Clinical trial results:
A Prospective, Single-Arm, Clinical-Setting Study to Describe Efficacy, Tolerability and Convenience of Teriflunomide Treatment Using Patient Reported Outcomes (PROs) in Relapsing Multiple Sclerosis (RMS) Patients

Summary

EudraCT number	2013-001439-34
Trial protocol	FI SE IT ES BE DE GB AT GR
Global end of trial date	19 November 2015

Results information

Result version number	v1 (current)
This version publication date	01 December 2016
First version publication date	01 December 2016

Trial information

Trial identification

Sponsor protocol code	LPS13567

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01895335
WHO universal trial number (UTN)	U1111-1139-8730

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.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	19 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe efficacy, tolerability and convenience of teriflunomide treatment through the evaluation of Patient Reported Outcomes (PROs).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject was participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 10
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	Sweden: 23
Country: Number of subjects enrolled	United Kingdom: 44
Country: Number of subjects enrolled	Austria: 24
Country: Number of subjects enrolled	Belgium: 40
Country: Number of subjects enrolled	Finland: 30
Country: Number of subjects enrolled	France: 138
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Chile: 12
Country: Number of subjects enrolled	United States: 545
Worldwide total number of subjects	1001
EEA total number of subjects	434

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)	946
From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 169 centres in 14 countries. A total of 1102 subjects were screened between June 14, 2013 and November 27, 2014 of whom 101 were screen failures. Screen failures were mainly due to exclusion criteria met.

Pre-assignment

Screening details:

A total of 1001 subjects were included and 1000 subjects were treated in the study. Dose of teriflunomide tablet was given according to local labelling 14 mg or 7 mg (Teriflunomide 14 mg was the recommended dosage worldwide, except in the US [where both 7 and 14 mg were available]).

Period 1

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

Arms

Arm title	Teriflunomide

Arm description:

Teriflunomide once daily (QD) for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Teriflunomide
Investigational medicinal product code	HMR1726
Other name	Aubagio®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Teriflunomide 14 mg or 7 mg according to local labeling, could be taken with or without food.

Number of subjects in period 1	Teriflunomide
Started	1001
Treated	1000
Completed	786
Not completed	215
Adverse events	106
Poor Compliance to Protocol	11
Other than Specified Above	44
Included But Not treated	1
Lack of efficacy	53

Baseline characteristics

Reporting groups	
Reporting group title	Teriflunomide
Reporting group description: Teriflunomide once daily (QD) for 48 weeks.	

Reporting group values	Teriflunomide	Total	
Number of subjects	1001	1001	
Age categorical Units: Subjects			
Adults (18-64 years)	946	946	
From 65-84 years	55	55	
Gender categorical Units: Subjects			
Female	756	756	
Male	245	245	

End points

End points reporting groups

Reporting group title	Teriflunomide
Reporting group description: Teriflunomide once daily (QD) for 48 weeks.	

Primary: Treatment Satisfaction Questionnaire for Medication (TSQM) Version 1.4 - Assessment of Global Satisfaction Subscale Score With Teriflunomide Treatment at Week 48

End point title	Treatment Satisfaction Questionnaire for Medication (TSQM) Version 1.4 - Assessment of Global Satisfaction Subscale Score With Teriflunomide Treatment at Week 48[1]

End point description:

TSQM version 1.4 is a global satisfaction scale used to assess the overall level of subject's satisfaction or dissatisfaction with their medications. It comprises of 14 items assessing the following 4 domains: effectiveness (questions: 1-3), side effects (questions: 4-8), convenience (questions: 9-11), global satisfaction (questions: 12-14). Primary outcome was the global satisfaction score. The score of the corresponding item was added based on the algorithm to create a score of 0 to 100. Higher scores indicated greater satisfaction in that domain. Efficacy population that included all treated subjects. Number of subjects analyzed=subjects with available data at specified time point.

End point type	Primary

End point timeframe:

Week 48

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	889			
Units: units on a scale				
arithmetic mean (standard deviation)	68.17 (± 27.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in TSQM Scores in Subjects Switching From Another Disease Modifying Therapy (DMT) at Week 4 and Week 48

End point title	Change From Baseline in TSQM Scores in Subjects Switching From Another Disease Modifying Therapy (DMT) at Week 4 and Week 48

End point description:

TSQM version 1.4 is a global satisfaction scale used to assess the overall level of subject's satisfaction or dissatisfaction with their medications. It comprises of 14 items assessing the following 4 domains: effectiveness (questions: 1-3), side effects (questions: 4-8), convenience (questions: 9-11), global

satisfaction (questions: 12-14). For each of the 4 domains, the scores of the corresponding items were added based on an algorithm to create a score of 0 to 100. Higher scores indicated greater satisfaction. Analysis was performed on Efficacy population. Number of subjects analyzed=subjects with available data at specified time points. Here, 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 48

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	594			
Units: units on a scale				
arithmetic mean (standard deviation)				
Global Satisfaction Score Change at Week 4 (n=482)	21.35 (± 27.51)			
Global Satisfaction Score Change at Week 48(n=457)	16.55 (± 34.29)			
Effectiveness Score Change at Week 4 (n=477)	12.02 (± 25.53)			
Effectiveness Score Change at Week 48 (n=453)	10.19 (± 28.9)			
Side effects Score Change at Week 4 (n=479)	24.31 (± 35.47)			
Side effects Score Change at Week 48 (n=456)	19.95 (± 39)			
Convenience Score Change at Week 4 (n=487)	34.64 (± 26.37)			
Convenience Score Change at Week 48 (n=461)	32.21 (± 27.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 4 in TSQM Scores in Naïve Subjects to Week 48

End point title	Change From Week 4 in TSQM Scores in Naïve Subjects to Week 48

End point description:

TSQM version 1.4 is a global satisfaction scale used to assess the overall level of subject's satisfaction or dissatisfaction with their medications. It comprises of 14 items assessing the following 4 domains: effectiveness (questions: 1-3), side effects (questions: 4-8), convenience (questions: 9-11), global satisfaction (questions: 12-14). For each of the 4 domains, the scores of the corresponding items were added based on an algorithm to create a score of 0 to 100. Higher scores indicated greater satisfaction. Analysis was performed on Efficacy population. Number of subjects analyzed=subjects with available data at specified time points. Here, 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Week 4, Week 48

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	285			
Units: units on a scale				
arithmetic mean (standard deviation)				
Change in Global Satisfaction Score (n=234)	-1.34 (± 23.59)			
Change in Effectiveness Score (n=231)	1.76 (± 27.48)			
Change in Side effects Score (n=234)	-5.44 (± 25.11)			
Change in Convenience Score (n=235)	0.33 (± 12.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disease Progression Using Patient Determined Disease Steps (PDDS) Score at Week 48

End point title	Change From Baseline in Disease Progression Using Patient Determined Disease Steps (PDDS) Score at Week 48

End point description:

PDDS scale developed to assess the disability in Multiple Sclerosis (MS) subjects and in assessing disease progression that focuses mainly on how subjects walk. PDDS scale consisted of 0 = normal; 1 = mild disability; 2 = moderate disability; 3 = gait disability; 4 = early cane; 5 = late cane; 6 = bilateral support; 7 = wheelchair/scooter and 8 = bedridden. A higher score represented higher level of disability. Analysis was performed on Efficacy population. Number of subjects analyzed=subjects with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	860			
Units: units on a scale				
arithmetic mean (standard deviation)	-0.01 (± 1.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Multiple Sclerosis Performance Scale (MSPS)

Score at Week 24 and Week 48

End point title	Change From Baseline in Multiple Sclerosis Performance Scale (MSPS) Score at Week 24 and Week 48

End point description:

MSPS was a self-reported measure for MS associated disability in which subjects were asked to indicate the category that best described their condition during the past month on the following 8 subscales: mobility, hand function, vision, fatigue, cognitive symptoms, bladder/bowel, sensory symptoms, and spasticity symptoms. MSPS used a single question to assess each of 8 subscales. All of the subscales ranged from 0=normal to 5=total disability, except mobility scale which ranged from 0=normal to 6=total disability. Total MSPS score ranged from 0 =normal to 41=greater disability, where higher score reflected greater disability. Analysis was performed on Efficacy population. Here, 'n' signifies number of subjects with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 48

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	1000			
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at Week 24 (n=854)	-0.61 (± 3.89)			
Change at Week 48 (n=875)	-0.06 (± 4.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Treated Relapse Rate

End point title	Annualized Treated Relapse Rate

End point description:

Annualized treated relapse rate was defined as the total number of treated relapses during the study treatment period divided by the total number subjects-years of treatment. Only events occurred during the treatment period (first drug administration to last drug administration) were considered for analysis. Analysis was performed on Efficacy population.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment (up to Week 48)

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	1000			
Units: relapses per subject-year				
number (not applicable)	0.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Relapse: Kaplan-Meier Estimates of the Probability of Treated Relapse at Week 4, Week 24 and Week 48

End point title	Time to Relapse: Kaplan-Meier Estimates of the Probability of Treated Relapse at Week 4, Week 24 and Week 48

End point description:

A treated relapse was defined as a relapse treated by a systemic corticosteroid treatment or by another DMT. If a subject had no treated relapse before treatment discontinuation/completion, then the subject was considered as free of treated relapse until the date of treatment discontinuation/completion. Only treated relapse occurred during the treatment period (first drug administration to last drug administration) were considered for analysis. Kaplan-Meier method was used to estimate the probability of treated MS relapse at 4, 24 and 48 weeks. Analysis was performed on Efficacy population.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment (up to Week 48)

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	1000			
Units: Percent probability of treated relapse				
number (confidence interval 95%)				
Percent Probability of Treated Relapse at Week 4	1.8 (1 to 2.6)			
Percent Probability of Treated Relapse at Week 24	9.4 (7.5 to 11.2)			
Percent Probability of Treated Relapse at Week 48	15.5 (13.2 to 17.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cognition Measured by Symbol Digit Modalities Test (SDMT) Score at Week 48

End point title	Change From Baseline in Cognition Measured by Symbol Digit Modalities Test (SDMT) Score at Week 48

End point description:

SDMT measures the time to pair abstract symbols with specific numbers. It is a simple substitution task that gives the examinee 90 seconds to pair specific numbers with given geometric figures as a measure for screening cognitive impairment. The score is computed as a ratio of number of correct responses

divided by the total number of responses. The test score range from 0 (worst outcome) to 1 (best outcome). Higher scores are indicative of better cognition function. Analysis was performed on Efficacy population. Number of subjects analyzed=subjects with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	854			
Units: units on a scale				
arithmetic mean (standard deviation)	0 (± 0.06)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of Adverse Events (AEs)

End point title	Overview of Adverse Events (AEs)

End point description:

Any untoward medical occurrence in a subject who received investigational medicinal product (IMP) was considered an AE without regard to possibility of causal relationship with this treatment. Treatment-emergent adverse events (TEAEs): AEs that developed or worsened or became serious from first study drug intake up to 112 days after last intake for subject with no accelerated elimination procedure (AEP) or to last AEP follow up visit for subjects with AEP. A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. Safety Population that included all treated subjects who received at least 1 dose or part of a dose of IMP.

End point type	Secondary

End point timeframe:

From first study drug intake up to 112 days after last intake for subject with no AEP or to last AEP follow up visit for subjects with AEP

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	1000			
Units: percentage of subjects				
number (not applicable)				
Any TEAE	82.3			
Any treatment emergent SAE	12.7			
Any TEAE leading to death	0.4			
Any TEAE leading to permanent discontinuation	10.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment Compliance of ≥80% During the Study Treatment Period

End point title	Percentage of Subjects With Treatment Compliance of ≥80% During the Study Treatment Period

End point description:

Percentage of compliance for a subject was defined as the number of days that the subject was compliant (1 tablet/day) divided by the exposure duration in days (from the first dose administration to the last dose administration) times 100. Analysis was performed on Safety population.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment (up to Week 48)

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	1000			
Units: percentage of subjects				
number (not applicable)	98.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Teriflunomide Treatment Exposure

End point title	Duration of Teriflunomide Treatment Exposure

End point description:

Duration of exposure was defined as last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations and regardless of dosage administered (14 mg or 7 mg). Analysis was performed on Safety population.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment (up to Week 48)

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	1000			
Units: Days				
arithmetic mean (standard deviation)	301.6 (± 89.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Multiple Sclerosis International Quality of Life (MusiQoL) Score at Week 48

End point title	Change From Baseline in Multiple Sclerosis International Quality of Life (MusiQoL) Score at Week 48

End point description:

The MusiQoL is a quality of life questionnaire that consists of 31 questions, divided into 9 dimensions: activities of daily living, physiological well-being, symptoms, relationship with friends, relationship with family, sentimental and sexual life, coping, rejection and relationship with healthcare system. All the 9 dimensions scores and the global scores are linearly transformed and standardized on 0 (worst outcome)-100 (best outcome) scale. Higher scores represents higher quality of life. Analysis was performed on Efficacy population. Number of subjects analyzed=subject with available data at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	826			
Units: units on a scale				
arithmetic mean (standard deviation)	0.99 (± 10.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Stern Leisure Activity Scale at Week 48

End point title	Change From Baseline in Stern Leisure Activity Scale at Week 48

End point description:

The Stern Leisure Activity Scale is a self-reported scale that consists of 13 questions assessing the subject's participation in leisure activities during the preceding month. One point is given for participation in each of the 13 activities and an aggregate score (range from 0 to 13) is obtained. ≤ 6 score is considered as low leisure activity and > 6 score as high leisure activity. Analysis was performed on Efficacy population. Number of subjects analyzed=subjects with available data at specified time points.

End point type	Secondary

End point timeframe:
Baseline, Week 48

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	845			
Units: units on a scale				
arithmetic mean (standard deviation)	0.07 (± 1.93)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expanded Disability Status Scale (EDSS) Score at Baseline and Week 48

End point title	Expanded Disability Status Scale (EDSS) Score at Baseline and Week 48

End point description:

EDSS is a method of quantifying disability in MS subjects and monitoring changes in the level of disability over time. EDSS quantifies disability in 8 functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other. EDSS scale ranges from 0 to 10 in 0.5 unit increments that represents higher levels of disability. EDSS score 1.0 to 4.5 refers to people with MS who are fully ambulatory; EDSS score 5.0 to 9.5 refers to impairment to ambulation; EDSS score 10 refers to death due to MS. Analysis was performed on Efficacy population. Number of subjects analyzed=subjects with available data at specified time points. Here, 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:
Baseline, Week 48

End point values	Teriflunomide			
Subject group type	Reporting group			
Number of subjects analysed	1000			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=981)	3.05 (± 1.94)			
Week 48 (n=886)	3.05 (± 1.98)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from signature of the informed consent form up to the last visit (Week 52) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are TEAEs that is AEs that developed/worsened from first study drug intake up to 112 days after last intake for subject with no AEP or to last AEP follow up visit for subjects in AEP. Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Teriflunomide

Reporting group description:

Teriflunomide once daily (QD) for 48 weeks.

Serious adverse events	Teriflunomide		
Total subjects affected by serious adverse events			
subjects affected / exposed	127 / 1000 (12.70%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	2 / 1000 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast Cancer			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibroma			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive Ductal Breast Carcinoma			

subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant Melanoma				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-Small Cell Lung Cancer Stage Iv				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Rectal Cancer				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine Leiomyoma				
subjects affected / exposed	2 / 1000 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep Vein Thrombosis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Essential Hypertension				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	6 / 1000 (0.60%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				

Abdominoplasty			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest Pain			
subjects affected / exposed	3 / 1000 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Non-Cardiac Chest Pain			
subjects affected / exposed	3 / 1000 (0.30%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Oedema Peripheral			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Female Genital Tract Fistula			

subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Menorrhagia				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian Cyst				
subjects affected / exposed	2 / 1000 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute Interstitial Pneumonitis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute Respiratory Failure				
subjects affected / exposed	2 / 1000 (0.20%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Asthmatic Crisis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atelectasis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic Obstructive Pulmonary Disease				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Cyst				

subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia Aspiration				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Acute Psychosis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Adjustment Disorder With Depressed Mood				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	2 / 1000 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Suicidal Ideation				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicide Attempt				
subjects affected / exposed	2 / 1000 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				

Alanine Aminotransferase Increased			
subjects affected / exposed	6 / 1000 (0.60%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Blood Pressure Increased			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium Test Positive			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibrin D Dimer Increased			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases Increased			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Weight Decreased			
subjects affected / exposed	2 / 1000 (0.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial Bones Fracture			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Intentional Overdose				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Myocardial Infarction				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary Artery Disease				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial Infarction				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Myocarditis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carpal Tunnel Syndrome				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral Sarcoidosis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular Accident				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cervicobrachial Syndrome			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Medication Overuse Headache			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple Sclerosis			
subjects affected / exposed	2 / 1000 (0.20%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Multiple Sclerosis Relapse			

subjects affected / exposed	21 / 1000 (2.10%)			
occurrences causally related to treatment / all	3 / 24			
deaths causally related to treatment / all	0 / 1			
Neuromyelitis Optica				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	4 / 1000 (0.40%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Toxic Encephalopathy				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient Ischaemic Attack				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Trigeminal Neuralgia				
subjects affected / exposed	2 / 1000 (0.20%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Uhthoff's Phenomenon				

subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness Unilateral			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal Artery Thrombosis			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Hernia Obstructive			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis Microscopic			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			

subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	2 / 1000 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal Reflux Disease				
subjects affected / exposed	2 / 1000 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hiatus Hernia				
subjects affected / exposed	2 / 1000 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Volvulus				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile Duct Stone				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary Colic				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				

subjects affected / exposed	2 / 1000 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eczema			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psoriasis			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	2 / 1000 (0.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertonic Bladder			

subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back Pain				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical Spinal Stenosis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral Disc Disorder				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral Disc Protrusion				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal Pain				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Periarthritis				

subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhabdomyolysis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium Difficile Colitis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium Difficile Infection				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	2 / 1000 (0.20%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	2 / 1000 (0.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Myelitis				

subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal Candidiasis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic Abscess				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Perichondritis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 1000 (0.40%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 1			
Pyelonephritis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 1000 (0.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Infection				

subjects affected / exposed	5 / 1000 (0.50%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Viral Infection			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic Acidosis			
subjects affected / exposed	1 / 1000 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Teriflunomide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	498 / 1000 (49.80%)		
Investigations			
Alanine Aminotransferase Increased			

subjects affected / exposed occurrences (all)	57 / 1000 (5.70%) 66		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 68 / 1000 (6.80%) 73		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 52 / 1000 (5.20%) 53		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	 172 / 1000 (17.20%) 200		
Nausea subjects affected / exposed occurrences (all)	 82 / 1000 (8.20%) 84		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	 229 / 1000 (22.90%) 235		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary Tract Infection subjects affected / exposed occurrences (all)	 54 / 1000 (5.40%) 56 62 / 1000 (6.20%) 71		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2013	Following changes were made: -Adherence to approved local labeling in various sections of the protocol was clarified. -Amended the exclusion to be in line with local approved labeling. -Clarified teriflunomide dosage as recommended per local labeling. -Clarified laboratory testing. -Updated safety monitoring according to local labeling. -Modified screening period to up to 2 weeks to accommodate sufficient turn-around time for test result when an approved interferon gamma release assay for tuberculosis (TB) screening was applied. -Added few clarifications for operational purposes (rescreening, redispensing). -Clarified regulatory approval status of teriflunomide. -Harmonized inconsistencies related to safety and efficacy: •Safety related: -Blood pressure measure requirement positions. -Added appendix in "Guidelines for management of specific laboratory abnormalities" listing "suspicion of rhabdomyolysis." -Added the Company Core Data Sheet. •Efficacy related: -Stern Leisure Activity Scale was replaced with the correct version (NOTE: although the study sites was using the correct version)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported