



## Clinical trial results:

**Long-term extension of the multinational, double-blind, placebo controlled study EFC6049 (HMR1726D/3001) to document the safety of two doses of teriflunomide (7 and 14 mg) in patients with multiple sclerosis (MS) with relapses**

### Summary

EudraCT number	2006-003361-14
Trial protocol	GB AT FI DE IT SE NL PT DK CZ EE
Global end of trial date	23 December 2015

### Results information

Result version number	v1 (current)
This version publication date	25 December 2016
First version publication date	25 December 2016

### Trial information

#### Trial identification

Sponsor protocol code	LTS6050
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00803049
WHO universal trial number (UTN)	-

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	10 February 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 December 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To document the long-term safety and tolerability of two doses of teriflunomide (7 mg/day and 14 mg/day) in MS subjects with relapses.

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 is 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	16 October 2006
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	Netherlands: 25
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Poland: 91
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	United Kingdom: 40
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Czech Republic: 17
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	France: 93
Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Canada: 139
Country: Number of subjects enrolled	Chile: 35
Country: Number of subjects enrolled	Russian Federation: 66

Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	Ukraine: 47
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	742
EEA total number of subjects	437

Notes:

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### 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)	742
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

#### Recruitment details:

The study was conducted at 117 centers in 21 countries between 16 October 2006 and 23 December 2015. A total of 742 subjects who completed study EFC6049 (2004-000555-42), entered in this extension study. Out of 742 subjects, 740 were treated and 2 subjects discontinued the study without receiving study treatment.

### Pre-assignment

#### Screening details:

Subjects who received placebo in EFC6049 study were randomized in 1:1 ratio to receive either teriflunomide 7 or 14 mg/day and, those who received teriflunomide 7 or 14 mg/day in EFC6049 received same double-blind treatment in this extension study until 292 weeks from the first subject enrolled or until teriflunomide was commercially available.

### Period 1

Period 1 title	Overall Period (overall 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
<b>Arm title</b>	Placebo/Teriflunomide 7 mg

#### Arm description:

Subjects who completed treatment of placebo (for teriflunomide) tablet once daily (QD) for 108 weeks in EFC6049 study, received teriflunomide tablet 7 mg QD for 288 weeks in this extension study.

Arm type	Experimental
Investigational medicinal product name	Teriflunomide
Investigational medicinal product code	HMR1726
Other name	Aubagio
Pharmaceutical forms	Tablet
Routes of administration	Oral use

#### Dosage and administration details:

Teriflunomide 7 mg administered QD orally for 288 weeks.

<b>Arm title</b>	Teriflunomide 7 mg/7 mg
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#### Arm description:

Subjects who completed treatment of teriflunomide 7 mg tablet QD for 108 weeks in EFC6049 study, continued their treatment with teriflunomide 7 mg tablet QD for 288 weeks in this extension study.

Arm type	Experimental
Investigational medicinal product name	Teriflunomide
Investigational medicinal product code	HMR1726
Other name	Aubagio
Pharmaceutical forms	Tablet
Routes of administration	Oral use

#### Dosage and administration details:

Teriflunomide 7 mg administered QD orally for 288 weeks.

<b>Arm title</b>	Placebo/Teriflunomide 14 mg
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Arm description:

Subjects who completed treatment of placebo (for teriflunomide tablet) QD for 108 weeks in EFC6049 study, received teriflunomide 14 mg tablet QD for 288 weeks in this extension study.

Arm type	Experimental
Investigational medicinal product name	Teriflunomide
Investigational medicinal product code	HMR1726
Other name	Aubagio
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Teriflunomide 14 mg administered QD orally for 288 weeks.

<b>Arm title</b>	Teriflunomide 14 mg/14 mg
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Arm description:

Subjects who completed treatment of teriflunomide 14 mg tablet QD for 108 weeks in EFC6049 study, continued their treatment with teriflunomide 14 mg tablet QD orally for 288 weeks in this extension study.

Arm type	Experimental
Investigational medicinal product name	Teriflunomide
Investigational medicinal product code	HMR1726
Other name	Aubagio
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Teriflunomide 14 mg administered QD orally for 288 weeks.

<b>Number of subjects in period 1</b>	Placebo/Teriflunomide 7 mg	Teriflunomide 7 mg/7 mg	Placebo/Teriflunomide 14 mg
Started	129	252	108
Treated	129	252	108
Completed	68	134	64
Not completed	61	118	44
Other than specified above	3	9	2
Consent withdrawn by subject	19	43	16
Adverse Event	21	33	13
Protocol violation	-	1	1
Randomized but not treated	-	-	-
Death	2	1	-
Progressive disease	6	10	6
Lost to follow-up	-	2	-
Lack of efficacy	10	19	6

<b>Number of subjects in period 1</b>	Teriflunomide 14 mg/14 mg
Started	253

Treated	251
Completed	151
Not completed	102
Other than specified above	5
Consent withdrawn by subject	44
Adverse Event	27
Protocol violation	-
Randomized but not treated	2
Death	2
Progressive disease	6
Lost to follow-up	3
Lack of efficacy	13

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo/Teriflunomide 7 mg
Reporting group description:	
Subjects who completed treatment of placebo (for teriflunomide) tablet once daily (QD) for 108 weeks in EFC6049 study, received teriflunomide tablet 7 mg QD for 288 weeks in this extension study.	

Reporting group title	Teriflunomide 7 mg/7 mg
Reporting group description:	
Subjects who completed treatment of teriflunomide 7 mg tablet QD for 108 weeks in EFC6049 study, continued their treatment with teriflunomide 7 mg tablet QD for 288 weeks in this extension study.	

Reporting group title	Placebo/Teriflunomide 14 mg
Reporting group description:	
Subjects who completed treatment of placebo (for teriflunomide tablet) QD for 108 weeks in EFC6049 study, received teriflunomide 14 mg tablet QD for 288 weeks in this extension study.	

Reporting group title	Teriflunomide 14 mg/14 mg
Reporting group description:	
Subjects who completed treatment of teriflunomide 14 mg tablet QD for 108 weeks in EFC6049 study, continued their treatment with teriflunomide 14 mg tablet QD orally for 288 weeks in this extension study.	

Reporting group values	Placebo/Teriflunomide 7 mg	Teriflunomide 7 mg/7 mg	Placebo/Teriflunomide 14 mg
Number of subjects	129	252	108
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	39.6	38	37.6
standard deviation	± 8.5	± 8.8	± 8.5
Gender categorical			
Units: Subjects			
Female	94	175	85
Male	35	77	23

Reporting group values	Teriflunomide 14 mg/14 mg	Total	
Number of subjects	253	742	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	38.6		
standard deviation	± 8.4	-	
Gender categorical			
Units: Subjects			
Female	182	536	
Male	71	206	





## End points

### End points reporting groups

Reporting group title	Placebo/Teriflunomide 7 mg
Reporting group description: Subjects who completed treatment of placebo (for teriflunomide) tablet once daily (QD) for 108 weeks in EFC6049 study, received teriflunomide tablet 7 mg QD for 288 weeks in this extension study.	
Reporting group title	Teriflunomide 7 mg/7 mg
Reporting group description: Subjects who completed treatment of teriflunomide 7 mg tablet QD for 108 weeks in EFC6049 study, continued their treatment with teriflunomide 7 mg tablet QD for 288 weeks in this extension study.	
Reporting group title	Placebo/Teriflunomide 14 mg
Reporting group description: Subjects who completed treatment of placebo (for teriflunomide tablet) QD for 108 weeks in EFC6049 study, received teriflunomide 14 mg tablet QD for 288 weeks in this extension study.	
Reporting group title	Teriflunomide 14 mg/14 mg
Reporting group description: Subjects who completed treatment of teriflunomide 14 mg tablet QD for 108 weeks in EFC6049 study, continued their treatment with teriflunomide 14 mg tablet QD orally for 288 weeks in this extension study.	
Subject analysis set title	Teriflunomide 7 mg/7 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects who received Teriflunomide 7 mg treatment in EFC6049 study were continued to receive the same treatment in this extension study. Teriflunomide 7 mg once daily (QD), orally for 288 weeks. Included 1 subject from Placebo/Teriflunomide 14 mg and 1 subject from Teriflunomide 14 mg/14 mg arm.	

### Primary: Percentage of Subjects With Treatment Emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects With Treatment Emergent Adverse Events (TEAEs) <sup>[1][2]</sup>
End point description: Adverse event (AE): any untoward medical occurrence in a subject who received investigational medicinal product (IMP) without regard to possibility of causal relationship with this treatment. TEAEs: AEs developed/worsened/became serious during on-treatment period (from time of first dose of study drug [in LTS6050] up to 4 weeks (28 days) after last dose of study drug). Serious adverse event (SAE): any untoward medical occurrence resulted in any of following outcomes: death, life-threatening, required initial/prolonged in-patient hospitalization, persistent/significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included both serious & non-serious AEs. Safety population: all subjects randomized in LTS6050 study & exposed to IMP during LTS6050 study treatment period, regardless of amount of treatment administered. Safety analysis was conducted as treatment received. Here, 99999 = percentage of subjects was 0 for this arm.	
End point type	Primary
End point timeframe: Baseline (LTS6050) up to 28 days after last dose of study drug up to 450 weeks	

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[2] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Placebo/Teriflunomide 7 mg	Placebo/Teriflunomide 14 mg	Teriflunomide 14 mg/14 mg	Teriflunomide 7 mg/7 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	129	107	250	254
Units: percentage of subjects				
number (not applicable)				
Any TEAE	93.8	94.4	91.2	91.3
Any Treatment Emergent SAE	24.8	21.5	24.8	28
Any TEAE Leading to Death	2.3	99999	0.8	0.8
Any TEAE Leading to Permanent Discontinuation	17.1	12.1	10.8	12.2

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to 12 Week Sustained Disability Progression (DP): Kaplan-Meier Estimates of the Rate of DP

End point title	Time to 12 Week Sustained Disability Progression (DP): Kaplan-Meier Estimates of the Rate of DP
End point description:	
Sustained DP: sustained increase of at least 1 point from baseline(EFC6049)expanded disability status scale(EDSS)score(0.5 point for subjects with baseline EDSS>5.5)persisting for at least 12weeks. Probability of DP at 12weeks estimated by Kaplan-Meier method on time to DP: date of first DP minus(-)date of randomization in EFC6049 study +1 day. Subjects free of DP(no DP observed on treatment)censored at date of last on-treatment EDSS evaluation in LTS6050.Kaplan-Meier method consists in computing probabilities of non-occurrence of event at any observed time of event and multiplying successive probabilities for time $\leq t$ by any earlier computed probabilities to estimate probability of being event-free for amount of time t. Analysis for end point performed on combined data of EFC6049&LTS6050 study, as pre-specified in protocol. Intent-to-treat(ITT)(EFC6049+LTS6050) population: all subjects randomized in both(EFC6049&LTS6050)studies that had at least 1-day IMP exposure during both studies.	
End point type	Secondary
End point timeframe:	
Up to 10.8 years (EFC6049: 108 weeks + LTS6050: 450 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	129	252	108	251
Units: Probability				
number (confidence interval 95%)	0.544 (0.441 to 0.646)	0.494 (0.423 to 0.565)	0.627 (0.444 to 0.811)	0.473 (0.403 to 0.543)

## Statistical analyses

Statistical analysis title	Placebo/Teriflunomide7mg vs. Teriflunomide 7mg/7mg
Statistical analysis description:	
Analysis was performed using Log-rank test with treatment, EDSS strata at baseline and region as	

covariates. Estimation was performed using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

Comparison groups	Placebo/Teriflunomide 7 mg v Teriflunomide 7 mg/7 mg
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2079 <sup>[3]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.824
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.602
upper limit	1.128

Notes:

[3] - Threshold for significance at 0.05 level.

<b>Statistical analysis title</b>	Placebo/Teriflunomide14mg vs. Teriflunomide14/14mg
Statistical analysis description:	
Analysis was performed using Log-rank test with treatment, EDSS strata at baseline and region as covariates. Estimation was performed using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.	
Comparison groups	Placebo/Teriflunomide 14 mg v Teriflunomide 14 mg/14 mg
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3039 <sup>[4]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.825
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.591
upper limit	1.152

Notes:

[4] - Threshold for significance at 0.05 level.

<b>Statistical analysis title</b>	Teriflunomide 7mg/7mg vs. Teriflunomide 14mg/14 mg
Statistical analysis description:	
Analysis was performed using Log-rank test with treatment, EDSS strata at baseline and region as covariates. Estimation was performed using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.	
Comparison groups	Teriflunomide 7 mg/7 mg v Teriflunomide 14 mg/14 mg
Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8271 <sup>[5]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.963

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.736
upper limit	1.26

Notes:

[5] - Threshold for significance at 0.05 level.

## Secondary: Time to 24 Week Sustained Disability Progression (DP): Kaplan-Meier Estimates of the Rate of DP

End point title	Time to 24 Week Sustained Disability Progression (DP): Kaplan-Meier Estimates of the Rate of DP
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End point description:

Sustained DP: sustained increase of at least 1 point from baseline (EFC6049) EDSS score (0.5 point for subjects with baseline EDSS>5.5) persisting for at least 24 weeks. Probability of DP at 24 weeks estimated by Kaplan-Meier method on time to DP: date of first DP minus (-) date of randomization in EFC6049 study +1 day. Subjects free of DP (no DP observed on treatment) censored at date of last on-treatment EDSS evaluation in LTS6050. Kaplan-Meier method consists in computing probabilities of non-occurrence of event at any observed time of event and multiplying successive probabilities for time  $\leq t$  by any earlier computed probabilities to estimate the probability of being event-free for amount of time t. Analysis for this end point performed on combined data of EFC6049 & LTS6050 study, as pre-specified in protocol. ITT (EFC6049 + LTS6050) population: all subjects randomized in both EFC6049 & LTS6050 studies that had at least 1-day IMP exposure during both EFC6049 & LTS6050 study.

End point type	Secondary
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End point timeframe:

Up to 10.8 years (EFC6049: 108 weeks + LTS6050: 450 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	129	252	108	251
Units: Probability				
number (confidence interval 95%)	0.444 (0.338 to 0.55)	0.434 (0.363 to 0.504)	0.518 (0.411 to 0.624)	0.438 (0.367 to 0.509)

## Statistical analyses

Statistical analysis title	Placebo/Teriflunomide 7mg vs. Teriflunomide 7mg/7mg
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Statistical analysis description:

Analysis was performed using Log-rank test with treatment, EDSS strata at baseline and region as covariates. Estimation was performed using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

Comparison groups	Placebo/Teriflunomide 7 mg v Teriflunomide 7 mg/7 mg
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8017 <sup>[6]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.961

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.678
upper limit	1.362

Notes:

[6] - Threshold for significance at 0.05 level.

<b>Statistical analysis title</b>	Placebo/Teriflunomide14mg vs. Teriflunomide14/14mg
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Statistical analysis description:

Analysis was performed using Log-rank test with treatment, EDSS strata at baseline and region as covariates. Estimation was performed using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

Comparison groups	Placebo/Teriflunomide 14 mg v Teriflunomide 14 mg/14 mg
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1866 <sup>[7]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.559
upper limit	1.117

Notes:

[7] - Threshold for significance at 0.05 level.

<b>Statistical analysis title</b>	Placebo/Teriflunomide7mg vs. Teriflunomide 14/14mg
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Statistical analysis description:

Analysis was performed using Log-rank test with treatment, EDSS strata at baseline and region as covariates. Estimation was performed using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

Comparison groups	Teriflunomide 7 mg/7 mg v Teriflunomide 14 mg/14 mg
Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8763 <sup>[8]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.767
upper limit	1.357

Notes:

[8] - Threshold for significance at 0.05 level.

## Secondary: Percentage of Subjects Free of Sustained Disability Progression (DP)

End point title	Percentage of Subjects Free of Sustained Disability Progression (DP)
End point description:	
Sustained DP was defined as sustained increase of at least 1 point from EFC6049 baseline EDSS score (0.5 point for subjects with baseline EDSS>5.5) persisting for at least 12 weeks & 24 weeks. EDSS: an ordinal scale in half-point increments that qualifies disability in subjects with MS. It consists of 8 ordinal rating scales assessing seven functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder, cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS), where higher scores indicates worse neurological function. Percentage of subjects who were considered as free of DP confirmed after 12 week & 24 week sustained progression were reported. Analysis for this end point was performed on the combined data of EFC6049 & LTS6050 study, as pre-specified in the protocol. ITT(EFC6049 + LTS6050)population.	
End point type	Secondary
End point timeframe:	
Up to 10.8 years since EFC6049 randomization (EFC6049: 108 weeks + LTS6050: 450 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	129	252	108	251
Units: Percentage of Subjects				
number (not applicable)				
Free of DP Sustained for 12 Weeks	45.6	50.6	37.3	52.7
Free of DP Sustained for 24 Weeks	55.6	56.6	48.2	56.2

## Statistical analyses

No statistical analyses for this end point

## Secondary: Annualized MS Relapse Rate (ARR): Poisson Regression Estimates

End point title	Annualized MS Relapse Rate (ARR): Poisson Regression Estimates
End point description:	
ARR was obtained from the total number of confirmed relapses that occurred during the treatment period divided by the sum of treatment durations in LTS6050 study only. 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. To account for the different treatment duration among participants, a Poisson regression model with robust error variance was used (total number of confirmed relapses as response variable; log-transformed treatment duration as "offset" variable; treatment group, region of enrolment and baseline EDSS stratum as covariates). ITT(LTS6050) population: all subjects who were randomized in the LTS6050 study and had at least 1-day IMP exposure during the LTS6050 study.	
End point type	Secondary
End point timeframe:	
Up to 8 years since LTS6050 randomization	

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	129	252	108	251
Units: relapses per subject-year				
number (confidence interval 95%)	0.216 (0.162 to 0.288)	0.183 (0.149 to 0.225)	0.176 (0.132 to 0.236)	0.16 (0.129 to 0.198)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Magnetic Resonance Imaging (MRI) Assessment: Change From Baseline in Total Volume of Abnormal Lesions (Burden of Disease [BOD]) at Week 192 Since LTS6050 Randomization

End point title	Magnetic Resonance Imaging (MRI) Assessment: Change From Baseline in Total Volume of Abnormal Lesions (Burden of Disease [BOD]) at Week 192 Since LTS6050 Randomization
End point description: BOD was assessed by cerebral MRI and defined as the total volume of all abnormal brain tissue (calculated as the sum of the total volume of T2-lesion component and T1-hypointense lesion component). ITT (LTS6050 population). Number of subjects analyzed=subjects with available data for this end point.	
End point type	Secondary
End point timeframe: Baseline, Week 192	

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	49	99	36	103
Units: millilitres (ml)				
arithmetic mean (standard deviation)	5.307 ( $\pm$ 9.088)	3.969 ( $\pm$ 11.135)	3.72 ( $\pm$ 6.696)	3.943 ( $\pm$ 9.685)

### 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 up to 28 days after the last dose of study drug up to Week 450, regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are TEAEs that is AEs that developed/worsened during the 'on treatment period' (the time from the first dose of study treatment to 4 weeks [28 days] after the last dose of study treatment).

Analysis was performed on safety population and was conducted as per the treatment received.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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### Reporting groups

Reporting group title	Placebo/Teriflunomide 7 mg
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Reporting group description:

Subjects who completed placebo (for teriflunomide) tablet once daily (QD) for 108 weeks in EFC6049 study received teriflunomide tablet 7 mg QD for 288 weeks in this extension study.

Reporting group title	Teriflunomide 7 mg/7 mg
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Reporting group description:

Subjects who completed teriflunomide 7 mg tablet QD for 108 weeks in EFC6049 study continued their treatment with teriflunomide 7 mg tablet QD for 288 weeks in this extension study. Included 2 subjects randomized in placebo and teriflunomide 14 mg arm respectively in EFC6049 study, incorrectly received at least 1 dose of teriflunomide 7 mg. In LTS6050 study, same subjects received correct dose of teriflunomide 14 mg but consistently included in Teriflunomide 7 mg/7 mg arm for safety analysis.

Reporting group title	Placebo/Teriflunomide 14 mg
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Reporting group description:

Subjects who completed placebo (for teriflunomide tablet) QD for 108 weeks in EFC6049 study received teriflunomide 14 mg tablet QD for 288 weeks in this extension study.

Excluded 1 subject randomized in placebo arm in EFC6049 study, incorrectly received at least 1 dose of teriflunomide 7 mg. In LTS6050 study, same subject received 14 mg dose but consistently included in teriflunomide 7 mg/7 mg arm for safety analysis.

Reporting group title	Teriflunomide 14 mg/14 mg
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Reporting group description:

Subjects who completed teriflunomide 14 mg tablet QD for 108 weeks in EFC6049 study continued their treatment with teriflunomide 14 mg tablet QD orally for 288 weeks in this extension study.

Excluded 1 subject randomized in 14 mg arm in EFC6049 study, incorrectly received at least 1 dose of teriflunomide 7 mg. In LTS6050 study, same subject received correct dose of 14 mg but consistently included in Teriflunomide 7 mg arm for safety analysis.

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	32 / 129 (24.81%)	71 / 254 (27.95%)	23 / 107 (21.50%)
number of deaths (all causes)	3	2	0
number of deaths resulting from adverse events	3	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			



subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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 Neoplasm			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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	1 / 129 (0.78%)	0 / 254 (0.00%)	2 / 107 (1.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal Cell Carcinoma			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Breast Cancer			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Cholesteatoma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (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
Colon Cancer Metastatic			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Malignant Melanoma			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Squamous Cell Carcinoma Of The Cervix			

subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Vascular disorders			
Venous Stenosis			
subjects affected / exposed	0 / 129 (0.00%)	3 / 254 (1.18%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Varicose Vein			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Surgical and medical procedures			
Mammoplasty			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Osteotomy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Chest Pain			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Adverse Drug Reaction			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Death			
subjects affected / exposed	1 / 129 (0.78%)	1 / 254 (0.39%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
General Physical Health Deterioration			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Sudden Death			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Social circumstances			
Miscarriage Of Partner			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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

Breast Hyperplasia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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	0 / 129 (0.00%)	2 / 254 (0.79%)	0 / 107 (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
Uterine Haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Breast Cyst			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Polyp			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Metrorrhagia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Ovarian Cyst			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Premenstrual Cramps			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Uterine Polyp			

subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Respiratory, thoracic and mediastinal disorders			
Nasal Septum Deviation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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 Embolism			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Epistaxis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Interstitial Lung Disease			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal Ideation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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	1 / 129 (0.78%)	1 / 254 (0.39%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Affective Disorder	subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Bipolar Disorder	subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Cholecystitis Chronic	subjects affected / exposed	1 / 129 (0.78%)	1 / 254 (0.39%)	0 / 107 (0.00%)
	occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Steatosis	subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Hepatocellular Injury	subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Hepatotoxicity	subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Investigations				
Alanine Aminotransferase Increased	subjects affected / exposed	4 / 129 (3.10%)	3 / 254 (1.18%)	3 / 107 (2.80%)
	occurrences causally related to treatment / all	4 / 4	2 / 3	3 / 3
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatic Enzyme Increased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Transaminases Increased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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	1 / 129 (0.78%)	1 / 254 (0.39%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Blood Pressure Increased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Lipase Increased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Injury, poisoning and procedural complications			
Hand Fracture			

subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Accidental Overdose			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle Fracture			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Cervical Vertebral Fracture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Fall			
subjects affected / exposed	1 / 129 (0.78%)	2 / 254 (0.79%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral Neck Fracture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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 Rupture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Road Traffic Accident			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Anastomotic Leak			



subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Concussion			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Fibula Fracture			
subjects affected / exposed	1 / 129 (0.78%)	1 / 254 (0.39%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head Injury			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Hepatic Rupture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip Fracture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint Dislocation			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Ligament Sprain			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Lower Limb Fracture			

subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Meniscus Injury			
subjects affected / exposed	1 / 129 (0.78%)	1 / 254 (0.39%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Fractures			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella Fracture			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Procedural Pain			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Radius Fracture			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Rib Fracture			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Traumatic Shock			

subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist Fracture			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Congenital, familial and genetic disorders			
Dolichocolon			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Cardiac disorders			
Myocardial Infarction			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Acute Myocardial Infarction			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Angina Pectoris			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Arteriosclerosis Coronary Artery			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Bradycardia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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 Failure Acute			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Coronary Artery Disease			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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 Arrest			
subjects affected / exposed	2 / 129 (1.55%)	0 / 254 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac Valve Disease			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Supraventricular Tachycardia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Epilepsy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Headache			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Paraplegia			

subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Seizure			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Syncope			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Uhthoff's Phenomenon			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Ageusia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Insufficiency			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Facial Neuralgia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial Aneurysm			

subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
<b>Muscle Spasticity</b>			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Posterior Reversible Encephalopathy Syndrome</b>			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
<b>Sciatica</b>			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
<b>Transient Ischaemic Attack</b>			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
<b>Blood and lymphatic system disorders</b>			
<b>Neutropenia</b>			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
<b>Anaemia</b>			
subjects affected / exposed	0 / 129 (0.00%)	2 / 254 (0.79%)	0 / 107 (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
<b>Ear and labyrinth disorders</b>			
<b>Vertigo</b>			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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

Eye disorders			
Uveitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Cystoid Macular Oedema			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal Detachment			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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	0 / 129 (0.00%)	2 / 254 (0.79%)	0 / 107 (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
Anal Fissure			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Anal Fistula			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Crohn's Disease			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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

Diarrhoea			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Diverticulum Intestinal			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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 Ulcer Haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Large Intestine Perforation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Mechanical Ileus			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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 Upper			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Colitis Microscopic			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Gastric Ulcer Haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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 Haemorrhage			



subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Hernial Eventration			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Mesenteric Haematoma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth Swelling			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Volvulus			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Skin and subcutaneous tissue disorders			
Alopecia Areata			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Decubitus Ulcer			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lichen Planus			

subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Pustular Psoriasis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Prolapse			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Nephrolithiasis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Mass			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Urinary Retention			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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	2 / 129 (1.55%)	5 / 254 (1.97%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Rotator Cuff Syndrome			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Arthralgia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Arthropathy			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back Pain			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Bone Cyst			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Spinal Stenosis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Osteonecrosis			

subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Tenosynovitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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			
Erysipelas			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Urinary Tract Infection			
subjects affected / exposed	1 / 129 (0.78%)	1 / 254 (0.39%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Abscess			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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	0 / 129 (0.00%)	2 / 254 (0.79%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Endometritis			

subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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 Infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Hepatitis A			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Perirectal Abscess			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Pneumonia			
subjects affected / exposed	0 / 129 (0.00%)	2 / 254 (0.79%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Streptococcal			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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 Tract Infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Sepsis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous Abscess			

subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Urosepsis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular Neuritis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Bone Abscess			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Bronchitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Bursitis Infective			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Diverticulitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 254 (0.00%)	0 / 107 (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
Gastroenteritis			
subjects affected / exposed	0 / 129 (0.00%)	2 / 254 (0.79%)	0 / 107 (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
Infected Dermal Cyst			

subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Oral Herpes			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Peritonitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Pneumonia Bacterial			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Postoperative Wound Infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Pyelonephritis			
subjects affected / exposed	2 / 129 (1.55%)	0 / 254 (0.00%)	0 / 107 (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
Tooth Abscess			
subjects affected / exposed	1 / 129 (0.78%)	1 / 254 (0.39%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubo-Ovarian Abscess			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	0 / 107 (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
Wound Infection			

subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Metabolism and nutrition disorders</b>			
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	0 / 107 (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
Diabetes Mellitus			
subjects affected / exposed	0 / 129 (0.00%)	0 / 254 (0.00%)	1 / 107 (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
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 129 (0.00%)	1 / 254 (0.39%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Teriflunomide 14 mg/14 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 250 (24.80%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
Meningioma			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroid Neoplasm			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine Leiomyoma			



subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal Cell Carcinoma			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast Cancer			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholesteatoma			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon Cancer Metastatic			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant Melanoma			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous Cell Carcinoma Of The Cervix			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous Stenosis			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Phlebitis			

subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicose Vein			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Mammoplasty			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteotomy			
subjects affected / exposed	0 / 250 (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	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 250 (0.80%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Chest Pain			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adverse Drug Reaction			

subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General Physical Health Deterioration			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sudden Death			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Miscarriage Of Partner			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	2 / 250 (0.80%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Breast Hyperplasia			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Menorrhagia			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Uterine Haemorrhage			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast Cyst			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical Polyp			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metrorrhagia			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian Cyst			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Premenstrual Cramps			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine Polyp			
subjects affected / exposed	0 / 250 (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 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pulmonary Embolism			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Interstitial Lung Disease			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal Ideation			
subjects affected / exposed	2 / 250 (0.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide Attempt			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Affective Disorder			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bipolar Disorder			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	2 / 250 (0.80%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cholecystitis Chronic			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic Steatosis			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatocellular Injury			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	6 / 250 (2.40%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Hepatic Enzyme Increased			
subjects affected / exposed	2 / 250 (0.80%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Transaminases Increased			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate Aminotransferase			

Increased				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood Alkaline Phosphatase Increased				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood Pressure Increased				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gamma-Glutamyltransferase Increased				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lipase Increased				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Hand Fracture				
subjects affected / exposed	2 / 250 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Accidental Overdose				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ankle Fracture				

subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical Vertebral Fracture				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femoral Neck Fracture				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ligament Rupture				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road Traffic Accident				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anastomotic Leak				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fibula Fracture				



subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Head Injury			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic Rupture			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip Fracture			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint Dislocation			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament Sprain			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower Limb Fracture			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meniscus Injury			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple Fractures			

subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Patella Fracture			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural Pain			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius Fracture			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rib Fracture			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tibia Fracture			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Traumatic Shock			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wrist Fracture			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Dolichocolon			

subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial Infarction			
subjects affected / exposed	3 / 250 (1.20%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Acute Myocardial Infarction			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina Pectoris			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis Coronary Artery			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure Acute			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary Artery Disease			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Arrest			

subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac Valve Disease			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Supraventricular Tachycardia			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Paraplegia			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uhthoff's Phenomenon			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ageusia			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular Insufficiency			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Facial Neuralgia			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intracranial Aneurysm			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscle Spasticity			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Posterior Reversible Encephalopathy Syndrome			

subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient Ischaemic Attack			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	0 / 250 (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 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Uveitis			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystoid Macular Oedema			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Retinal Detachment			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 250 (0.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Inguinal Hernia			
subjects affected / exposed	2 / 250 (0.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Anal Fissure			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal Fistula			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Crohn's Disease			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulum Intestinal			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Ulcer Haemorrhage			

subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Large Intestine Perforation			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mechanical Ileus			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain Upper			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis Microscopic			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric Ulcer Haemorrhage			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroduodenal Haemorrhage			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hernial Eventration			



subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mesenteric Haematoma			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mouth Swelling			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Volvulus			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Alopecia Areata			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Decubitus Ulcer			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lichen Planus			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pustular Psoriasis			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute Kidney Injury			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder Prolapse			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Mass			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary Retention			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	2 / 250 (0.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Rotator Cuff Syndrome				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Arthralgia				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthropathy				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Back Pain				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bone Cyst				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar Spinal Stenosis				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tenosynovitis				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				

Erysipelas				
subjects affected / exposed	2 / 250 (0.80%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Infection				
subjects affected / exposed	2 / 250 (0.80%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Anal Abscess				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium Difficile Colitis				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endometritis				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal Infection				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis A				

subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Perirectal Abscess				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia Streptococcal				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Tract Infection				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subcutaneous Abscess				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vestibular Neuronitis				

subjects affected / exposed	1 / 250 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
<b>Bone Abscess</b>				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
<b>Bronchitis</b>				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
<b>Bursitis Infective</b>				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
<b>Diverticulitis</b>				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
<b>Gastroenteritis</b>				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
<b>Infected Dermal Cyst</b>				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
<b>Oral Herpes</b>				
subjects affected / exposed	0 / 250 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
<b>Peritonitis</b>				

subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia Bacterial			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative Wound Infection			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tooth Abscess			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tubo-Ovarian Abscess			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound Infection			
subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	1 / 250 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes Mellitus			

subjects affected / exposed	0 / 250 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 250 (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 %

<b>Non-serious adverse events</b>	Placebo/Teriflunomide 7 mg	Teriflunomide 7 mg/7 mg	Placebo/Teriflunomide 14 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 129 (82.95%)	195 / 254 (76.77%)	95 / 107 (88.79%)
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 129 (7.75%)	22 / 254 (8.66%)	11 / 107 (10.28%)
occurrences (all)	10	22	11
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	17 / 129 (13.18%)	37 / 254 (14.57%)	17 / 107 (15.89%)
occurrences (all)	17	37	17
Influenza Like Illness			
subjects affected / exposed	1 / 129 (0.78%)	6 / 254 (2.36%)	1 / 107 (0.93%)
occurrences (all)	1	6	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 129 (10.85%)	22 / 254 (8.66%)	7 / 107 (6.54%)
occurrences (all)	14	22	7
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 129 (4.65%)	15 / 254 (5.91%)	8 / 107 (7.48%)
occurrences (all)	6	15	8
Depression			
subjects affected / exposed	10 / 129 (7.75%)	24 / 254 (9.45%)	11 / 107 (10.28%)
occurrences (all)	10	24	11



Anxiety subjects affected / exposed occurrences (all)	3 / 129 (2.33%) 3	6 / 254 (2.36%) 6	6 / 107 (5.61%) 6
Investigations			
Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	18 / 129 (13.95%) 18	36 / 254 (14.17%) 36	18 / 107 (16.82%) 18
Gamma-Glutamyltransferase Increased subjects affected / exposed occurrences (all)	4 / 129 (3.10%) 4	16 / 254 (6.30%) 16	2 / 107 (1.87%) 2
Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)	4 / 129 (3.10%) 4	18 / 254 (7.09%) 18	4 / 107 (3.74%) 4
Blood Pressure Increased subjects affected / exposed occurrences (all)	8 / 129 (6.20%) 8	10 / 254 (3.94%) 10	5 / 107 (4.67%) 5
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	9 / 129 (6.98%) 9	20 / 254 (7.87%) 20	8 / 107 (7.48%) 8
Contusion subjects affected / exposed occurrences (all)	4 / 129 (3.10%) 4	5 / 254 (1.97%) 5	8 / 107 (7.48%) 8
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	21 / 129 (16.28%) 21	42 / 254 (16.54%) 42	18 / 107 (16.82%) 18
Paraesthesia subjects affected / exposed occurrences (all)	6 / 129 (4.65%) 6	26 / 254 (10.24%) 26	13 / 107 (12.15%) 13
Dizziness subjects affected / exposed occurrences (all)	5 / 129 (3.88%) 5	14 / 254 (5.51%) 14	7 / 107 (6.54%) 7
Hypoaesthesia			

subjects affected / exposed occurrences (all)	4 / 129 (3.10%) 4	20 / 254 (7.87%) 20	10 / 107 (9.35%) 10
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 129 (0.78%)	7 / 254 (2.76%)	9 / 107 (8.41%)
occurrences (all)	1	7	9
Neutropenia			
subjects affected / exposed	2 / 129 (1.55%)	6 / 254 (2.36%)	6 / 107 (5.61%)
occurrences (all)	2	6	6
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 129 (12.40%)	24 / 254 (9.45%)	19 / 107 (17.76%)
occurrences (all)	16	24	19
Nausea			
subjects affected / exposed	10 / 129 (7.75%)	20 / 254 (7.87%)	10 / 107 (9.35%)
occurrences (all)	10	20	10
Constipation			
subjects affected / exposed	4 / 129 (3.10%)	10 / 254 (3.94%)	7 / 107 (6.54%)
occurrences (all)	4	10	7
Abdominal Pain Upper			
subjects affected / exposed	3 / 129 (2.33%)	16 / 254 (6.30%)	4 / 107 (3.74%)
occurrences (all)	3	16	4
Abdominal Pain			
subjects affected / exposed	5 / 129 (3.88%)	22 / 254 (8.66%)	8 / 107 (7.48%)
occurrences (all)	5	22	8
Toothache			
subjects affected / exposed	2 / 129 (1.55%)	13 / 254 (5.12%)	3 / 107 (2.80%)
occurrences (all)	2	13	3
Vomiting			
subjects affected / exposed	8 / 129 (6.20%)	8 / 254 (3.15%)	5 / 107 (4.67%)
occurrences (all)	8	8	5
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	2 / 129 (1.55%)	7 / 254 (2.76%)	1 / 107 (0.93%)
occurrences (all)	2	7	1
Rash			

subjects affected / exposed occurrences (all)	6 / 129 (4.65%) 6	11 / 254 (4.33%) 11	6 / 107 (5.61%) 6
Alopecia subjects affected / exposed occurrences (all)	11 / 129 (8.53%) 11	12 / 254 (4.72%) 12	18 / 107 (16.82%) 18
Renal and urinary disorders Micturition Urgency subjects affected / exposed occurrences (all)	8 / 129 (6.20%) 8	4 / 254 (1.57%) 4	3 / 107 (2.80%) 3
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all)	10 / 129 (7.75%) 10	37 / 254 (14.57%) 37	16 / 107 (14.95%) 16
Pain In Extremity subjects affected / exposed occurrences (all)	14 / 129 (10.85%) 14	27 / 254 (10.63%) 27	20 / 107 (18.69%) 20
Arthralgia subjects affected / exposed occurrences (all)	17 / 129 (13.18%) 17	31 / 254 (12.20%) 31	9 / 107 (8.41%) 9
Musculoskeletal Pain subjects affected / exposed occurrences (all)	1 / 129 (0.78%) 1	11 / 254 (4.33%) 11	1 / 107 (0.93%) 1
Muscle Spasms subjects affected / exposed occurrences (all)	6 / 129 (4.65%) 6	12 / 254 (4.72%) 12	4 / 107 (3.74%) 4
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	34 / 129 (26.36%) 34	71 / 254 (27.95%) 71	29 / 107 (27.10%) 29
Influenza subjects affected / exposed occurrences (all)	19 / 129 (14.73%) 19	39 / 254 (15.35%) 39	20 / 107 (18.69%) 20
Urinary Tract Infection subjects affected / exposed occurrences (all)	20 / 129 (15.50%) 20	31 / 254 (12.20%) 31	19 / 107 (17.76%) 19
Sinusitis			

subjects affected / exposed	7 / 129 (5.43%)	16 / 254 (6.30%)	5 / 107 (4.67%)
occurrences (all)	7	16	5
Upper Respiratory Tract Infection			
subjects affected / exposed	15 / 129 (11.63%)	29 / 254 (11.42%)	15 / 107 (14.02%)
occurrences (all)	15	29	15
Bronchitis			
subjects affected / exposed	10 / 129 (7.75%)	17 / 254 (6.69%)	9 / 107 (8.41%)
occurrences (all)	10	17	9
Gastroenteritis			
subjects affected / exposed	8 / 129 (6.20%)	10 / 254 (3.94%)	8 / 107 (7.48%)
occurrences (all)	8	10	8
Cystitis			
subjects affected / exposed	9 / 129 (6.98%)	8 / 254 (3.15%)	4 / 107 (3.74%)
occurrences (all)	9	8	4
Respiratory Tract Infection			
subjects affected / exposed	8 / 129 (6.20%)	10 / 254 (3.94%)	9 / 107 (8.41%)
occurrences (all)	8	10	9
Oral Herpes			
subjects affected / exposed	3 / 129 (2.33%)	17 / 254 (6.69%)	6 / 107 (5.61%)
occurrences (all)	3	17	6

<b>Non-serious adverse events</b>	Teriflunomide 14 mg/14 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	197 / 250 (78.80%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	37 / 250 (14.80%)		
occurrences (all)	37		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	26 / 250 (10.40%)		
occurrences (all)	26		
Influenza Like Illness			
subjects affected / exposed	13 / 250 (5.20%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	19 / 250 (7.60%) 19		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)  Depression subjects affected / exposed occurrences (all)  Anxiety subjects affected / exposed occurrences (all)	17 / 250 (6.80%) 17  15 / 250 (6.00%) 15  8 / 250 (3.20%) 8		
Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)  Gamma-Glutamyltransferase Increased subjects affected / exposed occurrences (all)  Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)  Blood Pressure Increased subjects affected / exposed occurrences (all)	32 / 250 (12.80%) 32  12 / 250 (4.80%) 12  11 / 250 (4.40%) 11  7 / 250 (2.80%) 7		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)  Contusion subjects affected / exposed occurrences (all)	34 / 250 (13.60%) 34  8 / 250 (3.20%) 8		
Nervous system disorders			

Headache			
subjects affected / exposed	42 / 250 (16.80%)		
occurrences (all)	42		
Paraesthesia			
subjects affected / exposed	23 / 250 (9.20%)		
occurrences (all)	23		
Dizziness			
subjects affected / exposed	14 / 250 (5.60%)		
occurrences (all)	14		
Hypoaesthesia			
subjects affected / exposed	13 / 250 (5.20%)		
occurrences (all)	13		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 250 (4.80%)		
occurrences (all)	12		
Neutropenia			
subjects affected / exposed	6 / 250 (2.40%)		
occurrences (all)	6		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	30 / 250 (12.00%)		
occurrences (all)	30		
Nausea			
subjects affected / exposed	29 / 250 (11.60%)		
occurrences (all)	29		
Constipation			
subjects affected / exposed	15 / 250 (6.00%)		
occurrences (all)	15		
Abdominal Pain Upper			
subjects affected / exposed	10 / 250 (4.00%)		
occurrences (all)	10		
Abdominal Pain			
subjects affected / exposed	9 / 250 (3.60%)		
occurrences (all)	9		
Toothache			

subjects affected / exposed occurrences (all)	9 / 250 (3.60%) 9		
Vomiting subjects affected / exposed occurrences (all)	8 / 250 (3.20%) 8		
Skin and subcutaneous tissue disorders			
Eczema subjects affected / exposed occurrences (all)	15 / 250 (6.00%) 15		
Rash subjects affected / exposed occurrences (all)	14 / 250 (5.60%) 14		
Alopecia subjects affected / exposed occurrences (all)	6 / 250 (2.40%) 6		
Renal and urinary disorders			
Micturition Urgency subjects affected / exposed occurrences (all)	9 / 250 (3.60%) 9		
Musculoskeletal and connective tissue disorders			
Back Pain subjects affected / exposed occurrences (all)	40 / 250 (16.00%) 40		
Pain In Extremity subjects affected / exposed occurrences (all)	32 / 250 (12.80%) 32		
Arthralgia subjects affected / exposed occurrences (all)	28 / 250 (11.20%) 28		
Musculoskeletal Pain subjects affected / exposed occurrences (all)	16 / 250 (6.40%) 16		
Muscle Spasms subjects affected / exposed occurrences (all)	13 / 250 (5.20%) 13		
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	81 / 250 (32.40%)		
occurrences (all)	81		
Influenza			
subjects affected / exposed	37 / 250 (14.80%)		
occurrences (all)	37		
Urinary Tract Infection			
subjects affected / exposed	36 / 250 (14.40%)		
occurrences (all)	36		
Sinusitis			
subjects affected / exposed	28 / 250 (11.20%)		
occurrences (all)	28		
Upper Respiratory Tract Infection			
subjects affected / exposed	28 / 250 (11.20%)		
occurrences (all)	28		
Bronchitis			
subjects affected / exposed	26 / 250 (10.40%)		
occurrences (all)	26		
Gastroenteritis			
subjects affected / exposed	14 / 250 (5.60%)		
occurrences (all)	14		
Cystitis			
subjects affected / exposed	9 / 250 (3.60%)		
occurrences (all)	9		
Respiratory Tract Infection			
subjects affected / exposed	7 / 250 (2.80%)		
occurrences (all)	7		
Oral Herpes			
subjects affected / exposed	6 / 250 (2.40%)		
occurrences (all)	6		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2007	Following changes were made: - Standardized and revised of 11-day washout procedure for all the subjects. - Safety parameters and monitoring were clarified. - Laboratory parameters and follow-up were clarified.
08 September 2008	Following changes were made: - Changed inclusion/exclusion criteria to exclude newly enrolled HIVpositive subjects from the study. All subjects were to sign a consent form for HIV testing. Previously enrolled subjects newly diagnosed with HIV were to consider discontinuation but were allowed to remain if they were not severely immunodeficient, did not require anti-retroviral nucleoside analogs, and were willing to undergo safety monitoring. - Addition of yearly HIV testing for HIV risk assessment; subjects instructed to report symptoms suggestive of immunodeficiency. - Contraception requirements to reflect ICH-M3 guidelines were updated. - Implementation of EDSS assessment after treatment discontinuation for at least 24 weeks from first increase onset to document disability progression after discontinuation. - Clarifications for harmonization of protocols within the teriflunomide development program.
27 April 2010	Following change was made: - Primary and secondary efficacy variables were modified for consistency with the previous EFC6049 study.
10 February 2011	Following changes were made: - Modified laboratory safety monitoring intervals based on the available safety profiles. - Modified the concomitant medications based on the updated drug interactions data (CYP2C9 substrates and CYP inducers). - Removed routine PK sampling but maintained unscheduled PK for safety, based on the available PK data. Appendix G of the protocol (Pharmacokinetic specifications [centrifugation/shipment] for plasma samples analyzed for teriflunomide) was removed since the central lab manual with the updated information was provided separately. - Added "peripheral neuropathy confirmed by nerve conduction studies" to the alert terms due to the potential risk of this event. - To shorten the washout (WO) period from 16 weeks to 4 weeks in order to allow subjects to terminate treatment more rapidly and move more quickly to new therapeutic and life projects, and to make laboratory information available immediately at the end of the drug elimination procedure.
30 January 2012	Following changes were made: - Extended the current extension study. - Stopped performing MRI for all subjects. - Sufficient MRI information had been obtained in this uncontrolled extension. - Modified the concomitant treatments based on the updated drug interactions data. - Modified components of follow up visits. - Vital sign was measured at follow up visits to document how blood pressure and heart rate evolved after discontinuation of teriflunomide.
15 May 2012	Following changes were made: - Modified the concomitant treatments based on the updated drug interactions data. - Modified components of follow up visits. - Vital sign was measured at follow up visits to document how blood pressure and heart rate evolved after discontinuation of teriflunomide.

24 January 2013	Following changes were made: - Reduction of scheduled study visits and visit contents. Clinical visits occurred only every 24 weeks up to the end of treatment, and included the following: - Adverse event reporting, concomitant medication, - Vital signs, physical examination, - Dispense study drugs: Accountability/Compliance, - EDSS / FS, - Clinical laboratory only at EOT visit. - New information regarding potential drug interactions.
13 July 2013	Following change was made: - To provide extension in the study.

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported