Clinical trial results:
A Multi-center, Randomized, Parallel-group, Rater-blinded Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis Plus a Long Term Extension Period

Summary

EudraCT number	2008-006226-34
Trial protocol	ES DE HU CZ IT GR FR BE GB
Global end of trial date	13 May 2015

Results information

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

Trial information

Trial identification

Sponsor protocol code	EFC10891

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00883337
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: TENERE

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette Chilly, Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effectiveness of 2 doses of teriflunomide in comparison to interferon-beta 1 a, evaluated by the time to failure, with failure being defined as either relapse or permanent study treatment discontinuation for any cause whichever comes first.

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 in, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 April 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 62
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 55
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Tunisia: 1
Worldwide total number of subjects	324
EEA total number of subjects	301

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)	323
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment initiated in April 2009 was completed in July 2010. A total of 369 subjects were screened at 54 sites in 13 countries. The common end date of core treatment period was 14 September 2011 (maximum treatment duration of 115 weeks). The end date of extension was 13 May 2015 (maximum treatment duration of 197 weeks).

Pre-assignment

Screening details:

Randomization was stratified by country and baseline disability (Expanded Disability Status Scale [EDSS] score ≤3.5 or >3.5). Assignment to groups was done centrally using an Interactive Voice Response System (IVRS] in a 1:1:1 ratio after confirmation of the selection criteria. 324 subjects were randomized at 53 sites.

Period 1

Period 1 title	Core Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	Teriflunomide 7 mg

Arm description:

Teriflunomide 7 mg once daily for 48 weeks.

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 for 48 weeks.

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. One Subject received teriflunomide 7 mg instead of teriflunomide 14 mg.

Arm title	Interferon beta-1-a (IFN-β-1a)

Arm description:

IFN-β-1a three times a week for 48 weeks.

Arm type	Active comparator
Investigational medicinal product name	Interferon beta-1a
Investigational medicinal product code	
Other name	Rebif®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IFN-β-1a subcutaneous (SC) injection at the same time on the same three days in the late afternoon or evening. Three subjects refused treatment with Rebif®.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: As per the trial design only assessor was blinded in the study.

Number of subjects in period 1	Teriflunomide 7 mg	Teriflunomide 14 mg	Interferon beta-1-a (IFN-β-1a)
Started	109	111	104
Treated	109	111	101
Completed	89	89	71
Not completed	20	22	33
Other than specified above	-	1	1
Adverse event	9	12	22
Poor compliance to protocol	-	-	1
Lost to follow-up	1	1	-
Wish to be pregnant	1	2	1
Lack of efficacy	7	4	2
Withdrawal by subject	2	2	6

Period 2

Period 2 title	Extension Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[2]

Arms

Are arms mutually exclusive?	Yes
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.

Arm title	IFN-β-1a / Teriflunomide 14 mg

Arm description:

Subjects received IFN-β-1a three times a week 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.

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: As per the trial design only assessor was blinded in the study.

Number of subjects in period 2[3]	Teriflunomide 7 mg / 14 mg	Teriflunomide 14 mg / 14 mg	IFN-β-1a / Teriflunomide 14 mg
Started	89	89	59
Completed	61	66	40
Not completed	28	23	19
Other than specified above	10	9	5
Adverse event	8	5	5
Poor compliance to protocol	1	1	1
Lost to follow-up	1	-	-
Lack of efficacy	8	8	8

Notes:

[3] - 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: 12 subjects completed the core period but didn't enter the extension period.

Baseline characteristics

Reporting groups	
Reporting group title	Teriflunomide 7 mg
Reporting group description:	
Teriflunomide 7 mg once daily for 48 weeks.	
Reporting group title	Teriflunomide 14 mg
Reporting group description:	
Teriflunomide 14 mg once daily for 48 weeks.	
Reporting group title	Interferon beta-1-a (IFN-β-1a)
Reporting group description:	
IFN-β-1a three times a week for 48 weeks.	

Reporting group values	Teriflunomide 7 mg	Teriflunomide 14 mg	Interferon beta-1-a (IFN-β-1a)
Number of subjects	109	111	104
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	32.5	36.8	37
standard deviation	± 9.2	± 10.3	± 10.6
Gender categorical Units: Subjects			
Female	70	78	71
Male	39	33	33
Region of Enrollment			
Due the small sample size in some countries, the countries were pooled as follows: - North America: Canada; - Eastern Europe: Czech Republic, Greece, Hungary and Poland; - Western Europe: Belgium, France, Germany, Italy, Spain, Switzerland and United Kingdom; subject in Tunisia was included in the Western Europe group.			
Units: Subjects			
North America	8	6	7
Eastern Europe	39	41	35
Western Europe	62	64	62
Multiple Sclerosis (MS) subtype Units: Subjects			
Relapsing Remitting	109	108	104
Secondary Progressive	0	1	0
Progressive Relapsing	0	2	0
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 seven functional systems (visual, brain-stem, 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	96	95	93
>3.5	13	16	11

Time since first diagnosis of MS			
Units: years			
arithmetic mean	3.72	3.68	3.82
standard deviation	± 5.19	± 6.24	± 5.69
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	9	7.9	9.79
standard deviation	± 13.96	± 10.34	± 10.72
Number of MS relapses within the past year			
Units: relapses			
median	1	1	1
full range (min-max)	0 to 3	0 to 4	0 to 5
Number of MS relapses within the past 2 years			
Units: relapses			
median	2	2	2
full range (min-max)	0 to 4	0 to 4	0 to 6

Reporting group values	Total		
Number of subjects	324		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	219		
Male	105		
Region of Enrollment			
Due the small sample size in some countries, the countries were pooled as follows: - North America: Canada; - Eastern Europe: Czech Republic, Greece, Hungary and Poland; - Western Europe: Belgium, France, Germany, Italy, Spain, Switzerland and United Kingdom; subject in Tunisia was included in the Western Europe group.			
Units: Subjects			
North America	21		
Eastern Europe	115		
Western Europe	188		
Multiple Sclerosis (MS) subtype			
Units: Subjects			
Relapsing Remitting	321		
Secondary Progressive	1		
Progressive Relapsing	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 seven functional systems (visual, brain-stem, 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	284		
>3.5	40		
Time since first diagnosis of MS Units: years arithmetic mean standard deviation	- -		
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	- -		
Number of MS relapses within the past year Units: relapses median full range (min-max)	- -		
Number of MS relapses within the past 2 years Units: relapses median full range (min-max)	- -		

End points

End points reporting groups

Reporting group title	Teriflunomide 7 mg
Reporting group description:	
Teriflunomide 7 mg once daily for 48 weeks.	
Reporting group title	Teriflunomide 14 mg
Reporting group description:	
Teriflunomide 14 mg once daily for 48 weeks.	

Reporting group title	Interferon beta-1-a (IFN-β-1a)
Reporting group description:	
IFN-β-1a three times a week for 48 weeks.	
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.	
Reporting group title	IFN-β-1a / Teriflunomide 14 mg
Reporting group description:	
Subjects received IFN-β-1a three times a week in core treatment period and teriflunomide 14 mg once daily in extension treatment period.	
Subject analysis set title	Teriflunomide 7 mg / 14 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received teriflunomide 7 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.	
Subject analysis set title	Teriflunomide 7 mg / 14 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received teriflunomide 7 mg once daily in core treatment period and teriflunomide 14 mg once daily in extension treatment period.	

Primary: Core Treatment Period: Overview of Failures

End point title	Core Treatment Period: Overview of Failures[1]
End point description:	
Failure was defined as the first occurrence of confirmed relapse or permanent treatment discontinuation (for any cause) which ever came first. If no events occurred, the subject was considered free of failure. 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. Intent-to-treat population: all randomized 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 and 118 weeks depending on when the subject was enrolled	

Notes:

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

End point values	Teriflunomide 7 mg	Teriflunomide 14 mg	Interferon beta-1-a (IFN-β-1a)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	111	104	
Units: Subjects				
Failure	53	42	44	
Free of Failure	56	69	60	

Statistical analyses

No statistical analyses for this end point

Primary: Core Treatment Period: Time to Failure: KaplanMeier Estimates of the Rate of Failure at Timepoints

End point title	Core Treatment Period: Time to Failure: KaplanMeier Estimates of the Rate of Failure at Timepoints

End point description:

Probability of disability progression at 24, 48 and 96 weeks was estimated using Kaplan-Meier method on the time to failure defined as the time from randomization to failure. Subjects free of failure were censored at the date of last treatment. 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. ITT population.

End point type	Primary

End point timeframe:

Core treatment period between 48 and 118 weeks depending on when the subject was enrolled

End point values	Teriflunomide 7 mg	Teriflunomide 14 mg	Interferon beta-1-a (IFN-β-1a)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	111	104	
Units: Percent probability				
number (confidence interval 95%)				
Probability of failure at 24 weeks	25.7 (17.5 to 33.9)	24.3 (16.3 to 32.3)	29.8 (21 to 38.6)	
Probability of failure at 48 weeks	35.8 (26.8 to 44.8)	33.3 (24.6 to 42.1)	36.5 (27.3 to 45.8)	
Probability of failure at 96 weeks	58.8 (46.1 to 71.4)	41.1 (30.9 to 51.4)	44.4 (34.3 to 54.4)	

Statistical analyses

Statistical analysis title	Teriflunomide 14 mg vs IFNβ-1-a

Statistical analysis description:

The study was sized to detect a difference between teriflunomide and Rebif groups in the time to failure at a significance level of 0.025 with a power of 81%.

Null hypothesis:
H1: No difference between teriflunomide 14 mg and Rebif
H2: No difference between teriflunomide 7 mg and Rebif

Comparison groups	Teriflunomide 14 mg v Interferon beta-1-a (IFN-β-1a)
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.5953 [3]
Method	Logrank

Notes:

[2] - Hochberg testing procedure:
-a-priori threshold for statistical significance ≤0.05 for the largest p-value of the 2 pair-wise comparisons.
-a-priori threshold for statistical significance ≤0.025 for the other p-value, if the largest p-value >0.05.
[3] - Two-sided Log Rank test with the region of enrollment and baseline EDSS stratum as stratification factors.

Statistical analysis title	Teriflunomide 7 mg vs IFNβ-1-a

Statistical analysis description:

Null hypothesis:
-H1: No difference between teriflunomide 14 mg and Rebif
-H2: No difference between teriflunomide 7 mg and Rebif

Comparison groups	Teriflunomide 7 mg v Interferon beta-1-a (IFN-β-1a)
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.519 [5]
Method	Logrank

Notes:

[4] - Hochberg testing procedure:
-a-priori threshold for statistical significance ≤0.05 for the largest p-value of the 2 pair-wise comparisons.
-a-priori threshold for statistical significance ≤0.025 for the other p-value, if the largest p-value >0.05.
[5] - Two-sided Log Rank test with the region of enrollment and baseline EDSS stratum as stratification factors.

Secondary: Core Treatment Period: Annualized Relapse Rate [ARR] - Poisson Regression Estimates

End point title	Core Treatment Period: Annualized Relapse Rate [ARR] - Poisson Regression Estimates

End point description:

ARR is obtained from the total number of confirmed relapses that occurred during the treatment period divided by the sum of the treatment durations. 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 enrollment and baseline EDSS stratum as covariates). ITT population.

End point type	Secondary

End point timeframe:

Core treatment period between 48 and 118 weeks depending on when the subject was enrolled.

End point values	Teriflunomide 7 mg	Teriflunomide 14 mg	Interferon beta-1-a (IFN-β-1a)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	111	104	
Units: Relapses per year				
number (confidence interval 95%)	0.41 (0.265 to 0.636)	0.259 (0.153 to 0.438)	0.216 (0.113 to 0.415)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Core Treatment Period: Change From Baseline 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 three areas; physical, cognitive, and social. FIS total score ranges from 0 (no problem) to 160 (extreme problem). Least-square means were estimated using a Mixed-effect model with repeated measures [MMRM] on FIS total score data (treatment group, region of enrollment, baseline EDSS stratum, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as factors). ITT population.

End point type	Secondary

End point timeframe:

Baseline (before randomization) and 48 weeks

End point values	Teriflunomide 7 mg	Teriflunomide 14 mg	Interferon beta-1-a (IFN-β-1a)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	111	104	
Units: Units on a scale				
least squares mean (standard error)	0.97 (± 2.96)	4.1 (± 3.03)	9.1 (± 3.21)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Treatment Satisfaction Questionnaire for Medication [TSQM] Scores

End point title	Core Treatment Period: Treatment Satisfaction Questionnaire for Medication [TSQM] Scores

End point description:

TSQM version 1.4 is an instrument to assess subjects' satisfaction with medication. It consists of 13 questions that cover three dimensions (effectiveness, side effects and convenience) plus a global satisfaction question. Four scores ranging from 0 to 100 (extremely satisfied) are obtained. Least-square means were estimated using a MMRM on TSQM score data (treatment group, region of

enrollment, baseline EDSS stratum, visit, treatment-by-visit interaction as factors). ITT population.

End point type	Secondary

End point timeframe:

48 weeks

End point values	Teriflunomide 7 mg	Teriflunomide 14 mg	Interferon beta-1-a (IFN-β-1a)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	111	104	
Units: Units on a scale				
least squares mean (standard error)				
Effectivness score	67.25 (± 2.7)	63.13 (± 2.75)	59.3 (± 2.97)	
Side effects score	95.29 (± 2.31)	93.15 (± 2.34)	71.38 (± 2.5)	
Convenience score	88.3 (± 1.97)	89.85 (± 1.98)	61.9 (± 2.11)	
Global satisfaction score	68.29 (± 2.77)	68.82 (± 2.78)	60.98 (± 2.94)	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Overview of Adverse Events [AEs]

End point title	Core Treatment Period: Overview of Adverse Events [AEs][6]

End point description:

AEs were any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the subject during the study. Safety population: all randomized and treated subjects. Subjects were considered according to the drug actually received. The subject randomized to teriflunomide 14 mg group who received teriflunomide 7 mg was analyzed in the teriflunomide 7 mg group.

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:

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

End point values	Teriflunomide 14 mg	Interferon beta-1-a (IFN-β-1a)	Teriflunomide 7 mg / 14 mg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	110	101	110	
Units: subjects				
Any AE	102	97	103	
Any serious AE	6	7	12	
Any AE leading to death	0	0	0	
Any AE leading to treatment discontinuation	12	22	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Treatment Period: Overview of AEs

End point title	Extension Treatment Period: Overview of AEs

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. Safety population: subjects were considered in the treatment group to which they were randomized regardless of the drug they actually received.

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	Teriflunomide 14 mg / 14 mg	IFN-β-1a / Teriflunomide 14 mg	Teriflunomide 7 mg / 14 mg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	88	59	90	
Units: subjects				
Any AE	76	48	83	
Any serious AE	13	12	9	
Any AE leading to death	0	0	0	
Any AE leading to treatment discontinuation	6	5	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Treatment Period: ARR Poisson Regression Estimates

End point title	Extension Treatment Period: ARR Poisson Regression Estimates

End point description:

ARR was obtained from the total number of confirmed relapses that occurred during the treatment period divided by the sum of the standardized treatment durations. 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 enrollment and baseline EDSS stratum as covariates). ITT population.

End point type	Secondary

End point timeframe:

Extension treatment period (Maximum: 197 weeks)

End point values	Teriflunomide 14 mg / 14 mg	IFN-β-1a / Teriflunomide 14 mg	Teriflunomide 7 mg / 14 mg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	89	59	89	
Units: Relapses per year				
number (confidence interval 95%)	0.193 (0.121 to 0.307)	0.252 (0.145 to 0.438)	0.236 (0.154 to 0.362)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 197) regardless of seriousness or relationship to Investigational Medicinal Product (IMP).

Adverse event reporting additional description:

The analysis was performed on the safety population as previously defined. Reported adverse events are treatment emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (up to 28 days after the last intake of IMP in the extension study treatment period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Core Treatment: Teriflunomide 7 mg

Reporting group description:

Teriflunomide 7 mg once daily (mean exposure of 456.62 days).

Reporting group title	Core Treatment:Teriflunomide 14 mg

Reporting group description:

Teriflunomide 14 mg once daily (mean exposure of 434.43 days).

Reporting group title	Core Treatment: IFN-β-1a

Reporting group description:

Interferon β-1a 3 times a week (mean exposure of 405.18 days).

Reporting group title	Extended Treatment: Teriflunomide 14 mg (After IFN-β-1a)

Reporting group description:

Teriflunomide 14 mg once daily in extended treatment period after Interferon β-1a 3 times a week in core treatment period (mean exposure of 1000.03 days).

Reporting group title	Extended Treatment: Teriflunomide 14 mg (After 7 mg)

Reporting group description:

Teriflunomide 14 mg once daily in extended treatment period after 7 mg in the core treatment period (mean exposure of 996.76 days).

Reporting group title	Extended Treatment: Teriflunomide 14 mg (After 14 mg)

Reporting group description:

Teriflunomide 14 mg once daily in extended treatment period after 14 mg in core treatment period (mean exposure of 1015.32 days).

Serious adverse events	Core Treatment: Teriflunomide 7 mg	Core Treatment:Terifluno	Core Treatment: IFN-β-1a
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 110 (10.91%)	6 / 110 (5.45%)	7 / 101 (6.93%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Leiomyoma			

subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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 Leiomyosarcoma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Varicose Vein			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep Vein Thrombosis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous Stenosis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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			
Gait Disturbance			

subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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			
Drug Hypersensitivity			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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			
Uterine Haemorrhage			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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 Polyp			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Nasal Septum Deviation			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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			
Suicide Attempt			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomania			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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	3 / 110 (2.73%)	1 / 110 (0.91%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm Fracture			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 101 (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
Cardiac disorders			
Coronary Artery Disease			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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 Tachycardia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 101 (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

Nervous system disorders			
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic Stroke			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic Neuritis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 101 (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
Sciatica			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal Neuralgia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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			
Thrombocytopenia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 101 (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

Neutropenia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	0 / 101 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye Oedema			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 101 (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
Optic Ischaemic Neuropathy			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 101 (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			
Duodenal Perforation			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's Disease			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 101 (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
Intestinal Obstruction			

subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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			
Cholecystitis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema Nodosum			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Disorder			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	1 / 101 (0.99%)
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 / 110 (0.00%)	1 / 110 (0.91%)	0 / 101 (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 Osteoarthritis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis Perforated			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Pyelonephritis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	0 / 101 (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
Anal Abscess			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	1 / 101 (0.99%)
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 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Infection			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	0 / 101 (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
Chronic Sinusitis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	0 / 101 (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
Meningitis Bacterial			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
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			
Hyperkalaemia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Extended Treatment: Teriflunomide 14 mg (After IFN-β-1a)	Extended Treatment: Teriflunomide 14 mg (After 7 mg)	Extended Treatment: Teriflunomide 14 mg (After 14 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 59 (20.34%)	9 / 90 (10.00%)	13 / 88 (14.77%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Leiomyoma			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyosarcoma			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Varicose Vein			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep Vein Thrombosis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	0 / 88 (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
Haematoma			

subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Venous Stenosis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Gait Disturbance			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	0 / 88 (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
Reproductive system and breast disorders			
Uterine Haemorrhage			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Polyp			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Nasal Septum Deviation			

subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Psychiatric disorders			
Suicide Attempt			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomania			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 59 (0.00%)	2 / 90 (2.22%)	0 / 88 (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
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Forearm Fracture			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
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			
Coronary Artery Disease			

subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Tachycardia			
subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	0 / 88 (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
Supraventricular Tachycardia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic Stroke			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic Neuritis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	0 / 88 (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
Sciatica			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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	0 / 59 (0.00%)	1 / 90 (1.11%)	0 / 88 (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
Trigeminal Neuralgia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
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 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye Oedema			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic Ischaemic Neuropathy			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Duodenal Perforation			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's Disease			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
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 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Skin and subcutaneous tissue disorders			
Erythema Nodosum			
subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	0 / 88 (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
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			

subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	0 / 88 (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
Musculoskeletal and connective tissue disorders			
Foot Deformity			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
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 Disorder			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Intervertebral Disc Protrusion			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Spinal Osteoarthritis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Infections and infestations			
Appendicitis Perforated			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Pyelonephritis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
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			
subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Abscess			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
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 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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 Infection			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Cellulitis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	0 / 88 (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
Cervicitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Sinusitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis Bacterial			

subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Pyelonephritis Acute			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	0 / 88 (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
Urinary Tract Infection			
subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	0 / 88 (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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Core Treatment: Teriflunomide 7 mg	Core Treatment:Terifluno	Core Treatment: IFN-β-1a
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 110 (77.27%)	92 / 110 (83.64%)	92 / 101 (91.09%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 110 (0.00%)	5 / 110 (4.55%)	4 / 101 (3.96%)
occurrences (all)	0	5	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 110 (6.36%)	6 / 110 (5.45%)	5 / 101 (4.95%)
occurrences (all)	7	6	5

Asthenia			
subjects affected / exposed	3 / 110 (2.73%)	1 / 110 (0.91%)	9 / 101 (8.91%)
occurrences (all)	3	1	9
Pyrexia			
subjects affected / exposed	10 / 110 (9.09%)	2 / 110 (1.82%)	3 / 101 (2.97%)
occurrences (all)	10	2	3
Influenza Like Illness			
subjects affected / exposed	4 / 110 (3.64%)	4 / 110 (3.64%)	49 / 101 (48.51%)
occurrences (all)	4	4	49
Injection Site Erythema			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	10 / 101 (9.90%)
occurrences (all)	0	0	10
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	3 / 110 (2.73%)	6 / 110 (5.45%)	1 / 101 (0.99%)
occurrences (all)	3	6	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 110 (6.36%)	4 / 110 (3.64%)	1 / 101 (0.99%)
occurrences (all)	7	4	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 110 (6.36%)	1 / 110 (0.91%)	5 / 101 (4.95%)
occurrences (all)	7	1	5
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	12 / 110 (10.91%)	9 / 110 (8.18%)	30 / 101 (29.70%)
occurrences (all)	12	9	30
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 110 (5.45%)	2 / 110 (1.82%)	2 / 101 (1.98%)
occurrences (all)	6	2	2
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	6 / 110 (5.45%)	3 / 110 (2.73%)	2 / 101 (1.98%)
occurrences (all)	6	3	2

Dizziness			
subjects affected / exposed	4 / 110 (3.64%)	1 / 110 (0.91%)	6 / 101 (5.94%)
occurrences (all)	4	1	6
Headache			
subjects affected / exposed	23 / 110 (20.91%)	17 / 110 (15.45%)	26 / 101 (25.74%)
occurrences (all)	23	17	26
Sciatica			
subjects affected / exposed	0 / 110 (0.00%)	0 / 110 (0.00%)	3 / 101 (2.97%)
occurrences (all)	0	0	3
Paraesthesia			
subjects affected / exposed	14 / 110 (12.73%)	11 / 110 (10.00%)	8 / 101 (7.92%)
occurrences (all)	14	11	8
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 110 (0.91%)	2 / 110 (1.82%)	4 / 101 (3.96%)
occurrences (all)	1	2	4
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 110 (0.91%)	1 / 110 (0.91%)	2 / 101 (1.98%)
occurrences (all)	1	1	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	19 / 110 (17.27%)	17 / 110 (15.45%)	9 / 101 (8.91%)
occurrences (all)	19	17	9
Abdominal Pain			
subjects affected / exposed	5 / 110 (4.55%)	7 / 110 (6.36%)	2 / 101 (1.98%)
occurrences (all)	5	7	2
Abdominal Pain Upper			
subjects affected / exposed	7 / 110 (6.36%)	7 / 110 (6.36%)	3 / 101 (2.97%)
occurrences (all)	7	7	3
Nausea			
subjects affected / exposed	10 / 110 (9.09%)	10 / 110 (9.09%)	4 / 101 (3.96%)
occurrences (all)	10	10	4
Dyspepsia			
subjects affected / exposed	4 / 110 (3.64%)	4 / 110 (3.64%)	0 / 101 (0.00%)
occurrences (all)	4	4	0
Vomiting			

subjects affected / exposed	6 / 110 (5.45%)	9 / 110 (8.18%)	4 / 101 (3.96%)
occurrences (all)	6	9	4
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 110 (5.45%)	22 / 110 (20.00%)	1 / 101 (0.99%)
occurrences (all)	6	22	1
Renal and urinary disorders			
Micturition Urgency			
subjects affected / exposed	2 / 110 (1.82%)	3 / 110 (2.73%)	1 / 101 (0.99%)
occurrences (all)	2	3	1
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	10 / 110 (9.09%)	11 / 110 (10.00%)	7 / 101 (6.93%)
occurrences (all)	10	11	7
Pain In Extremity			
subjects affected / exposed	11 / 110 (10.00%)	7 / 110 (6.36%)	4 / 101 (3.96%)
occurrences (all)	11	7	4
Arthralgia			
subjects affected / exposed	6 / 110 (5.45%)	7 / 110 (6.36%)	4 / 101 (3.96%)
occurrences (all)	6	7	4
Muscle Spasms			
subjects affected / exposed	6 / 110 (5.45%)	5 / 110 (4.55%)	3 / 101 (2.97%)
occurrences (all)	6	5	3
Myalgia			
subjects affected / exposed	2 / 110 (1.82%)	3 / 110 (2.73%)	7 / 101 (6.93%)
occurrences (all)	2	3	7
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	26 / 110 (23.64%)	24 / 110 (21.82%)	17 / 101 (16.83%)
occurrences (all)	26	24	17
Urinary Tract Infection			
subjects affected / exposed	8 / 110 (7.27%)	3 / 110 (2.73%)	6 / 101 (5.94%)
occurrences (all)	8	3	6
Bronchitis			
subjects affected / exposed	8 / 110 (7.27%)	4 / 110 (3.64%)	2 / 101 (1.98%)
occurrences (all)	8	4	2

Upper Respiratory Tract Infection			
subjects affected / exposed	8 / 110 (7.27%)	11 / 110 (10.00%)	9 / 101 (8.91%)
occurrences (all)	8	11	9
Oral Herpes			
subjects affected / exposed	9 / 110 (8.18%)	0 / 110 (0.00%)	2 / 101 (1.98%)
occurrences (all)	9	0	2
Pharyngitis			
subjects affected / exposed	8 / 110 (7.27%)	1 / 110 (0.91%)	3 / 101 (2.97%)
occurrences (all)	8	1	3
Influenza			
subjects affected / exposed	8 / 110 (7.27%)	9 / 110 (8.18%)	5 / 101 (4.95%)
occurrences (all)	8	9	5
Ear Infection			
subjects affected / exposed	3 / 110 (2.73%)	2 / 110 (1.82%)	2 / 101 (1.98%)
occurrences (all)	3	2	2
Gastroenteritis			
subjects affected / exposed	5 / 110 (4.55%)	6 / 110 (5.45%)	3 / 101 (2.97%)
occurrences (all)	5	6	3

Non-serious adverse events	Extended Treatment: Teriflunomide 14 mg (After IFN-β-1a)	Extended Treatment: Teriflunomide 14 mg (After 7 mg)	Extended Treatment: Teriflunomide 14 mg (After 14 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 59 (81.36%)	72 / 90 (80.00%)	65 / 88 (73.86%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 59 (11.86%)	7 / 90 (7.78%)	9 / 88 (10.23%)
occurrences (all)	7	7	9
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 59 (3.39%)	4 / 90 (4.44%)	4 / 88 (4.55%)
occurrences (all)	2	4	4
Asthenia			
subjects affected / exposed	3 / 59 (5.08%)	0 / 90 (0.00%)	2 / 88 (2.27%)
occurrences (all)	3	0	2
Pyrexia			

subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	1 / 88 (1.14%)
occurrences (all)	0	1	1
Influenza Like Illness			
subjects affected / exposed	6 / 59 (10.17%)	2 / 90 (2.22%)	0 / 88 (0.00%)
occurrences (all)	6	2	0
Injection Site Erythema			
subjects affected / exposed	0 / 59 (0.00%)	0 / 90 (0.00%)	0 / 88 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	2 / 88 (2.27%)
occurrences (all)	0	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 59 (8.47%)	4 / 90 (4.44%)	2 / 88 (2.27%)
occurrences (all)	5	4	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 59 (3.39%)	2 / 90 (2.22%)	1 / 88 (1.14%)
occurrences (all)	2	2	1
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 59 (3.39%)	5 / 90 (5.56%)	8 / 88 (9.09%)
occurrences (all)	2	5	8
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 59 (1.69%)	3 / 90 (3.33%)	0 / 88 (0.00%)
occurrences (all)	1	3	0
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	3 / 59 (5.08%)	3 / 90 (3.33%)	4 / 88 (4.55%)
occurrences (all)	3	3	4
Dizziness			
subjects affected / exposed	0 / 59 (0.00%)	3 / 90 (3.33%)	3 / 88 (3.41%)
occurrences (all)	0	3	3
Headache			

subjects affected / exposed	10 / 59 (16.95%)	5 / 90 (5.56%)	3 / 88 (3.41%)
occurrences (all)	10	5	3
Sciatica			
subjects affected / exposed	3 / 59 (5.08%)	1 / 90 (1.11%)	3 / 88 (3.41%)
occurrences (all)	3	1	3
Paraesthesia			
subjects affected / exposed	3 / 59 (5.08%)	3 / 90 (3.33%)	2 / 88 (2.27%)
occurrences (all)	3	3	2
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	3 / 59 (5.08%)	1 / 90 (1.11%)	2 / 88 (2.27%)
occurrences (all)	3	1	2
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	5 / 59 (8.47%)	5 / 90 (5.56%)	6 / 88 (6.82%)
occurrences (all)	5	5	6
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 59 (13.56%)	10 / 90 (11.11%)	15 / 88 (17.05%)
occurrences (all)	8	10	15
Abdominal Pain			
subjects affected / exposed	2 / 59 (3.39%)	6 / 90 (6.67%)	3 / 88 (3.41%)
occurrences (all)	2	6	3
Abdominal Pain Upper			
subjects affected / exposed	4 / 59 (6.78%)	3 / 90 (3.33%)	3 / 88 (3.41%)
occurrences (all)	4	3	3
Nausea			
subjects affected / exposed	1 / 59 (1.69%)	0 / 90 (0.00%)	2 / 88 (2.27%)
occurrences (all)	1	0	2
Dyspepsia			
subjects affected / exposed	3 / 59 (5.08%)	3 / 90 (3.33%)	1 / 88 (1.14%)
occurrences (all)	3	3	1
Vomiting			
subjects affected / exposed	1 / 59 (1.69%)	2 / 90 (2.22%)	1 / 88 (1.14%)
occurrences (all)	1	2	1
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	4 / 59 (6.78%)	4 / 90 (4.44%)	1 / 88 (1.14%)
occurrences (all)	4	4	1
Renal and urinary disorders			
Micturition Urgency			
subjects affected / exposed	3 / 59 (5.08%)	2 / 90 (2.22%)	2 / 88 (2.27%)
occurrences (all)	3	2	2
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	5 / 59 (8.47%)	5 / 90 (5.56%)	6 / 88 (6.82%)
occurrences (all)	5	5	6
Pain In Extremity			
subjects affected / exposed	4 / 59 (6.78%)	6 / 90 (6.67%)	4 / 88 (4.55%)
occurrences (all)	4	6	4
Arthralgia			
subjects affected / exposed	4 / 59 (6.78%)	6 / 90 (6.67%)	3 / 88 (3.41%)
occurrences (all)	4	6	3
Muscle Spasms			
subjects affected / exposed	2 / 59 (3.39%)	1 / 90 (1.11%)	2 / 88 (2.27%)
occurrences (all)	2	1	2
Myalgia			
subjects affected / exposed	1 / 59 (1.69%)	2 / 90 (2.22%)	1 / 88 (1.14%)
occurrences (all)	1	2	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 59 (5.08%)	11 / 90 (12.22%)	9 / 88 (10.23%)
occurrences (all)	3	11	9
Urinary Tract Infection			
subjects affected / exposed	3 / 59 (5.08%)	8 / 90 (8.89%)	7 / 88 (7.95%)
occurrences (all)	3	8	7
Bronchitis			
subjects affected / exposed	4 / 59 (6.78%)	4 / 90 (4.44%)	5 / 88 (5.68%)
occurrences (all)	4	4	5
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 59 (5.08%)	2 / 90 (2.22%)	5 / 88 (5.68%)
occurrences (all)	3	2	5

Oral Herpes			
subjects affected / exposed	0 / 59 (0.00%)	1 / 90 (1.11%)	4 / 88 (4.55%)
occurrences (all)	0	1	4
Pharyngitis			
subjects affected / exposed	5 / 59 (8.47%)	4 / 90 (4.44%)	4 / 88 (4.55%)
occurrences (all)	5	4	4
Influenza			
subjects affected / exposed	2 / 59 (3.39%)	3 / 90 (3.33%)	2 / 88 (2.27%)
occurrences (all)	2	3	2
Ear Infection			
subjects affected / exposed	3 / 59 (5.08%)	0 / 90 (0.00%)	1 / 88 (1.14%)
occurrences (all)	3	0	1
Gastroenteritis			
subjects affected / exposed	1 / 59 (1.69%)	7 / 90 (7.78%)	1 / 88 (1.14%)
occurrences (all)	1	7	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2011	Following changes were made: •Extension part of the study was elaborated, which was offered to all subjects randomized in EFC10891/TENERE and completed the treatment period - regardless of study arm (teriflunomide or interferon-beta 1a). This extension was an open-label study with all subjects treated with teriflunomide 14 mg/day. The extension was planned to last 48 weeks. •Teriflunomide elimination (washout) period was shortened from 16 weeks to 4 weeks to allow subjects to terminate treatment more rapidly. •Concomitant medications were modified, which could interfere with the study based on the updated drug interactions data (CYP2C9 substrate and CYP inducers). •Peripheral neuropathy confirmed by electrophysiological tests was added as an alert term. •Frequency of sample collection was reduced for PK based on available data of teriflunomide. •Clarification regarding reporting of AEs was required from signature of informed consent. •Rebif overdose, accountability and compliance, disposition of used syringes/cartridges, and other editorial corrections related to the IMP, were re-defined. •Clarification and corrected some inconsistencies throughout the protocol regarding neutropenia.
12 July 2012	• Extended the current extension period of the TENERE study up to when teriflunomide was commercially available in the country. • Modified the concomitant treatments based on the updated drug interactions data.
28 January 2013	•Reduction of scheduled study visits and visit contents for subjects completed a minimum 18 months/72 weeks in extension phase. •Clinical visits were performed every 24 weeks up to the end of treatment, and included adverse event reporting; recording of concomitant medication, vital signs, physical examination; dispense study drugs: accountability/compliance; EDSS /Functional System (FS); clinical laboratory only at EOT visit. •Central lab services would not be utilized. Lab tests were performed on local basis for all subjects. •Clarification that subjects continued on teriflunomide by obtaining it commercially after ending in this extension study, accelerated elimination procedure and follow-up visits were not required. •Updated on the PK handling procedure and sampling time. •New information regarding potential drug interactions •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).

09 May 2013	•Reduction of scheduled study visits and visit contents for subjects completed a minimum 72 weeks in extension phase. •Clinical visits was performed every 24 weeks up to the end of treatment, and included adverse event reporting; recording of concomitant medication, vital signs, physical examination; dispense study drugs: accountability/compliance; EDSS / FS; clinical laboratory only at EOT visit. •Central lab services was not be utilized except for post-accelerated elimination PK samples. Lab tests was performed on local basis for all subjects. •Clarification that subjects continued on teriflunomide by obtaining it commercially after ending in this extension study, accelerated elimination procedure and follow-up visits were not required. •Updated the PK handling procedure and sampling time. •New information regarding potential drug interactions. •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/24126064