subjects enrolled | Romania: 15 |
| Country: Number of subjects enrolled | Russian Federation: 227 |
| Country: Number of subjects enrolled | Serbia: 33 |
| Country: Number of subjects enrolled | Sweden: 14 |
| Country: Number of subjects enrolled | Turkey: 2 |
| Country: Number of subjects enrolled | Ukraine: 123 |
| Country: Number of subjects enrolled | United States: 39 |
| Worldwide total number of subjects | 1133 |
| EEA total number of subjects | 573 |

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) | 1133 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 1468 subjects screened. Among them, 1133 subjects were randomized in a 1:1 ratio to receive ponesimod 20 milligrams (mg) or teriflunomide 14 mg.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Ponesimod 20 mg |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ponesimod 20 mg (Maintenance) |
| Investigational medicinal product code | |
| Other name | JNJ-67896153, ACT-128800 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received 20 mg ponesimod over-encapsulated tablet once daily during maintenance phase.

| | |
|---|---|
| Investigational medicinal product name | Ponesimod 2 to 10 mg (Uptitration) |
| Investigational medicinal product code | |
| Other name | JNJ-67896153, ACT-128800 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received ponesimod 2 to 10 mg film-coated tablets once daily during uptitration phase.

| | |
|---|---|
| Investigational medicinal product name | Teriflunomide Matching Placebo (uptitration) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received teriflunomide matching placebo once daily during uptitration phase.

| | |
|---|---|
| **Arm title** | Teriflunomide 14 mg |

Arm description: -

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Teriflunomide 14 mg (maintenance) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

| | |
|---|---|
| Dosage and administration details:<br>Subjects received teriflunomide 14 mg over-encapsulated tablets once daily during the maintenance phase. | |
| Investigational medicinal product name | Teriflunomide 14 mg (uptitration) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details:<br>Subjects received teriflunomide 14 mg once daily during uptitration phase. | |
| Investigational medicinal product name | Ponesimod matching placebo (uptitration) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details:<br>Subjects received ponesimod matching placebo once daily during the uptitration phase. | |

| **Number of subjects in period 1** | Ponesimod 20 mg | Teriflunomide 14 mg |
|---|---|---|
| Started | 567 | 566 |
| Completed | 490 | 495 |
| Not completed | 77 | 71 |
| Consent withdrawn by subject | 41 | 36 |
| Death | - | 2 |
| Adverse event | 13 | 3 |
| Unspecified | 18 | 17 |
| Lost to follow-up | 2 | 3 |
| Lack of efficacy | 3 | 10 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Ponesimod 20 mg |
| Reporting group description: - | |
| Reporting group title | Teriflunomide 14 mg |
| Reporting group description: - | |

| Reporting group values | Ponesimod 20 mg | Teriflunomide 14 mg | Total |
|---|---|---|---|
| Number of subjects | 567 | 566 | 1133 |
| Title for AgeCategorical<br>Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 567 | 566 | 1133 |
| From 65 to 84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Title for AgeContinuous<br>Units: years | | | |
| arithmetic mean | 36.7 | 36.8 | |
| standard deviation | ± 8.74 | ± 8.74 | - |
| Title for Gender<br>Units: subjects | | | |
| Female | 363 | 372 | 735 |
| Male | 204 | 194 | 398 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Ponesimod 20 mg |
| Reporting group description: - | |
| Reporting group title | Teriflunomide 14 mg |
| Reporting group description: - | |

### Primary: Annualized Relapse Rate (ARR)

| | |
|---|---|
| End point title | Annualized Relapse Rate (ARR) |
| End point description: | |
| ARR was defined as the number of confirmed relapses according to the treating neurologist or principal investigator per subject-year. A relapse was defined as 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 the absence of fever or infection. Full Analysis Set (FAS) included all randomized subjects. | |
| End point type | Primary |
| End point timeframe: | |
| Up to Week 108 | |

| End point values | Ponesimod 20 mg | Teriflunomide 14 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 567 | 566 | | |
| Units: relapses per year | | | | |
| least squares mean (confidence interval 99%) | 0.202 (0.165 to 0.246) | 0.290 (0.244 to 0.345) | | |

### Statistical analyses

| Statistical analysis title | Statistical analysis |
|---|---|
| Comparison groups | Ponesimod 20 mg v Teriflunomide 14 mg |
| Number of subjects included in analysis | 1133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 |
| Method | Negative binomial regression model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.695 |
| Confidence interval | |
| level | Other: 99 % |
| sides | 2-sided |
| lower limit | 0.536 |
| upper limit | 0.902 |

## Secondary: Change from Baseline in Fatigue-related Symptoms as Measured by the Symptoms Domain of the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ–RMS) Score to Week 108

| End point title | Change from Baseline in Fatigue-related Symptoms as Measured by the Symptoms Domain of the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ–RMS) Score to Week 108 |
|---|---|

End point description:

FSIQ-RMS is a validated patient-reported outcome instrument. Its symptoms domain assesses multiple sclerosis (MS)-related symptoms of fatigue and has seven items. It has a daily recall period and is administered daily over the course of seven days. Each item of the domain is scored on an 11-point numerical rating scale. The total score for the domain is calculated as the average of the daily symptoms scores over the 7-day period. The domain score is standardized onto a scale of 0 to 100 with higher scores indicating more fatigue. FAS included all randomized subjects. Subjects with baseline and at least one available assessment at a post-baseline visit were included in the analysis. Here 'N' (number of subjects analyzed) signifies number of subjects analyzed in this endpoint.

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

End point timeframe:

Baseline and Week 108

| **End point values** | Ponesimod 20 mg | Teriflunomide 14 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 499 | 458 | | |
| Units: score on scale | | | | |
| least squares mean (confidence interval 95%) | -0.01 (-1.60 to 1.58) | 3.56 (1.96 to 5.16) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Cumulative Number of Combined Unique Active Lesions (CUAL) From Baseline to Week 108

| End point title | Cumulative Number of Combined Unique Active Lesions (CUAL) From Baseline to Week 108 |
|---|---|

End point description:

CUALs was calculated as sum of new Gadolinium-enhanced (Gd+) T1 lesions plus new or enlarging T2 lesions (without double-counting of lesions) based on the MRI scans up to Week 108. FAS included all randomized subjects. Here 'N' (number of subjects analyzed) signifies number of subjects analyzed in this endpoint.

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

End point timeframe:

Baseline and Week 108

| End point values | Ponesimod 20 mg | Teriflunomide 14 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 539 | 536 | | |
| Units: lesions per year | | | | |
| least squares mean (confidence interval 95%) | 1.405 (1.215 to 1.624) | 3.164 (2.757 to 3.631) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Event Rate Based on Time to First 12-week Confirmed Disability Accumulation (CDA) From Baseline up to EOS

| End point title | Event Rate Based on Time to First 12-week Confirmed Disability Accumulation (CDA) From Baseline up to EOS |
|---|---|

End point description:

Time to first 12-week CDA is defined as time from baseline to first onset of a 12-week CDA. A 12-week CDA was defined as an increase of at least 1.5 in Expanded Disability Status Scale (EDSS) for subjects with a baseline EDSS score of 0.0 or an increase of at least 1.0 in EDSS for subjects with a baseline EDSS score of 1.0 to 5.0, or an increase of at least 0.5 in EDSS for subjects with a baseline EDSS score greater than or equal to (>=) 5.5, which was confirmed after 12 weeks. Baseline EDSS was defined as the last EDSS score recorded prior to randomization. EDSS is a disability scale that ranges from 0 (normal) to 10.0 (death) in 0.5-point steps (1-point step from 0 to 1). It is based on standard neurological examination in conjunction with observations concerning ambulation. Percentage (%) of subjects with events (Kaplan-Meier [KM] estimates) were reported. FAS included all randomized subjects.

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

End point timeframe:

From Baseline up to EOS (Up to Week 108)

| End point values | Ponesimod 20 mg | Teriflunomide 14 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 567 | 566 | | |
| Units: percentage of subjects with events | | | | |
| number (confidence interval 95%) | 10.8 (8.4 to 13.7) | 13.2 (10.6 to 16.3) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Event Rate Based on Time to First 24-week Confirmed Disability Accumulation (CDA) From Baseline up to EOS

| End point title | Event Rate Based on Time to First 24-week Confirmed Disability Accumulation (CDA) From Baseline up to EOS |
|---|---|

End point description:

Time to first 24-week CDA is defined as time from baseline to first onset of a 24-week CDA. A 24-week CDA was defined as an increase of at least 1.5 in EDSS for subjects with a baseline EDSS score of 0.0 or an increase of at least 1.0 in EDSS for subjects with a baseline EDSS score of 1.0 to 5.0, or an increase of at least 0.5 in EDSS for subjects with a baseline EDSS score >= 5.5, which was confirmed after 24 weeks. Baseline EDSS was defined as the last EDSS score recorded prior to randomization. EDSS is a disability scale that ranges from 0 (normal) to 10.0 (death) in 0.5-point steps (1-point step from 0 to 1). It is based on standard neurological examination in conjunction with observations concerning ambulation. The percentage of subjects with events (Kaplan-Meier KM] estimates) was reported. FAS included all randomized subjects.

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

End point timeframe:

From Baseline up to EOS (Up to Week 108)

| **End point values** | Ponesimod 20 mg | Teriflunomide 14 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 567 | 566 | | |
| Units: percentage of subjects with events | | | | |
| number (confidence interval 95%) | 8.7 (6.6 to 11.4) | 10.5 (8.2 to 13.4) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 108

Adverse event reporting additional description:

The safety analysis set (SAF) included all subjects who received at least one dose of study treatment.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Ponesimod 20 mg |

Reporting group description: -

| | |
|---|---|
| Reporting group title | Teriflunomide 14 mg |

Reporting group description: -

| Serious adverse events | Ponesimod 20 mg | Teriflunomide 14 mg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 49 / 565 (8.67%) | 46 / 566 (8.13%) | |
| number of deaths (all causes) | 0 | 2 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal Cell Carcinoma | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eyelid Haemangioma | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive Ductal Breast Carcinoma | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant Melanoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pituitary Tumour Benign | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous Cell Carcinoma of the Cervix | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (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 / 565 (0.18%) | 2 / 566 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep Vein Thrombosis | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive Crisis | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Raynaud's Phenomenon | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis Superficial | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (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 | | | |

| | | | |
|---|---|---|---|
| Abortion Induced | | | |
| subjects affected / exposed | 2 / 565 (0.35%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoid Operation | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hysterectomy | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament Operation | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine Dilation and Curettage | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Breast Cyst | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial Hyperplasia | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometriosis | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 2 / 566 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian Cyst | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic Adhesions | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperventilation | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Conversion Disorder | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Depression | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Panic Attack | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 2 / 566 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic Enzyme Increased | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases Increased | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight Decreased | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 565 (0.00%) | 2 / 566 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur Fracture | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibula Fracture | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaw Fracture | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament Injury | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meniscus Injury | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple Injuries | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post Procedural Haematoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft Tissue Injury | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to Various Agents | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial Fibrillation | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary Artery Insufficiency | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Clonic Convulsion | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic Stroke | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of Consciousness | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar Radiculopathy | | | |
| subjects affected / exposed | 2 / 565 (0.35%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple Sclerosis | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Multiple Sclerosis Relapse | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Partial Seizures with Secondary Generalisation | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Restless Legs Syndrome | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trigeminal Neuralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Lymphadenitis | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 3 / 565 (0.53%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bowel Movement Irregularity | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal Ulcer Haemorrhage | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoidal Haemorrhage | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal Haemorrhage | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis Acute | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary Colic | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis Chronic | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 565 (0.18%) | 3 / 566 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-Induced Liver Injury | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis Toxic | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal Colic | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubulointerstitial Nephritis | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureterolithiasis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral Disc Protrusion | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myofascial Pain Syndrome | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatoid Arthritis | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (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 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovitis | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Abdominal Infection | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 3 / 565 (0.53%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes Zoster | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymph Node Abscess | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis Enteroviral | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pilonidal Cyst | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salpingitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 565 (0.18%) | 0 / 566 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vestibular Neuronitis | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 565 (0.00%) | 1 / 566 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Ponesimod 20 mg | Teriflunomide 14 mg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 339 / 565 (60.00%) | 343 / 566 (60.60%) | |
| Investigations | | | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 110 / 565 (19.47%) | 51 / 566 (9.01%) | |
| occurrences (all) | 164 | 56 | |
| Aspartate Aminotransferase Increased | | | |
| subjects affected / exposed | 36 / 565 (6.37%) | 19 / 566 (3.36%) | |
| occurrences (all) | 38 | 21 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 45 / 565 (7.96%) | 44 / 566 (7.77%) | |
| occurrences (all) | 50 | 45 | |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 64 / 565 (11.33%) | 72 / 566 (12.72%) | |
| occurrences (all) | 98 | 97 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 34 / 565 (6.02%) | 37 / 566 (6.54%) | |
| occurrences (all) | 38 | 42 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 20 / 565 (3.54%) | 44 / 566 (7.77%) | |
| occurrences (all) | 21 | 53 | |
| Nausea | | | |
| subjects affected / exposed | 43 / 565 (7.61%) | 47 / 566 (8.30%) | |
| occurrences (all) | 53 | 52 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 30 / 565 (5.31%) | 7 / 566 (1.24%) | |
| occurrences (all) | 35 | 7 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 18 / 565 (3.19%) | 72 / 566 (12.72%) | |
| occurrences (all) | 19 | 76 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back Pain | | | |
| subjects affected / exposed | 33 / 565 (5.84%) | 38 / 566 (6.71%) | |
| occurrences (all) | 40 | 40 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 109 / 565 (19.29%) | 95 / 566 (16.78%) | |
| occurrences (all) | 170 | 147 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 60 / 565 (10.62%) | 59 / 566 (10.42%) | |
| occurrences (all) | 92 | 95 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 31 / 565 (5.49%) | 29 / 566 (5.12%) | |
| occurrences (all) | 39 | 48 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 29 April 2015 | The Amendment-1 included the following main changes: A substudy assessment was added for patient preferences for different outcomes in the treatment of multiple sclerosis (MS) using an electronic MS Patient Preference Questionnaire. In addition, it was clarified that MS relapses were to be reported on the dedicated pages of the electronic Case Report Form (eCRF) and were not to be considered as adverse event (AEs). |
| 16 July 2015 | The Amendment-2 included the following main changes: Introduction of an exclusion criterion in the presence of signs suggestive of progressive multifocal leukoencephalopathy infection which could not be ruled out; Introduction of the electronic self-rated version of the Columbia-Suicide Severity Rating Scale (eC-SSRS) assessment to reliably and consistently monitor subjects for suicidal ideation or behavior during the study; and Monitoring of total white blood cell and total lymphocyte count every 4 weeks up to Week 24. |
| 05 February 2016 | The Amendment-3 included the following main changes: A standardized stepwise procedure for the confirmation and reporting of relapses was introduced. This included incorporating a relapse assessment questionnaire into the study (based on telephone calls and visits); Clarification that the treating neurologist was not to perform the Expanded Disability Status Scale (EDSS) and Functional System (FS) assessment and that no one was to alter EDSS and FS scores recorded by the efficacy assessor; Sensitivity analyses were added for the primary endpoint due to the adjusted collection of data for relapses introduced in this protocol amendment. Some clarifications were added to the existing sensitivity analyses; the definition of baseline assessments was added; the definitions of end of treatment (EOT) and end of study (EOS) were added; and the introduction of an adjudication board for major adverse cardiovascular events (MACE). |
| 14 November 2016 | The Amendment-4 included the following main changes: The procedure for teriflunomide plasma concentration testing after subject's discontinuation from study treatment was modified and not conducted at Follow-up Visit 1 and Follow-up Visit 2 (15 and 30 days after the last intake of study drug, respectively). This was mainly because an update from the central laboratory (dated 6 October 2016) showed an unexpectedly high number (that is, 33.0 percent [%] of all tests conducted) of reports with alerts indicating teriflunomide plasma concentration above the threshold of 0.02 mg/L. At that time, the total number of affected subjects was 11. The occurrence of these alerts increased the risk of unblinding of the treatment allocation. In addition, in the modified procedure, the timing for the teriflunomide concentration measurement for female subjects of childbearing potential and fertile male subjects was made dependent on compliance with the accelerated elimination procedure to confirm that contraception could be discontinued following treatment discontinuation. |
| 30 August 2017 | The Amendment-5 included the following main changes: Allowed testing of teriflunomide plasma concentration in any subject who had discontinued study drug if deemed necessary for the subject's safety, at the discretion of the investigator. In this event, the timing of the testing of teriflunomide plasma concentration remained dependent on study drug discontinuation and compliance with the accelerated elimination procedure, as assessed by the investigator. This amendment did not change the procedure for teriflunomide plasma concentration testing to be conducted for female subjects of childbearing potential and fertile male subjects, if needed, to confirm contraception discontinuation. |

| | |
|---|---|
| 05 December 2018 | The Amendment-6 included the following main changes: The number of secondary endpoints was reduced from five to four: two endpoints were moved from secondary (time to first relapse and percent change from baseline in brain volume) to exploratory, as these do not add substantial information on clinically important effects of the study drug on MS disease; one endpoint was moved from exploratory (time to 24-week disability) to secondary, to comply with the Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis. The multiple testing strategy to control the Type I error for testing secondary endpoints was modified according to a fallback type method to optimize the ability of the trial to achieve its objectives. |

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.

| |
|---|
| Low probability of the AC-058B301 / OPTIMUM study to provide a robust evaluation of the effect of ponesimod on disability accumulation compared to an active comparator. |

Notes: