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: 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: 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: 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 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 Units: years			
arithmetic mean	36.7	36.8	
standard deviation	± 8.74	± 8.74	-
Title for Gender 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: