Clinical trial results:
An International, Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Two Year Treatment With Teriflunomide 7 mg Once Daily and 14 mg Once Daily Versus Placebo in Patients With a First Clinical Episode Suggestive of Multiple Sclerosis Plus a Long Term Extension Period

Summary

EudraCT number	2006-001152-12
Trial protocol	CZ DE FI FR AT HU DK EE SK BG LT GB
Global end of trial date	05 February 2016

Results information

Result version number	v1 (current)
This version publication date	18 February 2017
First version publication date	18 February 2017

Trial information

Trial identification

Sponsor protocol code	EFC6260

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00622700
WHO universal trial number (UTN)	-
Other trial identifiers	Study name: TOPIC

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	29 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the effect of teriflunomide (14 mg/day and 7 mg/day) compared with placebo for reducing conversion of patients presenting with their clinical episode consistent with multiple sclerosis (MS) to clinical definite MS (CDMS), as defined by the occurrence of a second clinical relapse meeting specific criteria.

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	13 February 2008
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	Poland: 37
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Czech Republic: 58
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Estonia: 7
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 93
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Lithuania: 18
Country: Number of subjects enrolled	Canada: 42
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	Russian Federation: 32

Country: Number of subjects enrolled	Turkey: 40
Country: Number of subjects enrolled	Ukraine: 105
Country: Number of subjects enrolled	United States: 40
Country: Number of subjects enrolled	United Kingdom: 26
Worldwide total number of subjects	618
EEA total number of subjects	338

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)	618
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 846 subjects were screened, of which 618 randomized in core treatment period. Out of 618, 423 subjects entered extension treatment period. End date of core treatment period was 17 December 2012 (maximum treatment duration: 120 weeks).End date of extension treatment period was 05 February 2016 (maximum treatment duration: 283 weeks).

Pre-assignment

Screening details:

Subjects were randomized in 1:1:1 ratio to teriflunomide 7 mg, 14 mg or placebo in core treatment period. Those completing core period, given opportunity to enter long-term extension period (subjects originally given placebo re-randomized [1:1] to teriflunomide 7 mg/14 mg; those originally given 7 mg, 14 mg continued with the same fixed dose).

Period 1

Period 1 title	Core Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo matched to teriflunomide once daily.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo (for Teriflunomide) once daily in the morning of each day of the treatment period, with or without food.

Arm title	Teriflunomide 7 mg

Arm description:

Teriflunomide 7 mg once daily.

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 once daily in the morning of each day of the treatment period, with or without food.

Arm title	Teriflunomide 14 mg

Arm description:

Teriflunomide 14 mg once daily.

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 once daily in the morning of each day of the treatment period, with or without food.

Number of subjects in period 1	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Started	197	205	216
Completed	141	150	163
Not completed	56	55	53
Other than specified above	2	2	5
Consent withdrawn by subject	12	18	15
Adverse Event	18	25	18
Death	1	-	-
Progressive Disease	3	1	-
Lost to follow-up	1	1	1
Randomized but Not Treated	-	2	2
Lack of efficacy	19	6	12

Period 2

Period 2 title	Extension Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Teriflunomide 7 mg

Arm description:

Core treatment period: Placebo matched to teriflunomide tablet once daily orally. Extension treatment period: Teriflunomide 7 mg tablet once daily orally.

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 once daily in the morning of each day of the treatment period, with or without food.

Arm title	Teriflunomide 7 mg/7 mg

Arm description:

Core treatment period: Teriflunomide 7 mg tablet once daily orally. Extension treatment period: Teriflunomide 7 mg tablet once daily orally.

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 once daily in the morning of each day of the treatment period, with or without food.

Arm title	Placebo/Teriflunomide 14 mg

Arm description:

Core treatment period: Placebo matched to teriflunomide tablet once daily orally. Extension treatment period: Teriflunomide 14 mg tablet once daily orally.

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 once daily in the morning of each day of the treatment period, with or without food.

Arm title	Teriflunomide 14 mg/14 mg

Arm description:

Core treatment period: Teriflunomide 14 mg tablet once daily orally. Extension treatment period: Teriflunomide 14 mg tablet once daily orally.

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 once daily in the morning of each day of the treatment period, with or without food.

Number of subjects in period 2[1]	Placebo/Teriflunomide 7 mg	Teriflunomide 7 mg/7 mg	Placebo/Teriflunomide 14 mg
Started	64	142	67
Completed	43	103	50
Not completed	21	39	17
Other than specified above	-	-	1
Consent withdrawn by subject	11	16	6
Adverse Event	5	9	6
Progressive Disease	1	2	-
Lost to follow-up	-	1	-

Missing	2	3	1
Lack of efficacy	2	8	1
Protocol deviation	-	-	2

Number of subjects in period 2[1]	Teriflunomide 14 mg/14 mg
Started	150
Completed	120
Not completed	30
Other than specified above	1
Consent withdrawn by subject	10
Adverse Event	8
Progressive Disease	2
Lost to follow-up	-
Missing	-
Lack of efficacy	9
Protocol deviation	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects in "Placebo" arm (core treatment period) were re-randomized in 1:1 ratio to either teriflunomide 7 mg or 14 mg treatment arm in extension treatment period. 10, 8 and 13 subjects in "placebo, teriflunomide 7 mg and teriflunomide 14 mg" arms respectively completed core treatment period but did not enter in extension treatment period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to teriflunomide once daily.	
Reporting group title	Teriflunomide 7 mg
Reporting group description:	
Teriflunomide 7 mg once daily.	
Reporting group title	Teriflunomide 14 mg
Reporting group description:	
Teriflunomide 14 mg once daily.	

Reporting group values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Number of subjects	197	205	216
Age categorical			
Units: Subjects			
Age continuous			
Randomized population: all randomized participants according to the treatment group to which they were assigned in the core treatment period.			
Units: years			
arithmetic mean	32	31.6	32.8
standard deviation	± 8.4	± 9	± 8.1
Gender categorical			
Units: Subjects			
Female	135	130	154
Male	62	75	62
Region			
Units: Subjects			
Eastern Europe	94	96	101
Western Europe	76	74	74
Americas and Australia	27	35	41
Expanded Disability Status Scale (EDSS) Score			
EDSS is an ordinal scale in half-point increments that qualifies disability in participants with MS. It consists of 8 ordinal rating scales assessing seven functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS).			
Units: Units on a scale			
arithmetic mean	1.71	1.5	1.8
standard deviation	± 1	± 1.02	± 0.97

Reporting group values	Total		
Number of subjects	618		
Age categorical			
Units: Subjects			

Age continuous			
Randomized population: all randomized participants according to the treatment group to which they were assigned in the core treatment period.			
Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	419		
Male	199		
Region Units: Subjects			
Eastern Europe	291		
Western Europe	224		
Americas and Australia	103		
Expanded Disability Status Scale (EDSS) Score			
EDSS is an ordinal scale in half-point increments that qualifies disability in participants with MS. It consists of 8 ordinal rating scales assessing seven functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS).			
Units: Units on a scale arithmetic mean standard deviation	 - -		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo matched to teriflunomide once daily.	
Reporting group title	Teriflunomide 7 mg
Reporting group description:	
Teriflunomide 7 mg once daily.	
Reporting group title	Teriflunomide 14 mg
Reporting group description:	
Teriflunomide 14 mg once daily.	
Reporting group title	Placebo/Teriflunomide 7 mg
Reporting group description:	
Core treatment period: Placebo matched to teriflunomide tablet once daily orally. Extension treatment period: Teriflunomide 7 mg tablet once daily orally.	
Reporting group title	Teriflunomide 7 mg/7 mg
Reporting group description:	
Core treatment period: Teriflunomide 7 mg tablet once daily orally. Extension treatment period: Teriflunomide 7 mg tablet once daily orally.	
Reporting group title	Placebo/Teriflunomide 14 mg
Reporting group description:	
Core treatment period: Placebo matched to teriflunomide tablet once daily orally. Extension treatment period: Teriflunomide 14 mg tablet once daily orally.	
Reporting group title	Teriflunomide 14 mg/14 mg
Reporting group description:	
Core treatment period: Teriflunomide 14 mg tablet once daily orally. Extension treatment period: Teriflunomide 14 mg tablet once daily orally.	
Subject analysis set title	Teriflunomide 7 mg/ 7mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Core treatment period: Teriflunomide 7 mg tablet once daily orally. Extension treatment period: Teriflunomide 7 mg tablet once daily orally.	
Subject analysis set title	Teriflunomide 7 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Core treatement period: Teriflunomide 7 mg tablet once daily orally.	

Primary: Core Treatment Period: Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS)

End point title	Core Treatment Period: Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS)
End point description:	
Conversion to CDMS was defined by the occurrence of a relapse, which was defined as a new neurological abnormality separated by at least 30 days from onset of a preceding clinical event, presented for at least 24 hours and occurred in the absence of fever or known infection. Percent probability of conversion at 24, 48, and 108 weeks was estimated using Kaplan-Meier method. Intent-to-treat (ITT) population included all randomized subjects who had at least 1 day study medication exposure. Subjects were analyzed in the treatment group to which they were randomized.	
End point type	Primary
End point timeframe:	
Up to a maximum of 108 weeks depending on time of enrollment	

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197	203	214	
Units: percent probability				
number (confidence interval 95%)				
Percent Probability of Conversion at 24 weeks	14.3 (9.2 to 19.4)	8.7 (4.6 to 12.8)	9 (5 to 13)	
Percent Probability of Conversion at 48 weeks	26 (19.2 to 32.8)	14.2 (8.9 to 19.6)	13.7 (8.6 to 18.7)	
Percent Probability of Conversion at 108 weeks	35.9 (27.8 to 43.9)	27.6 (19.9 to 35.4)	24 (17 to 31)	

Statistical analyses

Statistical analysis title	Teriflunomide 14 mg vs. Placebo

Statistical analysis description:

A step-down hierarchical testing procedure, starting with the test of teriflunomide 14 mg versus placebo was used. Time to conversion to CDMS was analyzed using the Cox proportional hazard model with treatment, region, and baseline monofocal/multifocal status as covariates.

Comparison groups	Teriflunomide 14 mg v Placebo
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0087 [1]
Method	Wald chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.574
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.379
upper limit	0.869

Notes:

[1] - P-value was derived using Wald chi-squared test in the Cox proportional hazard model.

Statistical analysis title	Teriflunomide 7 mg vs. Placebo

Statistical analysis description:

A step-down hierarchical testing procedure was used. The second step was the test of teriflunomide 7 mg versus placebo for time to conversion to CDMS. Time to conversion to CDMS was analyzed using the Cox proportional hazard model with treatment, region, and baseline monofocal/multifocal status as covariates.

Comparison groups	Teriflunomide 7 mg v Placebo

Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0271 [2]
Method	Wald chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.628
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.416
upper limit	0.949

Notes:

[2] - P-value was derived using Wald chi-squared test in the Cox proportional hazard model.

Secondary: Core Treatment Period: Time to Conversion to Definite Multiple Sclerosis (DMS)

End point title	Core Treatment Period: Time to Conversion to Definite Multiple Sclerosis (DMS)

End point description:

Conversion to DMS was demonstrated by dissemination of MRI lesions in time (as per McDonald criteria) or a relapse, whichever occurs first. MRI Imaging criteria were detection of Gadolinium (Gd) enhancement at least 3 months after onset of initial clinical event, if not at site corresponding to initial event; detection of new T2 lesion if it appears at any time compared with reference scan (done at time of screening) done at least 30 days after onset of initial clinical event. Occurrence of relapse defined as new neurological abnormality separated by at least 30 days from onset of preceding clinical event, present for at least 24 hours & occurring in absence of fever or known infection. New clinical abnormality (neurological sign) that was consistent with subject's symptoms with increase in at least one Functional System (FS) or EDSS score compared to last EDSS assessment. Percent probability of conversion at 24, 48 & 108 weeks was estimated using Kaplan-Meier method. ITT population.

End point type	Secondary

End point timeframe:

Up to a maximum of 108 weeks depending on time of enrollment

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197	203	214	
Units: percent probability				
number (confidence interval 95%)				
Percent Probability of Conversion at 24 weeks	58.2 (51 to 65.4)	45.7 (38.5 to 52.9)	46 (39 to 53)	
Percent Probability of Conversion at 48 weeks	72.4 (65.7 to 79.1)	57.3 (49.8 to 64.7)	57.8 (50.6 to 64.9)	
Percent Probability of Conversion at 108 weeks	87 (81.2 to 92.7)	73.3 (66 to 80.7)	71.5 (64.5 to 78.4)	

Statistical analyses

Statistical analysis title	Teriflunomide 14 mg vs. Placebo

Statistical analysis description:

A step-down hierarchical testing procedure was used. The third step was the test of teriflunomide 14 mg versus placebo for time to conversion to DMS. This was analyzed using the Cox proportional hazard model with treatment, region, and baseline monofocal/multifocal status as covariates.

Comparison groups	Teriflunomide 14 mg v Placebo
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003 [3]
Method	Wald chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.651
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.515
upper limit	0.822

Notes:

[3] - P-value was derived using Wald chi-squared test in the Cox proportional hazard model.

Statistical analysis title	Teriflunomide 7 mg vs. Placebo

Statistical analysis description:

A step-down hierarchical testing procedure was used. The fourth step was the test of teriflunomide 7 mg versus placebo for time to conversion to DMS. This was analyzed using the Cox proportional hazard model with treatment, region, and baseline monofocal/multifocal status as covariates.

Comparison groups	Placebo v Teriflunomide 7 mg
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [4]
Method	Wald chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.686
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.871

Notes:

[4] - P-value was derived using Wald chi-squared test in the Cox proportional hazard model.

Secondary: Core Treatment Period: Annualized Relapse Rate (ARR)

End point title	Core Treatment Period: Annualized Relapse Rate (ARR)

End point description:

ARR was total number of confirmed relapses that occurred during the treatment period divided by the total number of subject-years treated. Each episode of relapse (appearance, or worsening of a clinical symptom that was stable for at least 30 days, that persisted for a minimum of 24 hours in the absence of fever) was to be confirmed by an increase in EDSS score or Functional System scores. ARR was assessed using Poisson regression model with robust error variance. To account for the different treatment durations among subjects, a Poisson regression model with robust error variance was used (total number of confirmed relapses onset between randomization date and last dose date as the response variable, treatment, region and baseline monofocal/multifocal status as covariates, and log-

transformed treatment duration as an offset variable). ITT population.

End point type	Secondary

End point timeframe:

Up to a maximum of 108 weeks depending on time of enrollment

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197	203	214	
Units: relapses per subject year				
number (confidence interval 95%)	0.284 (0.214 to 0.378)	0.19 (0.139 to 0.26)	0.194 (0.143 to 0.263)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Brain Magnetic Resonance Imaging (MRI) Assessment: Change From Baseline in Total Lesion Volume at Week 108

End point title	Core Treatment Period: Brain Magnetic Resonance Imaging (MRI) Assessment: Change From Baseline in Total Lesion Volume at Week 108

End point description:

The total lesion volume (burden of disease) was the total volumes of hyperintense on T2 plus hypointense on T1 as measured by MRI scan. Least-square means were estimated using a Mixed-effect model with repeated measures (MMRM) on cubic root transformed volume data with factors for treatment, baseline monofocal/multifocal status, region, visit, treatment-by-visit interaction, cubic root transformed baseline burden of disease, and baseline-by-visit interaction. ITT population, but including only subjects who had post-baseline data.

End point type	Secondary

End point timeframe:

Baseline, Week 108

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	75	99	
Units: milliliter				
least squares mean (standard error)	0.053 (± 0.033)	0.041 (± 0.032)	-0.038 (± 0.029)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Brain MRI Assessment: Number of Gadolinium Enhancing (Gd-enhancing) T1-lesions Per MRI Scan (Poisson Regression Estimates)

End point title	Core Treatment Period: Brain MRI Assessment: Number of Gadolinium Enhancing (Gd-enhancing) T1-lesions Per MRI Scan (Poisson Regression Estimates)

End point description:

Number of Gd-enhancing T1-lesions per scan was the total number of Gd-enhancing T1-lesions that occurred during the treatment period divided by the total number of scans performed during the treatment period. To account for the different numbers of scans performed among the subjects, a Poisson regression model with robust error variance was used (total number of Gd-enhancing T1-lesions as response variable, treatment, baseline monofocal/multifocal status, region and baseline number of Gd-enhancing T1-lesions as covariates, and log-transformed number of scans as an offset variable). ITT population, but including only subjects who had post-baseline data.

End point type	Secondary

End point timeframe:

Up to a maximum of 108 weeks depending on time of enrollment

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	84	74	
Units: lesions per scan				
number (confidence interval 95%)	0.953 (0.708 to 1.284)	0.749 (0.433 to 1.294)	0.395 (0.262 to 0.598)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Brain MRI Assessment: Volume of Gadolinium Enhancing (Gd-enhancing) T1-lesions Per MRI Scan

End point title	Core Treatment Period: Brain MRI Assessment: Volume of Gadolinium Enhancing (Gd-enhancing) T1-lesions Per MRI Scan

End point description:

Total volume of Gd-enhancing T1-lesions per scan was the sum of the volumes of Gd-enhancing T1-lesions observed during the treatment period divided by the total number of scans performed during the treatment period. To account for the different numbers of scans performed among the subjects, a Poisson regression model with robust error variance was used (total number of Gd-enhancing T1-lesions as response variable, treatment, baseline monofocal/multifocal status, region and baseline number of Gd-enhancing T1-lesions as covariates, and log-transformed number of scans as an offset variable). ITT population, but including only subjects who had post-baseline data.

End point type	Secondary

End point timeframe:

Up to a maximum of 108 weeks depending on time of enrollment

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	84	74	
Units: milliliters per scan				
number (not applicable)	0.079	0.058	0.034	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Brain MRI Assessment: Change From Baseline in Volume of Hypointense Post-Gadolinium T1 Lesion Component

End point title	Core Treatment Period: Brain MRI Assessment: Change From Baseline in Volume of Hypointense Post-Gadolinium T1 Lesion Component

End point description:

Volume of hypointense post-gadolinium T1 lesion component was measured by MRI scan. Least-square means were estimated using a Mixed-effect model with repeated measures (MMRM) on cubic root transformed volume data adjusted for baseline monofocal/multifocal status, region, visit, treatment-by-visit interaction, cubic root transformed baseline value, and baseline-by-visit interaction. ITT population, but including only subjects who had post-baseline data.

End point type	Secondary

End point timeframe:

Baseline, Week 108

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	75	99	
Units: milliliter				
least squares mean (standard error)	0.028 (± 0.018)	0.025 (± 0.018)	-0.033 (± 0.016)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Brain MRI Assessment: Change From Baseline in Volume of T2 Lesion Component

End point title	Core Treatment Period: Brain MRI Assessment: Change From Baseline in Volume of T2 Lesion Component

End point description:

Volume of T2 lesion component was measured by MRI scan. Least-square means were estimated using a Mixed-effect model with repeated measures (MMRM) on cubic root transformed volume data adjusted for baseline monofocal/multifocal status, region, visit, treatment-by-visit interaction, cubic root transformed baseline value, and baseline-by-visit interaction. ITT population, but including only subjects who had post-baseline data.

End point type	Secondary

End point timeframe:

Baseline, Week 108

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	75	99	
Units: milliliter				
least squares mean (standard error)	0.052 (± 0.033)	0.036 (± 0.032)	-0.035 (± 0.029)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Brain MRI Assessment: Percent Change From Baseline in Atrophy

End point title	Core Treatment Period: Brain MRI Assessment: Percent Change From Baseline in Atrophy

End point description:

Atrophy was measured by MRI scan. ITT population, but including only subjects who had post-baseline data.

End point type	Secondary

End point timeframe:

Baseline, Week 108

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	75	99	
Units: percent change				
arithmetic mean (standard deviation)	-0.386 (± 1.326)	-0.197 (± 1.218)	-0.366 (± 1.151)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Time to 12-Week Sustained Disability Progression

End point title	Core Treatment Period: Time to 12-Week Sustained Disability Progression

End point description:

The 12-week sustained disability progression was defined as increase from baseline of at least 1-point in EDSS score (at least 0.5-point for subjects with baseline EDSS score of greater than [>] 5.5) that persisted for at least 12 weeks. Percent probability of subjects free of 12-week sustained disability progression at 24, 48, and 108 weeks was estimated using Kaplan-Meier method. ITT population.

End point type	Secondary

End point timeframe:

Up to a maximum of 108 weeks depending on time of enrollment

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197	203	214	
Units: percent probability				
number (confidence interval 95%)				
Percent Probability at 24 weeks	96 (93 to 98.9)	94.3 (90.9 to 97.8)	97.9 (95.9 to 99.9)	
Percent Probability at 48 weeks	91.7 (87.3 to 96.1)	90.1 (85.4 to 94.7)	93.9 (90.2 to 97.6)	
Percent Probability at 108 weeks	85.5 (79.2 to 91.8)	86.5 (80.8 to 92.1)	89.2 (84.1 to 94.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Change From Baseline in EDSS at Week 108

End point title	Core Treatment Period: Change From Baseline in EDSS at Week 108

End point description:

EDSS was an ordinal scale in half-point increments that qualifies disability in subjects with MS. It consisted of 8 ordinal rating scales assessing seven functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS). Least-square means were estimated using a Mixed-effect model with repeated measures (MMRM) on cubic root transformed volume data adjusted for baseline monofocal/multifocal status, region, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction. ITT population, but including only subjects who had post-baseline data.

End point type	Secondary

End point timeframe:

Baseline, Week 108

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	82	102	
Units: units on a scale				
least squares mean (standard error)	0.069 (± 0.087)	-0.191 (± 0.086)	-0.166 (± 0.08)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Change From Baseline in Fatigue Impact Scale (FIS) Total Score at Week 108

End point title	Core Treatment Period: Change From Baseline in Fatigue Impact Scale (FIS) Total Score at Week 108

End point description:

FIS is a subject-reported scale that qualifies the impact of fatigue on daily life in subjects with MS. It consists of 40 statements that measure fatigue in three areas; physical, cognitive, and social. FIS total score ranges from 0 (no problem) to 160 (extreme problem). Least-square means were estimated using a Mixed-effect model with repeated measures [MMRM] on FIS total score data adjusted for or baseline monofocal/multifocal status, region, visit, treatment-by-visit interaction, baseline value and baseline-by-visit interaction. ITT population, but including only subjects who had post-baseline data.

End point type	Secondary

End point timeframe:

Baseline, Week 108

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	95	106	
Units: units on a scale				
least squares mean (standard error)	-2.537 (± 2.794)	-2.524 (± 2.71)	-1.827 (± 2.551)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Overview of Adverse Events (AEs)

End point title	Core Treatment Period: Overview of Adverse Events (AEs)[5]

End point description:

AEs are any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the subject during the study. Safety population included all randomized subjects exposed to study medication; analyzed according to drug actually received. In Placebo arm, 4 received teriflunomide 7 mg and 2 received teriflunomide 14 mg, hence they were included in respective teriflunomide arm. Subjects who were randomized but not treated were excluded (2 in each teriflunomide arm).

End point type	Secondary

End point timeframe:

From first study drug intake up to 112 days after last intake in the placebo-controlled period or up to first intake in the extension treatment period, whichever occurred first

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point is not reporting statistics for all the arms in the baseline period.

End point values	Placebo	Teriflunomide 14 mg	Teriflunomide 7 mg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	191	216	207	
Units: subjects				
number (not applicable)				
Any AE	155	183	161	
Any serious AE	18	24	18	
Any AE leading to death	1	0	0	
Any AE leading to treatment discontinuation	19	18	25	

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Treatment Period: Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS)

End point title	Extension Treatment Period: Time to Conversion to Clinically Definite Multiple Sclerosis (CDMS)

End point description:

Conversion to CDMS was defined by the occurrence of a relapse, which was defined as a new neurological abnormality separated by at least 30 days from onset of a preceding clinical event, presented for at least 24 hours and occurred in the absence of fever or known infection. Percent probability of conversion was estimated using Kaplan-Meier method. ITT Population: all randomized subjects in the extension who had at least 1 day IMP exposure. Subjects were analyzed according to the treatment group allocated by the randomization in the core study followed by the re-randomized treatment group during the extension period.

End point type	Secondary

End point timeframe:

From randomization in the core period up to 390 Weeks (Extension treatment period [maximum exposure: 283 Weeks])

End point values	Placebo/Teriflunomide 7 mg	Teriflunomide 7 mg/7 mg	Placebo/Teriflunomide 14 mg	Teriflunomide 14 mg/14 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64	142	67	150
Units: Percent probability				
number (confidence interval 95%)				
Percent Probability of Conversion at 24 Weeks	4.7 (0 to 9.9)	3.5 (0.5 to 6.6)	13.5 (5.3 to 21.6)	4.7 (1.3 to 8)
Percent Probability of Conversion at 48 Weeks	12.5 (4.4 to 20.6)	9.9 (5 to 14.8)	21.2 (11.3 to 31)	8.7 (4.2 to 13.3)
Percent Probability of Conversion at 72 Weeks	15.7 (6.8 to 24.6)	17.1 (10.9 to 23.4)	24.3 (13.9 to 34.6)	14.8 (9.1 to 20.6)

Percent Probability of Conversion at 96 Weeks	18.9 (9.3 to 28.6)	23.9 (16.7 to 31)	27.4 (16.6 to 38.2)	16.2 (10.3 to 22.1)
Percent Probability of Conversion at 120 Weeks	22.3 (12 to 32.7)	27.7 (20.2 to 35.2)	32.2 (20.8 to 43.6)	18.3 (12.1 to 24.6)
Percent Probability of Conversion at 144 Weeks	22.3 (12 to 32.7)	29.4 (21.7 to 37.1)	33.9 (22.3 to 45.4)	22 (15.3 to 28.8)
Percent Probability of Conversion at 168 Weeks	22.3 (12 to 32.7)	32.2 (24.2 to 40.3)	33.9 (22.3 to 45.4)	22.8 (16 to 29.7)
Percent Probability of Conversion at 192 Weeks	22.3 (12 to 32.7)	37.5 (28.6 to 46.4)	35.9 (24 to 47.8)	24.8 (17.6 to 32)
Percent Probability of Conversion at 216 Weeks	25.6 (13.9 to 37.3)	38.9 (29.8 to 48.1)	39.3 (26.3 to 52.3)	24.8 (17.6 to 32)
Percent Probability of Conversion at 240 Weeks	29.5 (16.1 to 42.9)	40.8 (31.3 to 50.4)	39.3 (26.3 to 52.3)	26.3 (18.7 to 34)
Percent Probability of Conversion at 264 Weeks	29.5 (16.1 to 42.9)	43 (32.9 to 53.2)	39.3 (26.3 to 52.3)	26.3 (18.7 to 34)
Percent Probability of Conversion at 288 Weeks	29.5 (16.1 to 42.9)	43 (32.9 to 53.2)	39.3 (26.3 to 52.3)	26.3 (18.7 to 34)
Percent Probability of Conversion at 312 Weeks	29.5 (16.1 to 42.9)	43 (32.9 to 53.2)	49.4 (28.3 to 70.5)	26.3 (18.7 to 34)
Percent Probability of Conversion at 336 Weeks	29.5 (16.1 to 42.9)	48.7 (34.7 to 62.7)	49.4 (28.3 to 70.5)	26.3 (18.7 to 34)

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Treatment Period: Overview of Adverse Events (AEs)

End point title	Extension Treatment Period: Overview of Adverse Events (AEs)

End point description:

AEs are any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the subject during the study. Safety population that consisted of all the randomized population who actually received at least 1 dose of the IMP in the extension and analyzed according to the treatment actually received in the core study followed by the treatment actually received in the extension treatment period. In Placebo/teriflunomide 7mg arm, 2 received 7mg in the core period; In Placebo/teriflunomide 14mg, 1 received 7mg in the core period, hence, they were included in the 7mg/7mg arm as received in the core period for consistency.

End point type	Secondary

End point timeframe:

From re-randomization up to 283 weeks

End point values	Placebo/Teriflunomide 7 mg	Placebo/Teriflunomide 14 mg	Teriflunomide 14 mg/14 mg	Teriflunomide 7 mg/ 7mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	62	66	150	145
Units: Subjects				
number (not applicable)				
Any AE	47	57	120	110
Any Serious AE	8	8	24	17
Any AE Leading to Death	0	0	0	0
Any AE leading to Permanent Discontinuation	5	5	7	8

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Liver Function: Number of Subjects With Potentially Clinically Significant Abnormalities (PCSA)

End point title	Core Treatment Period: Liver Function: Number of Subjects With Potentially Clinically Significant Abnormalities (PCSA)[6]

End point description:

PCSA values are abnormal values considered medically important by the Sponsor according to predefined criteria based on literature review.

Hepatic parameters thresholds were defined as follows:
•Alanine Aminotransferase (ALT) >3, 5, 10 or 20 upper limit of normal(ULN);
•Aspartate aminotransferase (AST) >3, 5, 10 or 20 ULN;
•Alkaline Phosphatase >1.5 ULN;
•Total Bilirubin (TB) >1.5, 2, or 3 ULN;
Safety population as described in Outcome Measure 13. Here 'n' signifies the number of subjects for the treatment group who had that parameter assessed at post-baseline.
- ALT >3 ULN and TB >2 ULN.

Safety population as described in Outcome Measure 13. Here, 'n' signifies the number of subjects for the treatment group who had that parameter assessed at post-baseline.

End point type	Secondary

End point timeframe:

From first study drug intake up to 112 days after last intake in the placebo-controlled period or up to first intake in the extension treatment period, whichever occurred first

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point is not reporting statistics for all the arms in the baseline period.

End point values	Placebo	Teriflunomide 14 mg	Teriflunomide 7 mg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	191	216	207	
Units: Subjects				
number (not applicable)				
ALT >3 ULN (n=190, 207, 216)	18	26	25	
ALT >5 ULN (n=190, 207, 216)	12	11	10	
ALT >10 ULN (n=190, 207, 216)	5	3	1	
ALT >20 ULN (n=190, 207, 216)	0	1	0	
AST >3 ULN (n=190, 207, 216)	9	10	12	
AST >5 ULN (n=190, 207, 216)	1	6	4	
AST >10 ULN (n=190, 207, 216	1	1	0	
AST >20 ULN (n=190, 207, 216)	0	1	0	
Alkaline Phosphatase >1.5 ULN (n=190, 207, 216)	0	1	0	
TB >1.5 ULN (n=190, 207, 216)	14	8	9	
TB >2 ULN (n=190, 207, 216)	8	3	0	

TB >3 ULN (n=190, 207, 216)	0	1	0	
ALT >3 ULN and TB >2 ULN (n=190, 207, 216)	2	2	0	

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 informed consent form upto final visit (upto 390 weeks [maximum exposure in core period:120 weeks & maximum exposure in extension period:283 weeks])regardless of seriousness/relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment-emergent AEs developed/worsened during 'on treatment period' (time from first dose of study drug upto 112 days after last intake in core treatment period [or upto 1st intake in extension period,whichever occurred first] or 28 days after last intake in extension treatment period). Safety population (described in OM #15).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Core treatment period: Placebo matched to teriflunomide tablet once daily orally.

Reporting group title	Teriflunomide 7 mg

Reporting group description:

Core treatment period: Teriflunomide 7 mg tablet once daily orally.

Reporting group title	Teriflunomide 14 mg

Reporting group description:

Core treatment period: Teriflunomide 14 mg tablet once daily orally.

Reporting group title	Placebo/Teriflunomide 7 mg

Reporting group description:

Core treatment period: Placebo matched to teriflunomide tablet once daily orally.

Extension treatment period: Teriflunomide 7 mg tablet once daily orally.

Reporting group title	Teriflunomide 7 mg/7 mg

Reporting group description:

Core treatment period: Teriflunomide 7 mg tablet once daily orally.

Extension treatment period: Teriflunomide 7 mg tablet once daily orally.

Reporting group title	Placebo/Teriflunomide 14 mg

Reporting group description:

Core treatment period: Placebo matched to teriflunomide tablet once daily orally.

Extension treatment period: Teriflunomide 14 mg tablet once daily orally.

Reporting group title	Teriflunomide 14 mg/14 mg

Reporting group description:

Core treatment period: Teriflunomide 14 mg tablet once daily orally.

Extension treatment period: Teriflunomide 14 mg tablet once daily orally.

Serious adverse events	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 191 (9.42%)	18 / 207 (8.70%)	24 / 216 (11.11%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix Carcinoma			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			
subjects affected / exposed	2 / 191 (1.05%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liposarcoma			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Meningioma Benign			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid Cancer			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Circulatory Collapse			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic Hypotension			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep Vein Thrombosis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion Threatened			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Hernia			

subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical Cyst			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial Hyperplasia			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fallopian Tube Cyst			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Cyst			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular Torsion			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Haemorrhage			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Nasal Septum Deviation			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment Disorder			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed Suicide			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric Decompensation			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Amylase Increased			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase Increased			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases Increased			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 191 (1.57%)	5 / 207 (2.42%)	4 / 216 (1.85%)
occurrences causally related to treatment / all	3 / 3	5 / 5	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight Decreased			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Facial Bones Fracture			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Limb Fracture			

subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle Fracture			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral Injury			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot Fracture			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Overdose			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament Sprain			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Dehiscence			

subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Supraventricular Tachycardia			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radicular Syndrome			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Axonal Neuropathy			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss Of Consciousness			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech Disorder			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Iron Deficiency Anaemia			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 191 (1.05%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Conjunctivitis Allergic			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Chronic Gastritis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss Syndrome			

subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental Cyst			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenal Ulcer			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic Ulcer			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radicular Cyst			

subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular Injury			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diffuse Alopecia			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema Nodosum			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial Cyst			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Disorder			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid Arthritis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal Wall Abscess			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Sinusitis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue Fever			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Abscess			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	2 / 216 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis Perforated			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital Infection			

subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious Mononucleosis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal Cyst			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Tuberculosis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 207 (0.48%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	1 / 191 (0.52%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Abscess			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	0 / 216 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 207 (0.00%)	1 / 216 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo/Teriflunomide 7 mg	Teriflunomide 7 mg/7 mg	Placebo/Teriflunomide 14 mg

Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 62 (12.90%)	17 / 145 (11.72%)	8 / 66 (12.12%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix Carcinoma			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liposarcoma			
subjects affected / exposed	1 / 62 (1.61%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Meningioma Benign			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid Cancer			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Circulatory Collapse			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic Hypotension			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep Vein Thrombosis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion Threatened			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Hernia			

subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical Cyst			
subjects affected / exposed	1 / 62 (1.61%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial Hyperplasia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fallopian Tube Cyst			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Cyst			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular Torsion			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Nasal Septum Deviation			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment Disorder			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed Suicide			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric Decompensation			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Amylase Increased			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase Increased			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases Increased			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight Decreased			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Facial Bones Fracture			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Limb Fracture			

subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle Fracture			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral Injury			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot Fracture			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Overdose			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament Sprain			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	0 / 62 (0.00%)	2 / 145 (1.38%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Dehiscence			

subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Supraventricular Tachycardia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radicular Syndrome			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Axonal Neuropathy			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss Of Consciousness			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech Disorder			
subjects affected / exposed	1 / 62 (1.61%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Iron Deficiency Anaemia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 62 (0.00%)	2 / 145 (1.38%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Conjunctivitis Allergic			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Chronic Gastritis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss Syndrome			

subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental Cyst			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenal Ulcer			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic Ulcer			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radicular Cyst			

subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular Injury			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diffuse Alopecia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema Nodosum			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	1 / 62 (1.61%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial Cyst			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Disorder			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid Arthritis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal Wall Abscess			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Sinusitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue Fever			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Abscess			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis Perforated			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital Infection			

subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious Mononucleosis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal Cyst			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Tuberculosis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Abscess			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 145 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Teriflunomide 14 mg/14 mg		

Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 150 (16.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix Carcinoma			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine Leiomyoma			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast Cancer			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liposarcoma			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meningioma			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal Meningioma Benign			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thyroid Cancer			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Circulatory Collapse			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic Hypotension			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep Vein Thrombosis			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abortion Threatened			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Hernia			

subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cervical Cyst			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial Hyperplasia			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fallopian Tube Cyst			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Menorrhagia			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian Cyst			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Testicular Torsion			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine Haemorrhage			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Nasal Septum Deviation			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Adjustment Disorder			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Completed Suicide			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric Decompensation			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide Attempt			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Amylase Increased			
subjects affected / exposed	2 / 150 (1.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Blood Creatine Phosphokinase Increased				
subjects affected / exposed	2 / 150 (1.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Aspartate Aminotransferase Increased				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lipase Increased				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transaminases Increased				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Alanine Aminotransferase Increased				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Weight Decreased				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Facial Bones Fracture				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper Limb Fracture				

subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ankle Fracture				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Craniocerebral Injury				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Foot Fracture				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intentional Overdose				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament Sprain				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia Fracture				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound Dehiscence				

subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Supraventricular Tachycardia			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 150 (0.67%)		
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 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radicular Syndrome			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Axonal Neuropathy			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Loss Of Consciousness			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Speech Disorder			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Iron Deficiency Anaemia				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphadenitis				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Conjunctivitis Allergic				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Chronic Gastritis				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenitis				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mallory-Weiss Syndrome				

subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dental Cyst				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroduodenal Ulcer				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal Hernia				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis Acute				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peptic Ulcer				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radicular Cyst				

subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis Acute			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatocellular Injury			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Diffuse Alopecia			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erythema Nodosum			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Synovial Cyst			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral Disc Disorder			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteochondrosis			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rheumatoid Arthritis			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal Wall Abscess			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute Sinusitis			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dengue Fever			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastroenteritis				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal Abscess				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis Perforated				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium Difficile Colitis				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	0 / 150 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Genital Infection				

subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infectious Mononucleosis			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pilonidal Cyst			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Tuberculosis			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis Acute			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal Abscess			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	0 / 150 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	117 / 191 (61.26%)	129 / 207 (62.32%)	135 / 216 (62.50%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	28 / 191 (14.66%)	32 / 207 (15.46%)	35 / 216 (16.20%)
occurrences (all)	28	32	35
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	1 / 191 (0.52%)	9 / 207 (4.35%)	5 / 216 (2.31%)
occurrences (all)	1	9	5
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 191 (1.05%)	5 / 207 (2.42%)	12 / 216 (5.56%)
occurrences (all)	2	5	12
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 191 (13.09%)	31 / 207 (14.98%)	30 / 216 (13.89%)
occurrences (all)	25	31	30
Dizziness			
subjects affected / exposed	7 / 191 (3.66%)	7 / 207 (3.38%)	11 / 216 (5.09%)
occurrences (all)	7	7	11
Paraesthesia			
subjects affected / exposed	9 / 191 (4.71%)	11 / 207 (5.31%)	22 / 216 (10.19%)
occurrences (all)	9	11	22
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 191 (7.33%)	10 / 207 (4.83%)	9 / 216 (4.17%)
occurrences (all)	14	10	9
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 191 (6.28%)	22 / 207 (10.63%)	15 / 216 (6.94%)
occurrences (all)	12	22	15
Nausea			

subjects affected / exposed	9 / 191 (4.71%)	11 / 207 (5.31%)	9 / 216 (4.17%)
occurrences (all)	9	11	9
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	8 / 191 (4.19%)	11 / 207 (5.31%)	2 / 216 (0.93%)
occurrences (all)	8	11	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	15 / 191 (7.85%)	12 / 207 (5.80%)	25 / 216 (11.57%)
occurrences (all)	15	12	25
Psychiatric disorders			
Depression			
subjects affected / exposed	11 / 191 (5.76%)	8 / 207 (3.86%)	8 / 216 (3.70%)
occurrences (all)	11	8	8
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	7 / 191 (3.66%)	14 / 207 (6.76%)	8 / 216 (3.70%)
occurrences (all)	7	14	8
Arthralgia			
subjects affected / exposed	6 / 191 (3.14%)	13 / 207 (6.28%)	7 / 216 (3.24%)
occurrences (all)	6	13	7
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	29 / 191 (15.18%)	24 / 207 (11.59%)	35 / 216 (16.20%)
occurrences (all)	29	24	35
Bronchitis			
subjects affected / exposed	5 / 191 (2.62%)	9 / 207 (4.35%)	8 / 216 (3.70%)
occurrences (all)	5	9	8
Sinusitis			
subjects affected / exposed	9 / 191 (4.71%)	7 / 207 (3.38%)	6 / 216 (2.78%)
occurrences (all)	9	7	6
Influenza			
subjects affected / exposed	9 / 191 (4.71%)	8 / 207 (3.86%)	16 / 216 (7.41%)
occurrences (all)	9	8	16
Upper Respiratory Tract Infection			

subjects affected / exposed	14 / 191 (7.33%)	23 / 207 (11.11%)	20 / 216 (9.26%)
occurrences (all)	14	23	20
Urinary Tract Infection			
subjects affected / exposed	10 / 191 (5.24%)	10 / 207 (4.83%)	20 / 216 (9.26%)
occurrences (all)	10	10	20

Non-serious adverse events	Placebo/Teriflunomide 7 mg	Teriflunomide 7 mg/7 mg	Placebo/Teriflunomide 14 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 62 (53.23%)	66 / 145 (45.52%)	38 / 66 (57.58%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 62 (0.00%)	5 / 145 (3.45%)	6 / 66 (9.09%)
occurrences (all)	0	5	6
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	4 / 62 (6.45%)	1 / 145 (0.69%)	1 / 66 (1.52%)
occurrences (all)	4	1	1
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 62 (4.84%)	4 / 145 (2.76%)	0 / 66 (0.00%)
occurrences (all)	3	4	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 62 (6.45%)	8 / 145 (5.52%)	8 / 66 (12.12%)
occurrences (all)	4	8	8
Dizziness			
subjects affected / exposed	1 / 62 (1.61%)	4 / 145 (2.76%)	2 / 66 (3.03%)
occurrences (all)	1	4	2
Paraesthesia			
subjects affected / exposed	3 / 62 (4.84%)	1 / 145 (0.69%)	3 / 66 (4.55%)
occurrences (all)	3	1	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 62 (3.23%)	3 / 145 (2.07%)	4 / 66 (6.06%)
occurrences (all)	2	3	4
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	4 / 62 (6.45%)	9 / 145 (6.21%)	4 / 66 (6.06%)
occurrences (all)	4	9	4
Nausea			
subjects affected / exposed	2 / 62 (3.23%)	7 / 145 (4.83%)	1 / 66 (1.52%)
occurrences (all)	2	7	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	0 / 62 (0.00%)	1 / 145 (0.69%)	2 / 66 (3.03%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 62 (3.23%)	3 / 145 (2.07%)	7 / 66 (10.61%)
occurrences (all)	2	3	7
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 62 (3.23%)	4 / 145 (2.76%)	3 / 66 (4.55%)
occurrences (all)	2	4	3
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	4 / 62 (6.45%)	5 / 145 (3.45%)	4 / 66 (6.06%)
occurrences (all)	4	5	4
Arthralgia			
subjects affected / exposed	1 / 62 (1.61%)	4 / 145 (2.76%)	2 / 66 (3.03%)
occurrences (all)	1	4	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 62 (14.52%)	14 / 145 (9.66%)	9 / 66 (13.64%)
occurrences (all)	9	14	9
Bronchitis			
subjects affected / exposed	4 / 62 (6.45%)	7 / 145 (4.83%)	2 / 66 (3.03%)
occurrences (all)	4	7	2
Sinusitis			
subjects affected / exposed	6 / 62 (9.68%)	4 / 145 (2.76%)	4 / 66 (6.06%)
occurrences (all)	6	4	4
Influenza			

subjects affected / exposed	3 / 62 (4.84%)	5 / 145 (3.45%)	5 / 66 (7.58%)
occurrences (all)	3	5	5
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 62 (3.23%)	5 / 145 (3.45%)	2 / 66 (3.03%)
occurrences (all)	2	5	2
Urinary Tract Infection			
subjects affected / exposed	3 / 62 (4.84%)	5 / 145 (3.45%)	5 / 66 (7.58%)
occurrences (all)	3	5	5

Non-serious adverse events	Teriflunomide 14 mg/14 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 150 (46.67%)		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 150 (2.00%)		
occurrences (all)	3		
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	2 / 150 (1.33%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 150 (3.33%)		
occurrences (all)	5		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 150 (4.00%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	4 / 150 (2.67%)		
occurrences (all)	4		
Paraesthesia			
subjects affected / exposed	4 / 150 (2.67%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed occurrences (all)	3 / 150 (2.00%) 3		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 14 / 150 (9.33%) 14 9 / 150 (6.00%) 9		
Respiratory, thoracic and mediastinal disorders Oropharyngeal Pain subjects affected / exposed occurrences (all)	 0 / 150 (0.00%) 0		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	 5 / 150 (3.33%) 5		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	 1 / 150 (0.67%) 1		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	 10 / 150 (6.67%) 10 4 / 150 (2.67%) 4		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Sinusitis	 15 / 150 (10.00%) 15 8 / 150 (5.33%) 8		

subjects affected / exposed	6 / 150 (4.00%)		
occurrences (all)	6		
Influenza			
subjects affected / exposed	4 / 150 (2.67%)		
occurrences (all)	4		
Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 150 (2.67%)		
occurrences (all)	4		
Urinary Tract Infection			
subjects affected / exposed	4 / 150 (2.67%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2007	Following changes were made: -Clarified that all subjects must sign HIV consent form, that the results of HIV testing must be available prior to randomization, and that subjects who were HIV positive were excluded from participating in teriflunomide clinical trials. -Changed the time between the occurrence of a progression in disability and the minimum time to confirm from 12 weeks to 24 weeks to reflect regulatory agency guidance that had been updated.
08 August 2008	-Added that annual HIV testing was performed during treatment and that subjects were instructed to inform the treating physician of any symptoms or events that could be suggestive of immunodeficiency. If found to be HIV positive during the course of the study treatment, the subject must be removed from treatment and undergo washout procedures. -Clarified that symptoms related to MS relapses would be collected as efficacy measures, and that MS relapses were excluded from the definition of AE/serious AE (SAE).
01 July 2009	-Added optional pharmacogenomic teriflunomide testing with aims at assessing the association between the main enzyme systems of teriflunomide metabolism and hepatic safety, and other potential associations between gene variations and clinical outcomes. -Clarified for handling of screen failure subjects.
07 October 2009	-Added that all subjects from a site with health authority approval and Institutional Review Board/Ethics Committee approval for genotyping who had been randomized into the study would also be asked to participate in the genotyping, on an optional basis.
23 February 2010	-Added details and processes for the extension period of the study. -Modified TEAE definition to be AEs that developed or worsened during the time from first dose of study medication in the placebo-controlled period up to the end of the 112th day after the last dose of study medication in the placebo-controlled period or the date of first dose of study medication in the extension period, whichever was earlier.
24 May 2011	-In the inclusion criteria, changed the onset of MS symptoms before randomization to 90 days. -Added to offer the study extension to subjects with at least 24 weeks of treatment after conversion to CDMS. -Decreased the frequency of abdominal ultrasound to one at screening and decreased the frequency of laboratory safety monitoring from every 2 weeks to every 4 weeks during the first 24 weeks of study then every 6 weeks until 48 weeks and every 12 weeks after 48 weeks until end of treatment. -Modified pharmacokinetics (PK) sampling to be at baseline, Week 36, end of treatment visit, and 2 and 4 weeks post-washout visits. -Shortened the washout period from 16 weeks to 4 weeks. -To be in alignment with the other Phase 3 pivotal trial (EFC6049 [NCT00134563]), change the confirmation of disability progression at 12 weeks instead of 24 weeks as the key secondary efficacy endpoint. The sustained disability progression for at least 24 weeks was defined and used as a supportive analysis. -Added proportion of disability-free subjects as assessed by the EDSS following 2 years of placebo-controlled period, and time to disability was changed from 24 weeks to 12 weeks.
23 August 2012	-The screening of subjects for the study was stopped on 23 Aug 2012. All subjects were to finish the core study and to perform the rollover to the extension part of the study by 30 November 2012. -Following sponsor’s decision to stop the placebo-controlled period of the study, the number of subjects was reduced to approximately 600.

12 December 2012	-For subjects who had completed a minimum of 18 months/72 weeks in the extension, the study visits occurred every 24 weeks and included the followings: adverse event reporting, vital signs, physical examination, dispense study drugs, accountability/compliance, concomitant medications, EDSS/FS. In addition, all centralized activities were suspended. -In addition, it addressed the following changes: updated on the PK handling procedure and sampling time; new information regarding potential drug interactions; updated on the investigational product kit dispensation. -This amendment clarified that at the end of the study (EOS), for subjects continuing on marketed teriflunomide by getting the commercial form, no elimination/washout procedure was required, and the last visit after study treatment was the last study visit (with no need of additional follow-up).
27 November 2013	-Clarified that FIS and Short Form generic health survey (36 items) (SF-36) were no longer be collected in the extension study. -Updated and clarified clinical laboratory collection, including final local laboratory assessment during extension end of treatment visit. -Allowed unblinding of subjects who were transition to commercial Aubagio at the end of the study. -Dosage reduction of activated charcoal for accelerated elimination procedure (reduced from 50 g 4 times daily for 11 days to 50g twice daily for 11 days). -A Phase I study (TES10852) had demonstrated that reduced dosage of activated charcoal, 50 g twice daily was better tolerated than 50 g 4 times daily and achieved about 98% decrease of the concentration of teriflunomide after 11 days.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported