Clinical trial results:
A Multi-center Double-blind Parallel-group Placebo-controlled Study of the Efficacy and Safety of Teriflunomide in Patients With Relapsing Multiple Sclerosis

Summary

EudraCT number	2007-004452-36
Trial protocol	GB NL BE CZ EE SK AT DE ES FR GR SE
Global end of trial date	18 June 2015

Results information

Result version number	v1 (current)
This version publication date	02 July 2016
First version publication date	02 July 2016

Trial information

Trial identification

Sponsor protocol code	EFC10531

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00751881
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: TOWER

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly, Mazarin, France, 91380
Public contact	Sanofi aventis recherche & développement, Trial Transparency Team, Contact-US@sanofi.com
Scientific contact	Sanofi aventis recherche & développement, Trial Transparency Team, 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	06 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the effect of two doses of teriflunomide, in comparison to placebo, on the frequency of multiple sclerosis (MS) relapses in subjects with relapsing MS.

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	26 August 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 213
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belarus: 53
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Chile: 11
Country: Number of subjects enrolled	China: 148
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	Estonia: 20
Country: Number of subjects enrolled	France: 64
Country: Number of subjects enrolled	Germany: 80
Country: Number of subjects enrolled	Greece: 22
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	Netherlands: 46
Country: Number of subjects enrolled	Philippines: 10
Country: Number of subjects enrolled	Poland: 48

Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Slovakia: 16
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Tunisia: 22
Country: Number of subjects enrolled	Turkey: 62
Country: Number of subjects enrolled	Ukraine: 173
Country: Number of subjects enrolled	United Kingdom: 25
Worldwide total number of subjects	1169
EEA total number of subjects	415

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1169
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1493 subjects were screened at 193 sites in 26 countries. The common end date for core treatment period was on 17 April 2012 (maximum treatment duration of 173 weeks). The extension study was completed on 18 June 2015 (maximum treatment duration was 174 weeks in addition to core treatment period).

Pre-assignment

Screening details:

Randomization was stratified by investigational site and Expanded Disability Status Scale (EDSS) score (≤3.5 or >3.5). Assignment to groups was done using an Interactive Voice Response System(IVRS) in 1:1:1 ratio. 1169 subjects were randomized at 190 sites. 780 subjects completed core treatment period and 751 were treated in extension study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo once daily.

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

Dosage and administration details:

Placebo (for teriflunomide) orally as a single dose in the morning of each day with water and may be taken with or without food.

Arm title	Teriflunomide 7 mg

Arm description:

Teriflunomide 7 mg once daily

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

Dosage and administration details:

Teriflunomide orally as a single dose in the morning of each day with water and may be taken with or without food.

Arm title	Teriflunomide 14 mg

Arm description:

Teriflunomide 14 mg once daily

Arm type	Experimental

Investigational medicinal product name	Teriflunomide
Investigational medicinal product code	HMR1726
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Teriflunomide orally as a single dose in the morning of each day with water and may be taken with or without food.

Number of subjects in period 1	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Started	389	408	372
Completed	263	273	244
Not completed	126	135	128
tolerability complaints	2	-	-
personal/family constraints	6	7	10
Other: protocol deviation	3	3	7
wish to parent	5	7	4
Adverse event, non-fatal	26	54	58
MS treatment change	6	4	4
Poor Compliance to Protocol	15	3	4
Lost to follow-up	6	4	3
subject's decision/unspecified	19	22	16
Not treated	1	1	2
Lack of efficacy	37	30	20

Period 2

Period 2 title	Extension Study Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo / Teriflunomide 14 mg

Arm description:

Subjects received placebo (for teriflunomide) once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.

Arm type	Experimental

Investigational medicinal product name	Teriflunomide
Investigational medicinal product code	HMR1726
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Teriflunomide orally as a single dose in the morning of each day with water and may be taken with or without food.

Arm title	Teriflunomide 7 mg / 14 mg

Arm description:

Subjects received teriflunomide 7 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.

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

Dosage and administration details:

Teriflunomide orally as a single dose in the morning of each day with water and may be taken with or without food.

Arm title	Teriflunomide 14 mg / 14 mg

Arm description:

Subjects received teriflunomide 14 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.

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

Dosage and administration details:

Teriflunomide orally as a single dose in the morning of each day with water and may be taken with or without food.

Number of subjects in period 2[1]	Placebo / Teriflunomide 14 mg	Teriflunomide 7 mg / 14 mg	Teriflunomide 14 mg / 14 mg
Started	253	265	233
Completed	188	194	167
Not completed	65	71	66
Other than specified above	26	30	18
Adverse event, non-fatal	18	20	21
Poor Compliance to Protocol	3	2	1
Lost to follow-up	4	9	6
Lack of efficacy	14	10	20

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 10 subjects (of placebo arm), 8 subjects (Teriflunomide 7 mg arm) and 11 subjects (Teriflunomide 14 mg arm) had completed core treatment period but did not enter in extension treatment period.

Baseline characteristics

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

Reporting group values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Number of subjects	389	408	372
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	38.1	37.4	38.2
standard deviation	± 9.1	± 9.4	± 9.4
Gender, Male/Female Units: subjects			
Female	273	300	258
Male	116	108	114
Region of Enrollment			
Due to the small sample size in some countries, the countries were pooled as follows: - Eastern Europe: Belarus, Czech Republic, Estonia, Greece, Poland, Romania, Slovakia and Ukraine - Western Europe and Africa: Austria, Belgium, France, Germany, Netherlands, Spain, Sweden and United Kingdom, Tunisia and Turkey - Asia and Australia: China, Philippines, Thailand and Australia - America: Canada, Chile, Mexico and the USA			
Units: Subjects			
Eastern Europe	117	124	116
Western Europe and Africa	121	127	120
Asia and Australia	67	65	55
America	84	92	81
MS subtype Units: Subjects			
Relapsing Remitting	379	393	366
Secondary Progressive	4	3	2
Progressive Relapsing	6	12	2
Information not available	0	0	2
Baseline EDSS score			
EDSS is an ordinal scale in half-point increments that qualifies disability in subjects with MS. It consists of 8 ordinal rating scales assessing 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS).			
Units: Subjects			

≤3.5	294	301	276
>3.5	95	107	96

Time since first diagnosis of MS			
The information was not available for one subject in the Teriflunomide 14 mg group			
Units: years			
arithmetic mean	4.92	5.3	5.27
standard deviation	± 5.66	± 5.45	± 5.9
Number of MS relapses within the past year			
The information was not available for 1 subject in the Placebo group and 1 subject in the Teriflunomide 14 mg group.			
Units: relapses			
median	1	1	1
full range (min-max)	0 to 7	0 to 5	0 to 5
Number of MS relapses within the past 2 years			
The information was not available for 2 subjects in the Teriflunomide 14 mg group.			
Units: relapses			
median	2	2	2
full range (min-max)	1 to 8	1 to 8	1 to 9
Time since most recent MS relapse onset			
The information was not available for one subject in the Teriflunomide 14 mg group.			
Units: months			
arithmetic mean	5.29	5.18	5.33
standard deviation	± 3.41	± 3.41	± 3.32

Reporting group values	Total		
Number of subjects	1169		
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: subjects			
Female	831		
Male	338		
Region of Enrollment			
Due to the small sample size in some countries, the countries were pooled as follows: - Eastern Europe: Belarus, Czech Republic, Estonia, Greece, Poland, Romania, Slovakia and Ukraine - Western Europe and Africa: Austria, Belgium, France, Germany, Netherlands, Spain, Sweden and United Kingdom, Tunisia and Turkey - Asia and Australia: China, Philippines, Thailand and Australia - America: Canada, Chile, Mexico and the USA			
Units: Subjects			
Eastern Europe	357		
Western Europe and Africa	368		
Asia and Australia	187		
America	257		

MS subtype Units: Subjects			
Relapsing Remitting	1138		
Secondary Progressive	9		
Progressive Relapsing	20		
Information not available	2		
Baseline EDSS score			
EDSS is an ordinal scale in half-point increments that qualifies disability in subjects with MS. It consists of 8 ordinal rating scales assessing 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS).			
Units: Subjects			
≤3.5	871		
>3.5	298		
Time since first diagnosis of MS			
The information was not available for one subject in the Teriflunomide 14 mg group			
Units: years arithmetic mean standard deviation	-		
Number of MS relapses within the past year			
The information was not available for 1 subject in the Placebo group and 1 subject in the Teriflunomide 14 mg group.			
Units: relapses median full range (min-max)	-		
Number of MS relapses within the past 2 years			
The information was not available for 2 subjects in the Teriflunomide 14 mg group.			
Units: relapses median full range (min-max)	-		
Time since most recent MS relapse onset			
The information was not available for one subject in the Teriflunomide 14 mg group.			
Units: months arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo once daily.	
Reporting group title	Teriflunomide 7 mg
Reporting group description: Teriflunomide 7 mg once daily	
Reporting group title	Teriflunomide 14 mg
Reporting group description: Teriflunomide 14 mg once daily	
Reporting group title	Placebo / Teriflunomide 14 mg
Reporting group description: Subjects received placebo (for teriflunomide) once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.	
Reporting group title	Teriflunomide 7 mg / 14 mg
Reporting group description: Subjects received teriflunomide 7 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.	
Reporting group title	Teriflunomide 14 mg / 14 mg
Reporting group description: Subjects received teriflunomide 14 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.	
Subject analysis set title	Teriflunomide 7 mg
Subject analysis set type	Full analysis
Subject analysis set description: Teriflunomide 7 mg once daily	
Subject analysis set title	Teriflunomide 7 mg / 14 mg
Subject analysis set type	Full analysis
Subject analysis set description: Core treatment period: Teriflunomide 7 mg once daily. Extension treatment period: Teriflunomide 14 mg once daily.	

Primary: Core Treatment Period: Annualized Relapse Rate (ARR): Poisson Regression Estimate

End point title	Core Treatment Period: Annualized Relapse Rate (ARR): Poisson Regression Estimate
End point description: ARR is obtained from the total number of confirmed relapses that occurred during the treatment period divided by the sum of treatment durations. 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 durations among subjects, 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). Intent-to-treat (ITT) population: all randomized and treated subjects. Subjects were considered in the treatment group to which they were randomized regardless of the drug they actually received.	
End point type	Primary
End point timeframe: Core treatment period between 48 - 152 weeks depending on time of enrollment	

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	388	407	370	
Units: relapses per year				
number (confidence interval 95%)	0.501 (0.432 to 0.581)	0.389 (0.332 to 0.457)	0.319 (0.267 to 0.381)	

Statistical analyses

Statistical analysis title	Placebo Vs Teriflunomide14mg

Statistical analysis description:

Null hypothesis:
- H1: No difference between Teriflunomide 14 mg and placebo
- H2: No difference between Teriflunomide 7 mg and placebo

The study was sized to have 94% power to detect a 25% relative risk reduction in ARR with teriflunomide compared to placebo at a 2-sided 0.05 significance level.

Comparison groups	Placebo v Teriflunomide 14 mg
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0001 [2]
Method	Regression, Poisson
Parameter estimate	Relative risk
Point estimate	0.637
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.512
upper limit	0.793

Notes:

[1] - Step down approach used to adjust for multiplicity:
- H1 tested first
- H2 tested only if the comparison H1 was statistically significant

[2] - A priori threshold for statistical significance for both comparisons ≤0.05.

Statistical analysis title	Placebo Vs Teriflunomide 7 mg

Statistical analysis description:

Step down approach used to adjust for multiplicity:
- H1 tested first
- H2 tested only if the comparison H1 was statistically significant

Comparison groups	Placebo v Teriflunomide 7 mg

Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0183 [4]
Method	Regression, Poisson
Parameter estimate	Relative risk
Point estimate	0.777
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.958

Notes:

[3] - Step down approach used to adjust for multiplicity: - H1 tested first - H2 tested only if the comparison H1 was statistically significant.
[4] - A prior threshold for statistical significance for both comparisons ≤0.05.

Secondary: Core Treatment Period: Time to Disability Progression Sustained for 12 Weeks

End point title	Core Treatment Period: Time to Disability Progression Sustained for 12 Weeks

End point description:

Probability of disability progression at 24, 48, 108 and 132 weeks was estimated using Kaplan-Meier method on the time to disability progression defined as the time from randomization to first 12-week sustained disability progression [i.e. increase from baseline of at least 1 point in EDSS score (at least 0.5 point for subjects with baseline EDSS score >5.5) that persisted for at least 12 weeks].

Subjects free of disability progression (no disability progression observed on treatment) were censored at the date of the last on-treatment EDSS evaluation.

Kaplan-Meier method consists in computing probabilities of non occurrence of event at any observed time of event and multiplying successive probabilities for time ≤t by any earlier computed probabilities to estimate the probability of being event-free for the amount of time t. Probability of event at time t is 1 minus the probability of being event-free for the amount of time t. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Core treatment period between 48 - 152 weeks depending on time of enrollment

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	388	407	370	
Units: percent probability				
number (confidence interval 95%)				
Probability of disability progression at 24 weeks	8 (5.2 to 10.7)	5.3 (3 to 7.6)	2.7 (0.9 to 4.4)	
Probability of disability progression at 48 weeks	14.2 (10.6 to 17.9)	12.1 (8.7 to 15.5)	7.8 (4.9 to 10.8)	
Probability of disability progression at 108 weeks	19.7 (15.2 to 24.1)	21.1 (16.1 to 26.1)	15.8 (11.2 to 20.4)	
Probability of disability progression at 132 weeks	21 (15.9 to 26)	22.2 (16.8 to 27.6)	15.8 (11.2 to 20.4)	

Statistical analyses

Statistical analysis title	Placebo Vs Teriflunomide 7 mg

Statistical analysis description:

Step down approach: S1 tested only if both comparisons on the primary outcome measure were statistically significant. S2 tested only if the
comparison S1 was statistically significant.

Comparison groups	Placebo v Teriflunomide 7 mg
Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.762 [6]
Method	Logrank

Notes:

[5] - A priori threshold for statistical significance ≤0.05. Two-sided Log-rank test stratified by region of enrollment and baseline EDSS stratum.
[6] - A prior threshold for statistical significance for both comparisons ≤0.05.

Statistical analysis title	Placebo Vs Teriflunomide 14mg

Statistical analysis description:

Null hypothesis: S1: No difference between Teriflunomide 14 mg and placebo. S2: No difference between Teriflunomide 7 mg and placebo. The study was also sized to have 75% power to detect a 37% hazard ratio reduction in time to disability progression with Teriflunomide compared to placebo.

Comparison groups	Placebo v Teriflunomide 14 mg
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0442 [8]
Method	Logrank

Notes:

[7] - Step down approach: S1 tested only if both comparisons on the primary outcome measure were statistically significant. S2 tested only if the
comparison S1 was statistically significant. A priori threshold for statistical significance ≤0.05. Two-sided Log-rank test stratified by region of enrollment and baseline EDSS stratum.
[8] - A prior threshold for statistical significance for both comparisons ≤0.05.

Secondary: Core Treatment Period: Time without relapse

End point title	Core Treatment Period: Time without relapse

End point description:

Probability of no relapse at 24, 48, 108 and 132 weeks was estimated using Kaplan-Meier method on the time to relapse defined as the time from randomization to first EDSS confirmed relapse.

Subjects free of confirmed relapse (no EDSS confirmed relapse observed on treatment) were censored at the date of the last study drug intake. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Core treatment period between 48 - 152 weeks depending on time of enrollment

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	388	407	370	
Units: percent probability				
number (confidence interval 95%)				
Probability of no relapse at 24 weeks	76.4 (72.1 to 80.7)	81.5 (77.6 to 85.4)	85.5 (81.8 to 89.2)	
Probability of no relapse at 48 weeks	60.6 (55.5 to 65.6)	71.9 (67.3 to 76.5)	76.3 (71.7 to 81)	
Probability of no relapse at 108 weeks	46.8 (41 to 52.6)	58.2 (52.6 to 63.8)	57.1 (50.5 to 63.7)	
Probability of no relapse at 132 weeks	37.7 (30.2 to 45.2)	55.4 (48.8 to 62)	51.5 (43.6 to 59.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Change From Baseline to Week 48 in EDSS total Score

End point title	Core Treatment Period: Change From Baseline to Week 48 in EDSS total Score

End point description:

EDSS was an ordinal scale in half-point increments that qualifies disability in subjects with MS. It consists of 8 ordinal rating scales assessing 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation.

EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS).

Baseline adjusted least-squares means at Week 48 were estimated using a Mixed-effect model with repeated measures (MMRM) on EDSS score data (treatment group, region of enrollment, baseline EDSS stratum, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as factors). All the timepoints from randomization up to Week 48 were included in the model. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline (before randomization), Week 12, Week 24, Week 36 and Week 48

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	388	407	370	
Units: units on a scale				
least squares mean (standard error)	0.089 (± 0.05)	0.042 (± 0.049)	-0.05 (± 0.052)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Change From Baseline to Week 48 in Fatigue Impact Scale (FIS) Total Score

End point title	Core Treatment Period: Change From Baseline to Week 48 in Fatigue Impact Scale (FIS) Total Score

End point description:

FIS is a subject-reported scale that qualifies the impact of fatigue on daily life in subjects with MS. It consists of 40 statements that measure fatigue in 3 areas; physical, cognitive, and social.

FIS total score ranges from 0 (no problem) to 160 (extreme problem).

Baseline adjusted least-squares means at Week 48 were estimated using a Mixed-effect model with repeated measures (MMRM) on FIS total score data (treatment group, region of enrollment, baseline EDSS stratum, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as factors). All the timepoints from randomization up to Week 48 were included in the model. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline (before randomization), Week 12, Week 24 and Week 48

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	388	407	370	
Units: units on a scale				
least squares mean (standard error)	4.669 (± 1.576)	2.512 (± 1.533)	1.915 (± 1.628)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Change From Baseline to Last Visit in FIS Total Score

End point title	Core Treatment Period: Change From Baseline to Last Visit in FIS Total Score

End point description:

Baseline adjusted least-squares means at last visit were estimated using an analysis of covariance (ANCOVA) model on collected data for FIS total score (treatment group, region of enrollment, baseline EDSS stratum, visit number for the last visit and baseline value as factors). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline (before randomization) and up to Week 152

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	388	407	370	
Units: units on a scale				
least squares mean (standard error)	6.311 (± 1.671)	4.464 (± 1.657)	2.043 (± 1.682)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Change from Baseline to Week 48 in Short Form Generic Health Survey - 36 items (SF-36) Summary Scores

End point title	Core Treatment Period: Change from Baseline to Week 48 in Short Form Generic Health Survey - 36 items (SF-36) Summary Scores

End point description:

SF-36 scale was a generic, self-administered, health-related quality-of-life (QOL) instrument. It was constructed such that the 36 questions represent 8 of the most important health concepts: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.

Two summary scores were obtained:
- the physical health component summary score,
- the mental health component summary score.

Both scores range from 0 to 100 and a high score indicates a more favourable health state.

Baseline adjusted least-squares means at week 48 were estimated using a MMRM on each summary score data (treatment group, region of enrollment, baseline EDSS stratum, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as factors). All the timepoints from randomization up to Week 48 were included in the model. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline (before randomization), Week 12, Week 24 and Week 48

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	388	407	370	
Units: units on a scale				
least squares mean (standard error)				
Physical health component	-1.082 (± 0.405)	-0.397 (± 0.396)	-0.105 (± 0.418)	
Mental health component	-2.913 (± 0.586)	-2.031 (± 0.571)	-1.434 (± 0.606)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Change From Baseline to Last Visit in SF-36 Summary Scores

End point title	Core Treatment Period: Change From Baseline to Last Visit in SF-36 Summary Scores

End point description:

Baseline adjusted least-squares means at last visit were estimated using ANCOVA model on collected data for each summary score (treatment group, region of enrollment, baseline EDSS stratum, visit number for the last visit and baseline value as factors). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline (before randomization) and up to Week 152

End point values	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	388	407	370	
Units: units on a scale				
least squares mean (standard error)				
Physical Health component	-1.629 (± 0.435)	-0.909 (± 0.441)	-0.638 (± 0.436)	
Mental Health component	-2.792 (± 0.592)	-1.704 (± 0.597)	-1.087 (± 0.593)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Overview of Adverse Events

End point title	Core Treatment Period: Overview of Adverse Events[9]

End point description:

Adverse Events (AE) were any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the subject during the study.
The 3 subjects in the placebo group who received teriflunomide were analyzed according to the teriflunomide dose.
The subject in the Teriflunomide 14 mg group who received 7 mg was analyzed in the Teriflunomide 7 mg group.
Analysis was performed on all randomized and treated subjects. Subjects were considered according to the drug actually received.

End point type	Secondary

End point timeframe:

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

Notes:

[9] - 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: As data is descriptive in nature, no statistical analysis is performed.

End point values	Placebo	Teriflunomide 14 mg	Teriflunomide 7 mg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	385	371	409	
Units: subjects				
number (not applicable)				
Any AE	320	320	344	
- Any serious AE	47	44	52	
- Any AE leading to death	1	2	1	
- Any AE leading to treatment discontinuation	24	58	53	

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Treatment Period: Overview of Treatment Emergent Adverse Events (TEAE)

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

End point description:

AEs were any unfavourable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the subject during the study.
Two subjects in placebo of core study received teriflunomide and were analyzed according to teriflunomide dose.
One subject in teriflunomide 14 mg in core study group who received 7 mg was analyzed in teriflunomide 7 mg group.
Analysis was performed on Safety population: all randomized subjects who received at least 1 dose of investigational product.

End point type	Secondary

End point timeframe:

From first intake of study drug in extension treatment period up to 28 days after the last intake in the extension treatment period

End point values	Placebo / Teriflunomide 14 mg	Teriflunomide 14 mg / 14 mg	Teriflunomide 7 mg / 14 mg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	251	233	267	
Units: subjects				
Any TEAE	203	188	200	
Any serious TEAE	16	29	33	
Any TEAE leading to death	1	1	3	

Any TEAE leading to treatment discontinuation	17	20	17	

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Treatment Period: Time to Disability Progression Sustained for 12 Weeks

End point title	Extension Treatment Period: Time to Disability Progression Sustained for 12 Weeks

End point description:

Probability of disability progression was estimated by Kaplan-Meier method on time to disability progression defined as time from randomization to first 12 week sustained disability progression [i.e. increase from baseline of at least 1 point in EDSS score (at least 0.5 point for subjects with baseline EDSS score >5.5) that persisted for at least 12 weeks]. Subjects free of disability progression were censored at date of the last on-treatment EDSS evaluation. Kaplan-Meier method consists in computing probabilities of non-occurrence of event at any observed time of event and multiplying successive probabilities for time ≤t by any earlier computed probabilities to estimate probability of being event free for amount of time t. Probability of event at time t was 1 minus the probability of being event-free for the amount of time t. Analysis was performed on ITT population (core+extension).

End point type	Secondary

End point timeframe:

Core treatment period (maximum: 173 weeks) and Extension treatment period (maximum: 174 weeks)

End point values	Placebo / Teriflunomide 14 mg	Teriflunomide 7 mg / 14 mg	Teriflunomide 14 mg / 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	265	233	
Units: probability				
number (confidence interval 95%)				
1 year	0.13 (0.089 to 0.172)	0.117 (0.078 to 0.156)	0.077 (0.043 to 0.112)	
2 year	0.19 (0.142 to 0.238)	0.175 (0.129 to 0.221)	0.147 (0.101 to 0.192)	
3 year	0.245 (0.191 to 0.299)	0.233 (0.181 to 0.285)	0.19 (0.139 to 0.241)	
4 year	0.307 (0.246 to 0.368)	0.27 (0.214 to 0.326)	0.248 (0.189 to 0.307)	
5 year	0.328 (0.262 to 0.395)	0.317 (0.25 to 0.384)	0.265 (0.203 to 0.327)	

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Treatment Period: ARR: Poisson Regression Estimate

End point title	Extension Treatment Period: ARR: Poisson Regression Estimate

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. A relapse is defined as the appearance of a new clinical sign/symptom or clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persists for a minimum of 24 hours in the absence of fever. Relapse was confirmed by an increase in EDSS score or Functional System scores. To account for the different treatment durations among subjects, 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). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Extension treatment period (Maximum: 174 weeks)

End point values	Placebo / Teriflunomide 14 mg	Teriflunomide 7 mg / 14 mg	Teriflunomide 14 mg / 14 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	253	265	233	
Units: relapses per year				
number (confidence interval 95%)	0.199 (0.156 to 0.254)	0.2 (0.155 to 0.257)	0.179 (0.132 to 0.243)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Core Treatment Period: Liver Function: Number of Subjects With Potentially Clinically Significant Abnormalities (PCSA)

End point title	Core Treatment Period: Liver Function: Number of Subjects With Potentially Clinically Significant Abnormalities (PCSA)[10]

End point description:

PCSA values were abnormal values considered medically important by the Sponsor according to predefined criteria based on literature review. Hepatic parameters thresholds were defined as follows: Alanine Aminotransferase (ALT) >3, 5, 10 or 20 upper limit of normal(ULN); Aspartate aminotransferase (AST) >3, 5, 10 or 20 ULN; Alkaline Phosphatase >1.5 ULN; Total Bilirubin (TB) >1.5 or 2 ULN; ALT >3 ULN and TB >2 ULN. Analysis was performed on all randomized and treated subjects.

End point type	Other pre-specified

End point timeframe:

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

Notes:

[10] - 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: As data is descriptive in nature, no statistical analysis is performed.

End point values	Placebo	Teriflunomide 14 mg	Teriflunomide 7 mg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	385	371	409	
Units: subjects				
number (not applicable)				
ALT >3 ULN	22	29	31	
ALT >5 ULN	14	11	10	
ALT >10 ULN	5	3	2	
AST >3 ULN	13	9	9	
AST >5 ULN	9	3	3	
Alkaline Phosphatase >1.5 ULN	5	2	4	
TB >1.5 ULN	9	8	6	
ALT >3 ULN and TB >2 ULN	2	0	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from signature of the Informed Consent Form up to the last visit (173 weeks in core treatment period and 174 weeks in extension treatment period) for the study.

Adverse event reporting additional description:

The analysis was performed on the safety population as previously defined and included all AE that developed or worsened and death that occurred during first intake of study drug up to 112 days after the last intake in the core study treatment period and up to 28 days after the last intake in the extension study treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo once daily

Reporting group title	Teriflunomide 7 mg

Reporting group description:

Teriflunomide 7 mg once daily

Reporting group title	Teriflunomide 14 mg

Reporting group description:

Teriflunomide 14 mg once daily

Reporting group title	Placebo/ Teriflunomide 14 mg

Reporting group description:

Core treatment period: Placebo once daily.
Extension treatment period: Teriflunomide 14 mg once daily.

Reporting group title	Teriflunomide 7 mg / 14 mg

Reporting group description:

Core treatment period: Teriflunomide 7 mg once daily.
Extension treatment period: Teriflunomide 14 mg once daily.

Reporting group title	Teriflunomide 14 mg / 14 mg

Reporting group description:

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

Serious adverse events	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 385 (12.21%)	52 / 409 (12.71%)	44 / 371 (11.86%)
number of deaths (all causes)	1	1	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			

subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Papillary Thyroid Cancer			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Acoustic Neuroma			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Invasive Lobular Breast Carcinoma			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Lipoma			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	2 / 371 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Blood Pressure Fluctuation			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock Haemorrhagic			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Ectopic Pregnancy			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
General Physical Health Deterioration			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Pain			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Pyrexia			
subjects affected / exposed	1 / 385 (0.26%)	2 / 409 (0.49%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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 Dysplasia			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Menopausal Symptoms			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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			
Lung Disorder			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Asthma			

subjects affected / exposed	2 / 385 (0.52%)	1 / 409 (0.24%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Haemoptysis			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Lung Consolidation			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Pleural Effusion			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Pulmonary Embolism			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Hypertension			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed Suicide			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Suicide Attempt			

subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	3 / 371 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Depression			
subjects affected / exposed	1 / 385 (0.26%)	1 / 409 (0.24%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major Depression			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental Disorder			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Suicidal Behaviour			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Suicidal Ideation			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine Aminotransferase Increased			

subjects affected / exposed	6 / 385 (1.56%)	6 / 409 (1.47%)	3 / 371 (0.81%)
occurrences causally related to treatment / all	4 / 6	5 / 6	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase Increased			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Enzyme Increased			
subjects affected / exposed	2 / 385 (0.52%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver Function Test Abnormal			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neutrophil Count Decreased			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Platelet Count Decreased			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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	1 / 385 (0.26%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight Decreased			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Intentional Overdose			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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 Injury			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle Fracture			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carbon Monoxide Poisoning			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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

Contusion			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Face Injury			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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	2 / 385 (0.52%)	2 / 409 (0.49%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral Neck Fracture			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Femur Fracture			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Foot Fracture			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Multiple Fractures			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Post Procedural Bile Leak			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Post Procedural Haemorrhage			

subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Postoperative Fever			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Radius Fracture			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Road Traffic Accident			
subjects affected / exposed	0 / 385 (0.00%)	2 / 409 (0.49%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Spinal Compression Fracture			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Splenic Rupture			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Traumatic Lung Injury			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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			
Developmental Hip Dysplasia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Choledochal Cyst			

subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Congenital Flat Feet			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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			
Atrioventricular Block Complete			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Ventricular Tachycardia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Atrial Fibrillation			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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 Occlusion			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Pericardial Effusion			

subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Sinus Bradycardia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Supraventricular Tachycardia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cervicobrachial Syndrome			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Multiple Sclerosis Relapse			
subjects affected / exposed	2 / 385 (0.52%)	1 / 409 (0.24%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial Seizures			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Sciatica			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Status Epilepticus			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Carpal Tunnel Syndrome			

subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Headache			
subjects affected / exposed	3 / 385 (0.78%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Hypoaesthesia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic Coma			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Intracranial Aneurysm			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Intraventricular Haemorrhage			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Neuropathy Peripheral			

subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Polyneuropathy			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Somnolence			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Subarachnoid Haemorrhage			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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	1 / 385 (0.26%)	1 / 409 (0.24%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar Insufficiency			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Microcytic Anaemia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Anaemia			

subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Autoimmune Thrombocytopenia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Disseminated Intravascular Coagulation			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 385 (0.00%)	2 / 409 (0.49%)	3 / 371 (0.81%)
occurrences causally related to treatment / all	0 / 0	2 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Vertigo			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Gastrointestinal disorders			

Gastropleural Fistula			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Haemorrhoids			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Intestinal Obstruction			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Abdominal Distension			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Lower			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Abdominal Pain Upper			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Colitis Ulcerative			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Diarrhoea			

subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Enterocolitis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Gastric Ulcer			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Gastritis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Haematemesis			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Haematochezia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Inguinal Hernia			

subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Small Intestinal Obstruction			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Stress Ulcer			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Vomiting			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	3 / 385 (0.78%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			

subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Chronic			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Gallbladder Perforation			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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 Dysplasia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis Toxic			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice Cholestatic			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Liver Injury			
subjects affected / exposed	1 / 385 (0.26%)	1 / 409 (0.24%)	0 / 371 (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
Non-Alcoholic Steatohepatitis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Glomerulonephritis Chronic			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
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 Artery Stenosis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Renal Cyst			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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			
Adrenal Insufficiency			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Goitre			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Musculoskeletal and connective tissue disorders			
Foot Deformity			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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

Fracture Nonunion			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Knee Deformity			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Back Pain			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Muscle Spasms			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Osteoarthritis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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			
Bronchitis			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Dengue Fever			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Furuncle			

subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Abscess Jaw			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Abscess Soft Tissue			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Appendiceal Abscess			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Sepsis			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cellulitis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Cytomegalovirus Infection			

subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Diarrhoea Infectious			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis Enterococcal			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Escherichia Bacteraemia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Hepatitis C			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Infected Bites			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Influenza			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Lung Abscess			

subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Neuroborreliosis			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Pelvic Abscess			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Perichondritis			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Peritonitis			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal Cyst			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Infection			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Pulmonary Tuberculosis			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Respiratory Tract Infection			
subjects affected / exposed	1 / 385 (0.26%)	1 / 409 (0.24%)	0 / 371 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Salpingo-Oophoritis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Sepsis			

subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Septic Shock			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Staphylococcal Bacteraemia			
subjects affected / exposed	1 / 385 (0.26%)	0 / 409 (0.00%)	0 / 371 (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
Staphylococcal Infection			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Tonsillitis			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis Gastrointestinal			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	2 / 385 (0.52%)	2 / 409 (0.49%)	2 / 371 (0.54%)
occurrences causally related to treatment / all	1 / 2	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Infection			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes Mellitus			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Hyperamylasaemia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Hyperlipasaemia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	0 / 371 (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
Obesity			
subjects affected / exposed	0 / 385 (0.00%)	0 / 409 (0.00%)	1 / 371 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 Diabetes Mellitus			
subjects affected / exposed	0 / 385 (0.00%)	1 / 409 (0.24%)	0 / 371 (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

Serious adverse events	Placebo/ Teriflunomide 14 mg	Teriflunomide 7 mg / 14 mg	Teriflunomide 14 mg / 14 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 251 (6.37%)	33 / 267 (12.36%)	29 / 233 (12.45%)
number of deaths (all causes)	1	3	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Papillary Thyroid Cancer			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acoustic Neuroma			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Invasive Lobular Breast Carcinoma			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Lipoma			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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			
Blood Pressure Fluctuation			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Shock Haemorrhagic			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Ectopic Pregnancy			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
General Physical Health Deterioration			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Pain			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Pyrexia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Immune system disorders			
Anaphylactic Reaction			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Cervical Dysplasia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Menopausal Symptoms			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Cyst			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Lung Disorder			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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

Atelectasis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Haemoptysis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Lung Consolidation			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Pleural Effusion			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Pulmonary Hypertension			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Psychiatric disorders			
Completed Suicide			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
Suicide Attempt			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Major Depression			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Mental Disorder			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Schizophrenia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Suicidal Behaviour			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Suicidal Ideation			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 251 (0.80%)	1 / 267 (0.37%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase Increased			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 251 (0.00%)	3 / 267 (1.12%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Liver Function Test Abnormal			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Neutrophil Count Decreased			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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

Platelet Count Decreased			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Transaminases Increased			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Weight Decreased			
subjects affected / exposed	1 / 251 (0.40%)	1 / 267 (0.37%)	0 / 233 (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
Injury, poisoning and procedural complications			
Intentional Overdose			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Injury			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle Fracture			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Carbon Monoxide Poisoning			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Contusion			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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

Face Injury			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Fall			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Femoral Neck Fracture			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Femur Fracture			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot Fracture			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Multiple Fractures			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Post Procedural Bile Leak			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Post Procedural Haemorrhage			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Postoperative Fever			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Radius Fracture			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Compression Fracture			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Splenic Rupture			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Traumatic Lung Injury			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Congenital, familial and genetic disorders			
Developmental Hip Dysplasia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choledochal Cyst			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Congenital Flat Feet			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular Block Complete			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Tachycardia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Coronary Artery Occlusion			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Myocardial Infarction			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Pericardial Effusion			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Sinus Bradycardia			

subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cervicobrachial Syndrome			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Sclerosis Relapse			
subjects affected / exposed	1 / 251 (0.40%)	1 / 267 (0.37%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial Seizures			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status Epilepticus			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
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 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Coma			

subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Headache			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Hydrocephalus			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Hypoaesthesia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Hypoglycaemic Coma			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Intracranial Aneurysm			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Intraventricular Haemorrhage			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Neuropathy Peripheral			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Polyneuropathy			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Somnolence			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Subarachnoid Haemorrhage			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Syncope			
subjects affected / exposed	1 / 251 (0.40%)	1 / 267 (0.37%)	0 / 233 (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
Vertebrobasilar Insufficiency			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Microcytic Anaemia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Autoimmune Thrombocytopenia			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Disseminated Intravascular Coagulation			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Thrombocytopenia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Vertigo			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastropleural Fistula			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haemorrhoids			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Distension			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Abdominal Pain			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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 Lower			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Abdominal Pain Upper			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Colitis Ulcerative			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Dysphagia			

subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Enterocolitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Gastric Ulcer			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Gastric Ulcer Haemorrhage			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Gastritis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Haematemesis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haematochezia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Small Intestinal Obstruction			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Stress Ulcer			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Vomiting			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Chronic			

subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Gallbladder Perforation			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Hepatic Dysplasia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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 Toxic			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Jaundice Cholestatic			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Liver Injury			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Non-Alcoholic Steatohepatitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Renal and urinary disorders			

Acute Kidney Injury			
subjects affected / exposed	0 / 251 (0.00%)	2 / 267 (0.75%)	0 / 233 (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
Glomerulonephritis Chronic			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Renal Artery Stenosis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Renal Cyst			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal Insufficiency			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Goitre			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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			
Foot Deformity			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture Nonunion			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee Deformity			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back Pain			
subjects affected / exposed	1 / 251 (0.40%)	1 / 267 (0.37%)	0 / 233 (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
Muscle Spasms			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Osteoarthritis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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			
Bronchitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue Fever			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Furuncle			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess Jaw			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Abscess Soft Tissue			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Appendiceal Abscess			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Bacterial Sepsis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Cellulitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Cytomegalovirus Infection			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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 Infectious			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Endocarditis Enterococcal			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Escherichia Bacteraemia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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 C			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Infected Bites			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Influenza			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Lung Abscess			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Neuroborreliosis			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Osteomyelitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Paronychia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Pelvic Abscess			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Perichondritis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Pilonidal Cyst			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 251 (0.00%)	2 / 267 (0.75%)	0 / 233 (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
Pneumonia Bacterial			

subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Post Procedural Infection			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Tuberculosis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 267 (0.00%)	0 / 233 (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
Pyelonephritis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Salpingo-Oophoritis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Sepsis			
subjects affected / exposed	1 / 251 (0.40%)	1 / 267 (0.37%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic Shock			

subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Staphylococcal Bacteraemia			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Staphylococcal Infection			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Tonsillitis			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Tuberculosis Gastrointestinal			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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	0 / 251 (0.00%)	2 / 267 (0.75%)	0 / 233 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Infection			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	1 / 233 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes Mellitus			

subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Hyperamylasaemia			
subjects affected / exposed	0 / 251 (0.00%)	2 / 267 (0.75%)	0 / 233 (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
Hyperlipasaemia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 267 (0.37%)	0 / 233 (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
Obesity			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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
Type 1 Diabetes Mellitus			
subjects affected / exposed	0 / 251 (0.00%)	0 / 267 (0.00%)	0 / 233 (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

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

Non-serious adverse events	Placebo	Teriflunomide 7 mg	Teriflunomide 14 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	247 / 385 (64.16%)	270 / 409 (66.01%)	254 / 371 (68.46%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	27 / 385 (7.01%)	43 / 409 (10.51%)	48 / 371 (12.94%)
occurrences (all)	27	43	48
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	14 / 385 (3.64%)	22 / 409 (5.38%)	23 / 371 (6.20%)
occurrences (all)	14	22	23
Vascular disorders			

Hypertension			
subjects affected / exposed	8 / 385 (2.08%)	17 / 409 (4.16%)	16 / 371 (4.31%)
occurrences (all)	8	17	16
Nervous system disorders			
Headache			
subjects affected / exposed	41 / 385 (10.65%)	61 / 409 (14.91%)	47 / 371 (12.67%)
occurrences (all)	41	61	47
Hypoaesthesia			
subjects affected / exposed	16 / 385 (4.16%)	22 / 409 (5.38%)	23 / 371 (6.20%)
occurrences (all)	16	22	23
Dizziness			
subjects affected / exposed	23 / 385 (5.97%)	17 / 409 (4.16%)	25 / 371 (6.74%)
occurrences (all)	23	17	25
Paraesthesia			
subjects affected / exposed	23 / 385 (5.97%)	27 / 409 (6.60%)	22 / 371 (5.93%)
occurrences (all)	23	27	22
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	10 / 385 (2.60%)	19 / 409 (4.65%)	18 / 371 (4.85%)
occurrences (all)	10	19	18
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	40 / 385 (10.39%)	33 / 409 (8.07%)	37 / 371 (9.97%)
occurrences (all)	40	33	37
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	39 / 385 (10.13%)	45 / 409 (11.00%)	35 / 371 (9.43%)
occurrences (all)	39	45	35
Nausea			
subjects affected / exposed	27 / 385 (7.01%)	38 / 409 (9.29%)	36 / 371 (9.70%)
occurrences (all)	27	38	36
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 385 (3.12%)	21 / 409 (5.13%)	12 / 371 (3.23%)
occurrences (all)	12	21	12
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	16 / 385 (4.16%)	42 / 409 (10.27%)	50 / 371 (13.48%)
occurrences (all)	16	42	50
Psychiatric disorders			
Depression			
subjects affected / exposed	25 / 385 (6.49%)	28 / 409 (6.85%)	18 / 371 (4.85%)
occurrences (all)	25	28	18
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	30 / 385 (7.79%)	28 / 409 (6.85%)	32 / 371 (8.63%)
occurrences (all)	30	28	32
Arthralgia			
subjects affected / exposed	15 / 385 (3.90%)	30 / 409 (7.33%)	20 / 371 (5.39%)
occurrences (all)	15	30	20
Pain In Extremity			
subjects affected / exposed	21 / 385 (5.45%)	19 / 409 (4.65%)	25 / 371 (6.74%)
occurrences (all)	21	19	25
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	65 / 385 (16.88%)	51 / 409 (12.47%)	44 / 371 (11.86%)
occurrences (all)	65	51	44
Influenza			
subjects affected / exposed	19 / 385 (4.94%)	22 / 409 (5.38%)	22 / 371 (5.93%)
occurrences (all)	19	22	22
Urinary Tract Infection			
subjects affected / exposed	36 / 385 (9.35%)	38 / 409 (9.29%)	26 / 371 (7.01%)
occurrences (all)	36	38	26
Sinusitis			
subjects affected / exposed	16 / 385 (4.16%)	25 / 409 (6.11%)	24 / 371 (6.47%)
occurrences (all)	16	25	24
Upper Respiratory Tract Infection			
subjects affected / exposed	42 / 385 (10.91%)	35 / 409 (8.56%)	33 / 371 (8.89%)
occurrences (all)	42	35	33

Non-serious adverse events	Placebo/ Teriflunomide 14 mg	Teriflunomide 7 mg / 14 mg	Teriflunomide 14 mg / 14 mg
Total subjects affected by non-serious adverse events			

subjects affected / exposed	152 / 251 (60.56%)	153 / 267 (57.30%)	138 / 233 (59.23%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	27 / 251 (10.76%)	8 / 267 (3.00%)	9 / 233 (3.86%)
occurrences (all)	27	8	9
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 251 (1.59%)	7 / 267 (2.62%)	7 / 233 (3.00%)
occurrences (all)	4	7	7
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 251 (3.98%)	13 / 267 (4.87%)	12 / 233 (5.15%)
occurrences (all)	10	13	12
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 251 (3.98%)	15 / 267 (5.62%)	17 / 233 (7.30%)
occurrences (all)	10	15	17
Hypoaesthesia			
subjects affected / exposed	12 / 251 (4.78%)	6 / 267 (2.25%)	8 / 233 (3.43%)
occurrences (all)	12	6	8
Dizziness			
subjects affected / exposed	3 / 251 (1.20%)	8 / 267 (3.00%)	4 / 233 (1.72%)
occurrences (all)	3	8	4
Paraesthesia			
subjects affected / exposed	12 / 251 (4.78%)	5 / 267 (1.87%)	4 / 233 (1.72%)
occurrences (all)	12	5	4
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 251 (0.80%)	13 / 267 (4.87%)	20 / 233 (8.58%)
occurrences (all)	2	13	20
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 251 (3.59%)	12 / 267 (4.49%)	6 / 233 (2.58%)
occurrences (all)	9	12	6
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	14 / 251 (5.58%)	18 / 267 (6.74%)	20 / 233 (8.58%)
occurrences (all)	14	18	20
Nausea			
subjects affected / exposed	14 / 251 (5.58%)	10 / 267 (3.75%)	8 / 233 (3.43%)
occurrences (all)	14	10	8
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 251 (1.99%)	6 / 267 (2.25%)	3 / 233 (1.29%)
occurrences (all)	5	6	3
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	36 / 251 (14.34%)	6 / 267 (2.25%)	5 / 233 (2.15%)
occurrences (all)	36	6	5
Psychiatric disorders			
Depression			
subjects affected / exposed	8 / 251 (3.19%)	15 / 267 (5.62%)	10 / 233 (4.29%)
occurrences (all)	8	15	10
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	12 / 251 (4.78%)	13 / 267 (4.87%)	13 / 233 (5.58%)
occurrences (all)	12	13	13
Arthralgia			
subjects affected / exposed	7 / 251 (2.79%)	9 / 267 (3.37%)	9 / 233 (3.86%)
occurrences (all)	7	9	9
Pain In Extremity			
subjects affected / exposed	7 / 251 (2.79%)	9 / 267 (3.37%)	9 / 233 (3.86%)
occurrences (all)	7	9	9
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	22 / 251 (8.76%)	21 / 267 (7.87%)	22 / 233 (9.44%)
occurrences (all)	22	21	22
Influenza			
subjects affected / exposed	8 / 251 (3.19%)	14 / 267 (5.24%)	16 / 233 (6.87%)
occurrences (all)	8	14	16
Urinary Tract Infection			

subjects affected / exposed	8 / 251 (3.19%)	12 / 267 (4.49%)	10 / 233 (4.29%)
occurrences (all)	8	12	10
Sinusitis			
subjects affected / exposed	5 / 251 (1.99%)	10 / 267 (3.75%)	9 / 233 (3.86%)
occurrences (all)	5	10	9
Upper Respiratory Tract Infection			
subjects affected / exposed	11 / 251 (4.38%)	12 / 267 (4.49%)	7 / 233 (3.00%)
occurrences (all)	11	12	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2008	Following changes were made: Eliminated the interferon calibrator arm from the study design and formal assessment of mood disorders; -Addition of human immunodeficiency virus (HIV) testing at screening and annually; - Removed secondary efficacy variables: Hospital Anxiety and Depression Scale and Suicidality Tracking Scale from the statistical section;- Revised inclusion criteria to assure that subjects were properly informed of alternate available treatment options; - Changed the plan of coding AEs into 4 levels: Preferred Term (PT), High Level Group Term (HLGT), High Level Term (HLT) and primary System Organ Class (SOC) instead of 2 levels: PT and SOC; - Updated the contraception requirements for subjects to reflect methods that were more in line with International Conference on Harmonization (ICH) M3 guidelines; -Clarified the required qualifications for the examining neurologist; - Clarified the method for collecting symptoms related to multiple sclerosis relapses; - Updated and clarified the procedure to handle premature withdrawals for time to disability progression analysis.
01 July 2009	-Implemented pulmonary function testing in a subset of subjects to aid in documentation of the safety profile of the compound in regard to pulmonary disease; - Added optional pharmacogenomic teriflunomide testing with aims at assessing the association between the main enzyme systems of teriflunomide metabolism and hepatic safety, and other potential associations between gene variations and clinical outcomes; - clarified the procedure for handling subjects who were screen failures and were not randomized.
07 October 2009	Expanded the population of subjects who had opt to participate in the pharmacogenomic testing to include any randomized subject at any stage of the study.
19 January 2011	-Changed the time-point for confirmation of disability progression to 12 weeks instead of 24 weeks; - Added other secondary efficacy variables: time to first confirmed relapse; proportion of subjects without relapse; proportion of subjects free of disability progression at 6 months, 1 year and 2 years; change from baseline in EDSS; - Added analysis of ARR and time to disability progression using the per protocol (PP) population; - Added an interim analysis to provide additional evidence on the benefit/risk of teriflunomide for regulatory purposes; - Added a few subject disposition categories; - Specified the methods of the extension study to include dose of teriflunomide duration of extension, and frequency of liver and pancreatic monitoring; - Shortened the teriflunomide elimination (washout) period from 16 weeks to 4 weeks in order to allow subjects to terminate treatment more rapidly; - Modified the exclusion criteria and concomitant medication restrictions based on updated drug interactions data; - Added peripheral neuropathy confirmed by electrophysiological tests as an alert term to provide better documentation on the cases; - Corrected inconsistencies throughout the protocol; - Added an exploratory investigation of specific cell surface marker expression on T-cell and B-cell lymphocytes populations.
12 April 2012	-This amendment applied to the extension study only; - Extended the current duration of the extension study until teriflunomide was commercially available in the country where the subject lives; - Changed the name of the company from Sanofi-Aventis to Sanofi; - Added a digital photographic documentation of the scalp of subjects in the extension study with hair thinning who voluntarily agreed upon; Clarified how the confirmation of disease progression was done.
27 June 2012	-This amendment applied to the extension study only; - Extended the duration of the study so that the extension lasted until the last enrolled subject in this open-label portion completed 84 weeks of treatment.

24 January 2013	-This amendment applied to the extension study only; - Reduction of scheduled study visits and visit contents for subjects who have completed a minimum 18 months/72 weeks in extension phase; - Clinical visits were performed every 24 weeks up to the EOT and included: AE reporting, recording of concomitant medication, vital signs, physical examination, dispense study drugs, EDSS / FS and clinical laboratory only at EOT visit. Laboratory visits were not to be performed except EOT visit; -Clarification that if the subject continued on teriflunomide by obtaining it commercially after ending in this extension study, no accelerated elimination procedure was required, and the last visit was the EOT visit; follow-up visits were not required; - Dosage reduction of activated charcoal for accelerated elimination procedure (reduced from 50g 4 times daily for 11 days to 50g twice daily for 11 days).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24461574