Clinical trial results:
A Two Year, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Trial to Evaluate Efficacy, Safety, Tolerability, and Pharmacokinetics of Teriflunomide Administered Orally Once Daily in Pediatric Patients With Relapsing Forms of Multiple Sclerosis Followed by an Open-label Extension

Summary

EudraCT number	2011-005249-12
Trial protocol	EE BE ES GR PL GB FR LT Outside EU/EEA IE NL BG PT SI IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	29 January 2021
First version publication date	29 January 2021

Trial information

Trial identification

Sponsor protocol code	EFC11759

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02201108
WHO universal trial number (UTN)	U1111-1124-0983

Notes:

Sponsors

Sponsor organisation name	Genzyme, a Sanofi Company
Sponsor organisation address	50 Binney Street, Cambridge, Massachusetts, United States, 02142
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001094-PIP01-10
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	Interim
Date of interim/final analysis	27 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of teriflunomide in comparison to placebo on disease activity as measured by time to first clinical relapse after randomisation in children and adolescents 10 to 17 years of age with relapsing forms of multiple sclerosis.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric patients. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia might have been used to minimise distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Turkey: 32
Country: Number of subjects enrolled	China: 37
Country: Number of subjects enrolled	Morocco: 2
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Lebanon: 4

Country: Number of subjects enrolled	Tunisia: 4
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Ukraine: 7
Worldwide total number of subjects	166
EEA total number of subjects	35

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)	16
Adolescents (12-17 years)	150
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 57 active centres in 21 countries. A total of 185 subjects were screened between 16 July 2014 and 27 December 2017, of which 166 subjects were enrolled and randomised. A total of 19 subjects failed screening mainly due to meeting exclusion criteria.

Pre-assignment

Screening details:

Subjects were randomly assigned to receive either teriflunomide or placebo in a 2:1 ratio (109 teriflunomide and 57 placebo) via Interactive Voice Response System. Randomisation was stratified by the country and subject's pubertal status. Data reported based on the primary completion date of 25 October 2019.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matching to teriflunomide tablet orally once daily (QD) for 96 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A single tablet of placebo (matched to teriflunomide) was administered orally QD with or without food in the morning preferably at the same time each day of the double-blind treatment period (i.e., 96 weeks).

Arm title	Teriflunomide

Arm description:

Subjects received 1 Teriflunomide tablet, 3.5 milligrams (mg) (in case of body weight [BW] up to 40 kilograms [kg]) or 7 mg (in case of BW greater than [>]40 kg) orally QD for 8 weeks. After 8 weeks, based on subjects predicted pharmacokinetic (PK) parameters, teriflunomide was administered in following manner up to 96 weeks:if predicted PK parameters less than or equal to (<=)95th percentile of adult range after 7 mg QD:1 tablet of 7 mg daily (for BW up to 40 kg) or 1 tablet of 14 mg daily (for BW>40 kg);or if predicted PK parameters >95th percentile of adult range:1 tablet of 3.5 mg daily (for BW up to 40 kg) or 1 tablet of 7 mg daily (for BW>40 kg). The adult range (5th-95th percentile) of predicted steady state PK parameters for 7 mg dose was defined as maximum concentration observed (Cmax) ranging from 8.03 to 49.10 micrograms per millilitre (mcg/mL) and area under the curve from time 0 hour to 24 hours (AUC0-24) ranging from 184 to 1160 micrograms*hour per millilitre (mcg*h/mL).

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

Dosage and administration details:

Teriflunomide (3.5 mg or 7 mg or 14 mg) film-coated tablet was administered orally QD with or without food in the morning preferably at the same time each day of the double-blind treatment period (i.e., 96 weeks).

Number of subjects in period 1	Placebo	Teriflunomide
Started	57	109
On-going subjects	0 [1]	58 [2]
Completed	53	102
Not completed	4	7
Consent withdrawn by subject	2	-
Adverse Event	-	6
Lack of efficacy	2	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: On-going subjects represent the 58 subjects of Teriflunomide arm who entered the open-label period post double-blind treatment period.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: On-going subjects represent the 58 subjects of Teriflunomide arm who entered the open-label period post double-blind treatment period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matching to teriflunomide tablet orally once daily (QD) for 96 weeks.	
Reporting group title	Teriflunomide
Reporting group description:	
Subjects received 1 Teriflunomide tablet, 3.5 milligrams (mg) (in case of body weight [BW] up to 40 kilograms [kg]) or 7 mg (in case of BW greater than [>]40 kg) orally QD for 8 weeks. After 8 weeks, based on subjects predicted pharmacokinetic (PK) parameters, teriflunomide was administered in following manner up to 96 weeks:if predicted PK parameters less than or equal to (<=)95th percentile of adult range after 7 mg QD:1 tablet of 7 mg daily (for BW up to 40 kg) or 1 tablet of 14 mg daily (for BW>40 kg);or if predicted PK parameters >95th percentile of adult range:1 tablet of 3.5 mg daily (for BW up to 40 kg) or 1 tablet of 7 mg daily (for BW>40 kg). The adult range (5th-95th percentile) of predicted steady state PK parameters for 7 mg dose was defined as maximum concentration observed (Cmax) ranging from 8.03 to 49.10 micrograms per millilitre (mcg/mL) and area under the curve from time 0 hour to 24 hours (AUC0-24) ranging from 184 to 1160 micrograms*hour per millilitre (mcg*h/mL).	

Reporting group values	Placebo	Teriflunomide	Total
Number of subjects	57	109	166
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	14.7	14.6	
standard deviation	± 2.1	± 2.0	-
Gender categorical Units: Subjects			
Female	39	72	111
Male	18	37	55
Race Units: Subjects			
Caucasian/White	42	75	117
Black	1	4	5
Asian/Oriental	12	25	37
Other	2	5	7

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matching to teriflunomide tablet orally once daily (QD) for 96 weeks.

Reporting group title	Teriflunomide

Reporting group description:

Subjects received 1 Teriflunomide tablet, 3.5 milligrams (mg) (in case of body weight [BW] up to 40 kilograms [kg]) or 7 mg (in case of BW greater than [>]40 kg) orally QD for 8 weeks. After 8 weeks, based on subjects predicted pharmacokinetic (PK) parameters, teriflunomide was administered in following manner up to 96 weeks:if predicted PK parameters less than or equal to (<=)95th percentile of adult range after 7 mg QD:1 tablet of 7 mg daily (for BW up to 40 kg) or 1 tablet of 14 mg daily (for BW>40 kg);or if predicted PK parameters >95th percentile of adult range:1 tablet of 3.5 mg daily (for BW up to 40 kg) or 1 tablet of 7 mg daily (for BW>40 kg). The adult range (5th-95th percentile) of predicted steady state PK parameters for 7 mg dose was defined as maximum concentration observed (Cmax) ranging from 8.03 to 49.10 micrograms per millilitre (mcg/mL) and area under the curve from time 0 hour to 24 hours (AUC0-24) ranging from 184 to 1160 micrograms*hour per millilitre (mcg*h/mL).

Subject analysis set title	Teriflunomide 7 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects with BW >40 kg received 1 Teriflunomide tablet, 7 mg orally QD for 8 weeks. After 8 weeks, based on subject's predicted PK parameters, teriflunomide was administered in following manner up to 96 weeks: if predicted PK parameters <= 95th percentile of adult range after 7 mg QD: 1 tablet of 7 mg daily (for BW up to 40 kg) or 1 tablet of 14 mg daily (for BW >40 kg); or if predicted PK parameters >95th percentile of adult range: 1 tablet of 3.5 mg daily (for BW up to 40 kg) or 1 tablet of 7 mg daily (for BW >40 kg).

Subject analysis set title	Teriflunomide 14 mg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

After 8 weeks, based on subject's predicted PK parameters, teriflunomide was administered in following manner up to 96 weeks: if predicted PK parameters <= 95th percentile of adult range after 7 mg QD: 1 tablet of 7 mg daily (for BW up to 40 kg) or 1 tablet of 14 mg daily (for BW >40 kg); or if predicted PK parameters >95th percentile of adult range: 1 tablet of 3.5 mg daily (for BW up to 40 kg) or 1 tablet of 7 mg daily (for BW >40 kg).

Primary: Time to First Confirmed Clinical Relapse

End point title	Time to First Confirmed Clinical Relapse

End point description:

Time to first clinical relapse:duration (in weeks) between randomisation & first confirmed clinical relapse. Clinical relapses:new/recurrent neurological symptoms not associated with fever/infection, lasted at least 24 hours & accompanied by new objective neurological findings upon neurological examination & documented by standardised, quantified functional system score (FSSs) which included 8 items:rated on different scales:brain stem, cerebellar & cerebral functions rated on scale of 0 to 5;visual, pyramidal, sensory & bowel/bladder rated on scale of 0 to 6 & ambulation on scale of 0 to 12 where higher score in each scale indicated worsened neurological function. Confirmed clinical relapse were reviewed & confirmed by independent Relapse Adjudication Panel. Subject without confirmed clinical relapse;considered as clinical relapse free until end of Week 96. Analysed on Intent-to-treat (ITT) population:all randomised subjects analysed according to treatment allocated by randomisation.

End point type	Primary

End point timeframe:

Baseline up to Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	109		
Units: weeks				
median (full range (min-max))	39.14 (0.1 to 98.0)	75.29 (0.1 to 98.7)		

Statistical analyses

Statistical analysis title	Teriflunomide versus Placebo

Statistical analysis description:

Hazard ratio (HR) was estimated using a Cox proportional-hazards model with factors for treatment group, region, pubertal status, age, and number of relapses in the year prior to randomisation as covariates and with robust variance estimation. Derived from log-rank test with stratification of region and pubertal status.

Comparison groups	Placebo v Teriflunomide
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2949 [1]
Method	Stratified Log-Rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.657
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.388
upper limit	1.113

Notes:

[1] - Threshold for significance was < 0.05.

Secondary: Probability of Subjects Who Were Clinical Relapse Free at Weeks 24, 48, 72 and 96

End point title	Probability of Subjects Who Were Clinical Relapse Free at Weeks 24, 48, 72 and 96

End point description:

Subject was considered free of clinical relapse if the subject had no confirmed clinical relapse before treatment discontinuation/completion in 96 weeks treatment period. Clinical relapses: new/recurrent neurological symptoms not associated with fever/infection, lasted at least 24 hours, & accompanied by new objective neurological findings upon neurological examination & documented by standardised, quantified FSSs which included 8 items: rated on different scales: brain stem, cerebellar & cerebral functions rated on scale of 0 to 5; visual, pyramidal, sensory & bowel/bladder rated on scale of 0 to 6 & ambulation on scale of 0 to 12, where higher score in each scale indicated worsened neurological function. New/recurrent symptoms occurred less than 30 days following onset of relapse were considered part of same relapse. Probability of subjects who were clinical relapse free at specified weeks was estimated by Kaplan-Meier method and reported. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Weeks 24, 48, 72 and 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	109		
Units: probability of relapse free subjects				
number (confidence interval 95%)				
Week 24	0.750 (0.615 to 0.844)	0.807 (0.720 to 0.870)		
Week 48	0.590 (0.444 to 0.710)	0.684 (0.587 to 0.763)		
Week 72	0.531 (0.379 to 0.662)	0.619 (0.517 to 0.705)		
Week 96	0.455 (0.293 to 0.603)	0.594 (0.491 to 0.683)		

Statistical analyses

No statistical analyses for this end point

Secondary: Magnetic Resonance Imaging (MRI) Assessment: Number of New or Enlarged T2 Lesions Per MRI Scan

End point title	Magnetic Resonance Imaging (MRI) Assessment: Number of New or Enlarged T2 Lesions Per MRI Scan

End point description:

Number of new or enlarged T2 lesions per scan was defined as the total number of new or enlarged T2 lesion that occurred during the 96 weeks treatment period divided by the total number of scans performed during 96 weeks. To account for the different numbers of scans performed among the subjects, a negative binomial regression model with robust variance estimation was used. The model included the total number of new or enlarged T2-lesions as the response variable, with treatment group, region, pubertal status and age as covariates and log-transformed number of scans as an offset variable. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	109		
Units: lesions per scan				
number (confidence interval 95%)	10.515 (4.705 to 23.500)	4.735 (2.122 to 10.567)		

Statistical analyses

Statistical analysis title	Teriflunomide versus Placebo

Statistical analysis description:

A hierarchical testing method was used to control Type-I error. Testing was then performed sequentially in the order the endpoints were reported. The hierarchical testing sequence continued only when

previous endpoint was statistically significant at 5%.

Comparison groups	Placebo v Teriflunomide
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [2]
Method	Negative binomial regression model
Parameter estimate	Relative risk ratio
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.285
upper limit	0.711

Notes:

[2] - Negative binomial regression model with robust variance estimation: total number of new/enlarged T2-lesions as response variable;treatment group, region, baseline pubertal status & age as covariates; log-transformed number of scans as offset variable.

Secondary: Magnetic Resonance Imaging Assessment: Number of T1 Gadolinium (Gd)-Enhancing T1 Lesions Per MRI Scan

End point title	Magnetic Resonance Imaging Assessment: Number of T1 Gadolinium (Gd)-Enhancing T1 Lesions Per MRI Scan

End point description:

The number of T1 Gd-Enhancing lesions per scan was defined as the total number of lesions that occurred during the 96 weeks treatment period divided by the total number of scans performed during 96 weeks. To account for the different number of scans performed among the subjects, a negative binomial regression model with robust variance estimation was used. The model included the total number of T1-lesions as the response variable, with treatment group, region, pubertal status and age as covariates and log-transformed number of scans as an offset variable. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	109		
Units: lesions per scan				
number (confidence interval 95%)	7.505 (2.482 to 22.695)	1.897 (0.656 to 5.489)		

Statistical analyses

Statistical analysis title	Teriflunomide versus Placebo

Statistical analysis description:

Testing according to the hierarchical testing procedure (hypothesis formally tested only if the preceding endpoint was significant at 5%).

Comparison groups	Placebo v Teriflunomide

Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Negative binomial regression model
Parameter estimate	Relative risk ratio
Point estimate	0.253
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.126
upper limit	0.505

Notes:

[3] - P-value and relative risk ratio was calculated by negative binomial regression model with robust variance estimation: total number of T1 Gd-enhancing T1 lesions as response variable, treatment group, region, baseline T1 Gd-enhancing T1 lesion count, baseline pubertal status and age as covariates and log-transformed number of scans as offset variable.

[4] - Negative binomial regression model with robust variance estimation: total number of T1 Gd-enhancing T1 lesions as response variable, treatment group, region, pubertal status & age as covariates and log-transformed number of scans as offset variable.

Secondary: Magnetic Resonance Imaging Assessment: Change From Baseline in Volume of T2 Lesions at Weeks 24, 48, 72 and 96

End point title	Magnetic Resonance Imaging Assessment: Change From Baseline in Volume of T2 Lesions at Weeks 24, 48, 72 and 96

End point description:

Volume of T2 lesions was measured by MRI scan. Analysis was performed on ITT population. Here, 'n' = number of subjects analysed for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, 72 and 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	109		
Units: millilitres				
least squares mean (standard error)				
Week 24 (n = 44, 96)	0.148 (± 0.047)	0.075 (± 0.042)		
Week 48 (n = 24, 72)	0.135 (± 0.051)	0.060 (± 0.044)		
Week 72 (n = 18, 64)	0.204 (± 0.054)	0.065 (± 0.045)		
Week 96 (n = 16, 54)	0.201 (± 0.054)	0.073 (± 0.045)		

Statistical analyses

Statistical analysis title	Week 24: Teriflunomide versus Placebo

Statistical analysis description:

Analysis performed using a Mixed-effect model with repeated measures (MMRM) adjusted for pubertal status, region, visit, treatment-by-visit interaction and cubic root transformed baseline volume.

Comparison groups	Placebo v Teriflunomide
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0462 [5]
Method	MMRM
Parameter estimate	Least Square (LS) Mean difference
Point estimate	-0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.144
upper limit	-0.001
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

[5] - P-value and LS Mean difference was calculated by MMRM analysis adjusted for pubertal status at baseline, region, visit, treatment-by-visit interaction and cubic root transformed baseline volume.

Statistical analysis title	Week 48: Teriflunomide versus Placebo

Statistical analysis description:

Analysis performed using a MMRM adjusted for pubertal status, region, visit, treatment-by-visit interaction and cubic root transformed baseline volume.

Comparison groups	Placebo v Teriflunomide
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0917 [6]
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-0.074
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.161
upper limit	0.012
Variability estimate	Standard error of the mean
Dispersion value	0.044

Notes:

[6] - P-value and LS Mean difference was calculated by MMRM analysis adjusted for pubertal status at baseline, region, visit, treatment-by-visit interaction and cubic root transformed baseline volume.

Statistical analysis title	Week 72: Teriflunomide versus Placebo

Statistical analysis description:

Analysis performed using a MMRM adjusted for pubertal status, region, visit, treatment-by-visit interaction and cubic root transformed baseline volume.

Comparison groups	Placebo v Teriflunomide

Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0052 [7]
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-0.139
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.235
upper limit	-0.043
Variability estimate	Standard error of the mean
Dispersion value	0.048

Notes:

[7] - P-value and LS Mean difference was calculated by MMRM analysis adjusted for pubertal status at baseline, region, visit, treatment-by-visit interaction and cubic root transformed baseline volume.

Statistical analysis title	Week 96: Teriflunomide versus Placebo

Statistical analysis description:

Analysis performed using a MMRM adjusted for pubertal status, region, visit, treatment-by-visit interaction and cubic root transformed baseline volume.

Comparison groups	Placebo v Teriflunomide
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [8]
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.225
upper limit	-0.031
Variability estimate	Standard error of the mean
Dispersion value	0.049

Notes:

[8] - P-value and LS Mean difference was calculated by MMRM analysis adjusted for pubertal status at baseline, region, visit, treatment-by-visit interaction and cubic root transformed baseline volume.

Secondary: Magnetic Resonance Imaging Assessment: Change From Baseline in Volume of T1 Hypointense Lesions

End point title	Magnetic Resonance Imaging Assessment: Change From Baseline in Volume of T1 Hypointense Lesions

End point description:

Volume of T1 hypointense lesions was measured by MRI scan. Analysis was performed on ITT population. Here, 'n' = number of subjects analysed for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, 72 and 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	109		
Units: millilitres				
arithmetic mean (standard deviation)				
Week 24 (n = 44, 96)	0.4 (± 1.3)	0.0 (± 0.7)		
Week 48 (n = 23, 72)	0.2 (± 0.6)	0.3 (± 2.8)		
Week 72 (n = 18, 63)	0.1 (± 0.7)	0.1 (± 0.6)		
Week 96 (n = 16, 53)	0.1 (± 0.5)	0.1 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Magnetic Resonance Imaging Assessment: Number of New T1 Hypointense Lesions Per MRI Scan

End point title	Magnetic Resonance Imaging Assessment: Number of New T1 Hypointense Lesions Per MRI Scan

End point description:

The number of new T1 hypointense lesions were obtained from MRI scans. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline up to Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	109		
Units: lesions				
number (not applicable)	714	848		

Statistical analyses

Statistical analysis title	Teriflunomide versus Placebo

Statistical analysis description:

P-value and relative risk ratio was calculated by negative binomial regression model with robust variance estimation, with total number of new hypointense T1 lesions as response variable, with treatment group, region, baseline pubertal status and age as covariates and log-transformed number of scans as an offset variable.

Comparison groups	Placebo v Teriflunomide

Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0236 [9]
Method	Negative binomial regression model
Parameter estimate	Relative risk ratio
Point estimate	0.507
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.281
upper limit	0.913

Notes:

[9] - Negative binomial regression model with robust variance estimation:total number of new T1 hypointense lesions as response variable;treatment group, region, baseline pubertal status & age covariates; log-transformed number of scans as offset variable.

Secondary: Magnetic Resonance Imaging Assessment: Percentage of Subjects Free of New or Enlarged MRI T2-Lesions

End point title	Magnetic Resonance Imaging Assessment: Percentage of Subjects Free of New or Enlarged MRI T2-Lesions

End point description:

Percentage of subjects who were free of new or enlarged T2 lesions at Weeks 48 and 96 were reported. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Weeks 48 and 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	109		
Units: percentage of subjects				
number (not applicable)				
Week 48	10.5	17.4		
Week 96	3.5	10.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Magnetic Resonance Imaging Assessment: Percent Change From Baseline in Brain Volume at Weeks 24, 48, 72 and 96

End point title	Magnetic Resonance Imaging Assessment: Percent Change From Baseline in Brain Volume at Weeks 24, 48, 72 and 96

End point description:

Percent change from baseline in brain volume (assessed using MRI scans of the Brain) at Weeks 24, 48, 72 and 96 was reported. Analysis was performed on ITT population. Here, 'n' = number of subjects analysed for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, 72 and 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	109		
Units: percent change				
arithmetic mean (standard deviation)				
Week 24 (n =42, 90)	-0.3 (± 0.7)	-0.2 (± 0.8)		
Week 48 (n =23, 68)	-0.5 (± 1.0)	-0.5 (± 0.9)		
Week 72 (n =18, 58)	-0.8 (± 1.2)	-0.7 (± 1.1)		
Week 96 (n =15, 50)	-0.9 (± 1.2)	-0.8 (± 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Assessment: Change From Baseline in Total Number of Correct Substitutions Measured by Symbol Digit Modalities Test (SDMT) at Weeks 24, 48, 72 and 96

End point title	Cognitive Assessment: Change From Baseline in Total Number of Correct Substitutions Measured by Symbol Digit Modalities Test (SDMT) at Weeks 24, 48, 72 and 96

End point description:

SDMT measures the time to pair abstract symbols with specific numbers. It is a simple substitution task that gives the examinee 90 seconds to pair specific numbers with given geometric figures as a measure for screening cognitive impairment. The score is the number of correct substitution and ranged from 0 (worst outcome) to 110 (best outcome), where higher score indicated better cognitive function. Analysis was performed on ITT population. Here, 'n' = number of subjects analysed for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, 72 and 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	109		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 24 (n = 44, 94)	4.6 (± 11.6)	4.8 (± 9.2)		
Week 48 (n = 24, 69)	6.2 (± 13.5)	6.1 (± 10.3)		
Week 72 (n = 19, 63)	7.0 (± 12.7)	6.0 (± 11.2)		
Week 96 (n = 16, 53)	9.1 (± 10.9)	8.3 (± 11.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Assessment: Change From Baseline in Number of Completed Items Measured by Symbol Digit Modalities Test at Weeks 24, 48, 72 and 96

End point title	Cognitive Assessment: Change From Baseline in Number of Completed Items Measured by Symbol Digit Modalities Test at Weeks 24, 48, 72 and 96

End point description:

SDMT measures the time to pair abstract symbols with specific numbers. It is a simple substitution task that gives the examinee 90 seconds to pair specific numbers with given geometric figures as a measure for screening cognitive impairment. The score is the number of completed items and ranged from 0 (worst outcome) to 110 (best outcome), where higher score indicated better cognitive function. Analysis was performed on ITT population. Here, 'n' = number of subjects analysed for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 48, 72 and 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	109		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 24 (n = 44, 94)	3.4 (± 11.3)	3.8 (± 9.0)		
Week 48 (n = 24, 69)	5.4 (± 13.3)	5.0 (± 10.1)		
Week 72 (n = 19, 63)	5.6 (± 13.0)	4.8 (± 11.0)		
Week 96 (n = 16, 53)	7.6 (± 11.0)	7.1 (± 11.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Assessment: Change From Baseline in Brief Visuospatial Memory Test-Revised (BVMT-R) Scores at Week 96

End point title	Cognitive Assessment: Change From Baseline in Brief Visuospatial Memory Test-Revised (BVMT-R) Scores at Week 96

End point description:

The BVMT consists of three trials in which subjects must recall shapes by drawing figures on a blank page (response booklet) after being given the opportunity to memorise the figures (given in BMVT-R form) for 10 seconds. BMVT-R form consists of six figures. Points are awarded based on the accuracy of the drawn figure and by correct placement on the blank page. A minimum of 0 to 12 points/scores are

awarded per trial, so a subject can score between 0 and 36 points for all three trials (by adding the points/score from each trial), where higher score indicates better outcome. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	36		
Units: score on a scale				
arithmetic mean (standard deviation)	1.9 (± 10.7)	0.8 (± 6.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Assessment: Change From Baseline in Trail Making Test- Part A (TMT-A) Test Scores (in Seconds) at Week 96

End point title	Cognitive Assessment: Change From Baseline in Trail Making Test- Part A (TMT-A) Test Scores (in Seconds) at Week 96

End point description:

'Trail Making Test Part A' is a neuropsychological test of visual attention and task switching. The task requires a subject to 'connect-the-dots' of 25 consecutive numbers (1, 2, 3,etc.) in sequential order on a sheet of paper or computer screen. The goal of the subject is to finish the test as quickly as possible, and the time taken to complete the test used as the primary performance metric (in seconds). This is a timed test and the number of seconds to complete the task is recorded. Maximum time allowed is 300 seconds. A lower score indicated better cognitive function. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	13		
Units: seconds				
arithmetic mean (standard deviation)	3.8 (± 11.8)	-3.1 (± 19.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Assessment: Change From Baseline in Trail Making Test B (TMT-B) Test Scores (in Seconds) at Week 96

End point title	Cognitive Assessment: Change From Baseline in Trail Making Test B (TMT-B) Test Scores (in Seconds) at Week 96

End point description:

TMT-B is a cognitive test that gives a measure of various aspects of cognitive performance. It is used to measure cognitive fatigue. The test consists of 25 circles containing 13 sequential numbers (1-13) and 12 sequential letters (A-L) positioned. The test evaluates the time (in seconds) to correctly order letters and numbers in alternate order (1, A, 2, B etc.). Maximum time allowed is 300 seconds, where less time/lower score indicates better cognitive function/performance. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	13		
Units: seconds				
arithmetic mean (standard deviation)	-14.4 (± 29.6)	-29.5 (± 56.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Assessment: Change From Baseline in Beery Visual-motor Integration (BVMI) Scores at Week 96

End point title	Cognitive Assessment: Change From Baseline in Beery Visual-motor Integration (BVMI) Scores at Week 96

End point description:

The Beery VMI is a non-verbal assessment that assessed the extent to which individuals can integrate their visual and motor abilities. The subjects were provided with geometric designs ranging from simple line drawings to more complex figures and were asked to copy the designs. The test consisted of 24 figures. One point was scored for each successful copy of drawings and no scoring was given when the subject failed to copy the drawings properly. Each successful copying of drawings was summed up and the total was scored on a scale ranged from 0 to 24, where higher score indicated better visual construction skills/better visual and motor abilities and lower score indicated poor visual construction skills/poor visual and motor abilities. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	47		
Units: scores on a scale				
arithmetic mean (standard deviation)	0.6 (± 2.2)	-0.3 (± 4.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Assessment: Change From Baseline in Wechsler Abbreviated Scale of Intelligence-II (WASI-II) Vocabulary Total Raw Scores at Week 96

End point title	Cognitive Assessment: Change From Baseline in Wechsler Abbreviated Scale of Intelligence-II (WASI-II) Vocabulary Total Raw Scores at Week 96

End point description:

The WASI-II: Vocabulary test is a quick estimate of an individual's level of intellectual functioning which comprised of 31 total items that require the subject to orally define 3 images and 28 words presented both orally and visually. Items 1 to 3 rated on a score of 0 or 1, items 4 and 5 rated on a score of 0 or 2, items 6 to 31 rated on a scale of 0 to 2. Each item score was summed up to derive the total score which was ranged from 0 (minimum score) to 59 (maximum score), where higher score indicated better level of intellectual functioning/higher level of intelligence. Analysis was performed on ITT population. Here, "Number of subjects analysed" = subjects with available data for this endpoint. 99999 was used as a space filler and specified that the standard deviation was not calculated, since only 1 subject was assessed.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: scores on a scale				
arithmetic mean (standard deviation)	5.0 (± 99999)	4.0 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Assessment: Change From Baseline in Delis-Kaplan Executive Function System (D-KEFS) Letter Fluency Total Correct Raw Score at Week 96

End point title	Cognitive Assessment: Change From Baseline in Delis-Kaplan Executive Function System (D-KEFS) Letter Fluency Total Correct Raw Score at Week 96

End point description:

Letter fluency is a condition measured in Delis-Kaplan Executive Function System (D-KEFS). Subjects are asked to name as many words as they can, starting with a specified letter for 60 seconds. The words

cannot be names, places, numbers or grammatical variants of previous answers. Repeated answers are not scored as a correct response. There are 3 trials, with 3 different letters. The total number of correct responses is totaled for all 3 trials and a letter fluency score is given. A higher score is considered better. There is no set range as the score depends on how many correct words the subject relays in the given time period. Analysis was performed on ITT population. Here, "number of subjects analysed"=subjects with available data for this endpoint. Here, 99999 was used as a space filler and specified that the standard deviation was not calculated, since only 1 subject was assessed.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	2		
Units: scores on a scale				
arithmetic mean (standard deviation)	-3.0 (± 99999)	4.0 (± 9.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Assessment: Change From Baseline in Delis-Kaplan Executive Function System Category Fluency Total Correct Raw Score at Week 96

End point title	Cognitive Assessment: Change From Baseline in Delis-Kaplan Executive Function System Category Fluency Total Correct Raw Score at Week 96

End point description:

Category fluency is a condition measured in the D-KEFS. It measures subject's ability to generate words from three different categories (e.g., fruits, vegetables and animals), within a minute for each category. Total score is number of correct words for each category with no points for repetitions or non-words. Score range 0 to unlimited, where 0 = low score, higher score indicates better performance. Analysis was performed on ITT population. Here, "number of subjects Analysed"=subjects with available data for this endpoint. Here, 99999 was used as a space filler and specified that the standard deviation was not calculated, since only 1 subject was assessed.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	2		
Units: score on a scale				
arithmetic mean (standard deviation)	6.0 (± 99999)	5.0 (± 5.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive Assessment - Selective Reminding Test (SRT): Change From Baseline in Total Number of Words on Delayed Recall at Week 96

End point title	Cognitive Assessment - Selective Reminding Test (SRT): Change From Baseline in Total Number of Words on Delayed Recall at Week 96

End point description:

SRT is a test to assess verbal learning and memory. During the administration of the SRT only the examiner and the subject should be in the testing room. A list of twelve words is read aloud by the examiner at a rate of one word per two seconds. The subject is asked to recall all twelve words after a 30 minute delay. Only the words that are missed on the preceding trial are given in the consecutive trial. The total score represents a sum score of total 6 trials, therefore the range is from 0-72. The lower the value the worse the outcome, higher value indicates better recall. Analysis was performed on ITT population. Here, "number of subjects analysed"=subjects with available data for this endpoint. 99999 was used as a space filler and specified that the standard deviation was not calculated, since only 1 subject was assessed.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Placebo	Teriflunomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	2		
Units: scores on a scale				
arithmetic mean (standard deviation)	1.0 (± 99999)	-0.5 (± 2.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Steady-state Trough Concentration (Ctrough) of Teriflunomide

End point title	Pharmacokinetics: Steady-state Trough Concentration (Ctrough) of Teriflunomide

End point description:

Ctrough was defined as the concentration reached by the drug before the next dose is administered. Data for this endpoint was planned to be collected and analysed separately for each dose of teriflunomide. Analysis was performed on PK population which included all randomised subjects exposed to double-blind study medication and had at least 1 PK sample taken. PK samples for teriflunomide 3.5 mg were collected during the PK run-in but all subjects were switched to teriflunomide 7 mg after Week 8. Hence, plasma concentration of teriflunomide 7 mg and 14 mg were reported. Here, 'number of subjects analysed'=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose on Week 36

End point values	Teriflunomide 7 mg	Teriflunomide 14 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	66		
Units: micrograms per millilitre				
arithmetic mean (standard deviation)	53.1 (± 25.3)	67.8 (± 41.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from signature of the informed consent form up to 96 weeks.

Adverse event reporting additional description:

Reported AEs were treatment-emergent AEs (TEAEs), that developed/worsened during TEAE period (time from 1st intake of investigational medicinal product (IMP) to last intake of IMP in 96-weeks double-blind treatment period). Safety population: all randomized subjects exposed to double-blind study drug, regardless of amount of treatment administered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matching to teriflunomide tablet orally QD for 96 weeks.

Reporting group title	Teriflunomide

Reporting group description:

Subjects received 1 teriflunomide tablet, 3.5 mg (in case of BW up to 40 kg) or 7 mg (in case of BW >40 kg) orally QD for 8 weeks. After 8 weeks, based on subjects predicted PK parameters, teriflunomide was administered in following manner up to 96 weeks: if predicted PK parameters <=95th percentile of adult range after 7 mg QD: 1 tablet of 7 mg daily (for BW up to 40 kg) or 1 tablet of 14 mg daily (for BW >40 kg); or if predicted PK parameters >95th percentile of adult range: 1 tablet of 3.5 mg daily (for BW up to 40 kg) or 1 tablet of 7 mg daily (for BW >40 kg). The adult range (5th - 95th percentile) of predicted steady state PK parameters for a 7 mg dose was defined as Cmax ranging from 8.03 to 49.10 mcg/mL and AUC0-24 ranging from 184 to 1160 mcg*h/mL.

Serious adverse events	Placebo	Teriflunomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 57 (10.53%)	12 / 109 (11.01%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 57 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases Increased			

subjects affected / exposed	0 / 57 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Joint Dislocation			
subjects affected / exposed	1 / 57 (1.75%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 57 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Nerve Injury			
subjects affected / exposed	0 / 57 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Familial Mediterranean Fever			
subjects affected / exposed	1 / 57 (1.75%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	0 / 57 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 57 (1.75%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 57 (1.75%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal Fissure			
subjects affected / exposed	1 / 57 (1.75%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Fistula			
subjects affected / exposed	0 / 57 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	0 / 57 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 57 (1.75%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			

subjects affected / exposed	1 / 57 (1.75%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Tuberculosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Teriflunomide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 57 (70.18%)	85 / 109 (77.98%)	
Vascular disorders			
Orthostatic Hypotension			
subjects affected / exposed	2 / 57 (3.51%)	0 / 109 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 57 (5.26%)	4 / 109 (3.67%)	
occurrences (all)	5	6	
Influenza Like Illness			
subjects affected / exposed	1 / 57 (1.75%)	3 / 109 (2.75%)	
occurrences (all)	1	3	
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 57 (0.00%)	4 / 109 (3.67%)	
occurrences (all)	0	4	
Pyrexia			
subjects affected / exposed	2 / 57 (3.51%)	6 / 109 (5.50%)	
occurrences (all)	2	9	
Reproductive system and breast			

disorders			
Dysmenorrhoea			
subjects affected / exposed	3 / 57 (5.26%)	1 / 109 (0.92%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 57 (5.26%)	6 / 109 (5.50%)	
occurrences (all)	3	7	
Dyspnoea			
subjects affected / exposed	0 / 57 (0.00%)	3 / 109 (2.75%)	
occurrences (all)	0	3	
Nasal Congestion			
subjects affected / exposed	1 / 57 (1.75%)	3 / 109 (2.75%)	
occurrences (all)	1	3	
Oropharyngeal Pain			
subjects affected / exposed	2 / 57 (3.51%)	7 / 109 (6.42%)	
occurrences (all)	2	8	
Rhinitis Allergic			
subjects affected / exposed	0 / 57 (0.00%)	3 / 109 (2.75%)	
occurrences (all)	0	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 57 (5.26%)	4 / 109 (3.67%)	
occurrences (all)	3	6	
Depression			
subjects affected / exposed	2 / 57 (3.51%)	2 / 109 (1.83%)	
occurrences (all)	2	2	
Insomnia			
subjects affected / exposed	3 / 57 (5.26%)	0 / 109 (0.00%)	
occurrences (all)	3	0	
Investigations			
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 57 (0.00%)	4 / 109 (3.67%)	
occurrences (all)	0	6	
Neutrophil Count Decreased			

subjects affected / exposed	0 / 57 (0.00%)	3 / 109 (2.75%)	
occurrences (all)	0	5	
Protein Urine Present			
subjects affected / exposed	1 / 57 (1.75%)	3 / 109 (2.75%)	
occurrences (all)	1	4	
Weight Decreased			
subjects affected / exposed	2 / 57 (3.51%)	6 / 109 (5.50%)	
occurrences (all)	2	7	
Weight Increased			
subjects affected / exposed	0 / 57 (0.00%)	3 / 109 (2.75%)	
occurrences (all)	0	4	
White Blood Cell Count Decreased			
subjects affected / exposed	1 / 57 (1.75%)	4 / 109 (3.67%)	
occurrences (all)	1	7	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	3 / 57 (5.26%)	4 / 109 (3.67%)	
occurrences (all)	6	4	
Contusion			
subjects affected / exposed	0 / 57 (0.00%)	4 / 109 (3.67%)	
occurrences (all)	0	4	
Fall			
subjects affected / exposed	4 / 57 (7.02%)	6 / 109 (5.50%)	
occurrences (all)	5	8	
Ligament Sprain			
subjects affected / exposed	2 / 57 (3.51%)	1 / 109 (0.92%)	
occurrences (all)	2	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 57 (0.00%)	3 / 109 (2.75%)	
occurrences (all)	0	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 57 (7.02%)	9 / 109 (8.26%)	
occurrences (all)	5	9	
Headache			

subjects affected / exposed	13 / 57 (22.81%)	18 / 109 (16.51%)	
occurrences (all)	18	30	
Hypoaesthesia			
subjects affected / exposed	3 / 57 (5.26%)	6 / 109 (5.50%)	
occurrences (all)	5	7	
Paraesthesia			
subjects affected / exposed	1 / 57 (1.75%)	12 / 109 (11.01%)	
occurrences (all)	2	20	
Presyncope			
subjects affected / exposed	0 / 57 (0.00%)	3 / 109 (2.75%)	
occurrences (all)	0	3	
Tremor			
subjects affected / exposed	2 / 57 (3.51%)	1 / 109 (0.92%)	
occurrences (all)	3	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 57 (1.75%)	3 / 109 (2.75%)	
occurrences (all)	1	3	
Neutropenia			
subjects affected / exposed	0 / 57 (0.00%)	3 / 109 (2.75%)	
occurrences (all)	0	5	
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	2 / 57 (3.51%)	3 / 109 (2.75%)	
occurrences (all)	2	3	
Tinnitus			
subjects affected / exposed	1 / 57 (1.75%)	3 / 109 (2.75%)	
occurrences (all)	1	3	
Eye disorders			
Eye Pain			
subjects affected / exposed	4 / 57 (7.02%)	4 / 109 (3.67%)	
occurrences (all)	8	4	
Vision Blurred			
subjects affected / exposed	2 / 57 (3.51%)	2 / 109 (1.83%)	
occurrences (all)	3	3	
Visual Impairment			

subjects affected / exposed	2 / 57 (3.51%)	0 / 109 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 57 (1.75%)	12 / 109 (11.01%)	
occurrences (all)	1	15	
Abdominal Pain Upper			
subjects affected / exposed	2 / 57 (3.51%)	6 / 109 (5.50%)	
occurrences (all)	2	9	
Diarrhoea			
subjects affected / exposed	4 / 57 (7.02%)	8 / 109 (7.34%)	
occurrences (all)	4	9	
Nausea			
subjects affected / exposed	4 / 57 (7.02%)	9 / 109 (8.26%)	
occurrences (all)	5	11	
Vomiting			
subjects affected / exposed	5 / 57 (8.77%)	5 / 109 (4.59%)	
occurrences (all)	5	6	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 57 (3.51%)	0 / 109 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	4 / 57 (7.02%)	5 / 109 (4.59%)	
occurrences (all)	4	5	
Alopecia			
subjects affected / exposed	7 / 57 (12.28%)	23 / 109 (21.10%)	
occurrences (all)	7	25	
Rash			
subjects affected / exposed	2 / 57 (3.51%)	4 / 109 (3.67%)	
occurrences (all)	2	4	
Endocrine disorders			
Autoimmune Thyroiditis			
subjects affected / exposed	2 / 57 (3.51%)	1 / 109 (0.92%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	3 / 57 (5.26%)	2 / 109 (1.83%)	
occurrences (all)	7	2	
Back Pain			
subjects affected / exposed	2 / 57 (3.51%)	5 / 109 (4.59%)	
occurrences (all)	3	6	
Muscle Spasms			
subjects affected / exposed	2 / 57 (3.51%)	2 / 109 (1.83%)	
occurrences (all)	2	2	
Muscular Weakness			
subjects affected / exposed	2 / 57 (3.51%)	1 / 109 (0.92%)	
occurrences (all)	2	1	
Musculoskeletal Pain			
subjects affected / exposed	0 / 57 (0.00%)	3 / 109 (2.75%)	
occurrences (all)	0	3	
Pain In Extremity			
subjects affected / exposed	2 / 57 (3.51%)	4 / 109 (3.67%)	
occurrences (all)	2	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 57 (1.75%)	5 / 109 (4.59%)	
occurrences (all)	1	5	
Gastroenteritis			
subjects affected / exposed	3 / 57 (5.26%)	3 / 109 (2.75%)	
occurrences (all)	3	3	
Influenza			
subjects affected / exposed	4 / 57 (7.02%)	10 / 109 (9.17%)	
occurrences (all)	4	16	
Nasopharyngitis			
subjects affected / exposed	5 / 57 (8.77%)	28 / 109 (25.69%)	
occurrences (all)	6	49	
Pharyngitis			
subjects affected / exposed	1 / 57 (1.75%)	7 / 109 (6.42%)	
occurrences (all)	1	8	
Respiratory Tract Infection Viral			

subjects affected / exposed	0 / 57 (0.00%)	4 / 109 (3.67%)	
occurrences (all)	0	7	
Rhinitis			
subjects affected / exposed	2 / 57 (3.51%)	4 / 109 (3.67%)	
occurrences (all)	3	8	
Sinusitis			
subjects affected / exposed	2 / 57 (3.51%)	4 / 109 (3.67%)	
occurrences (all)	2	4	
Tinea Versicolour			
subjects affected / exposed	2 / 57 (3.51%)	1 / 109 (0.92%)	
occurrences (all)	2	1	
Tonsillitis			
subjects affected / exposed	2 / 57 (3.51%)	4 / 109 (3.67%)	
occurrences (all)	2	4	
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 57 (10.53%)	23 / 109 (21.10%)	
occurrences (all)	23	64	
Metabolism and nutrition disorders			
Vitamin D Deficiency			
subjects affected / exposed	2 / 57 (3.51%)	2 / 109 (1.83%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2013	Following changes were made: 1 MRI added at Weeks 24, 48 and 96 to strengthen MRI data; 1 MRI added at Week 36 in case of at least 5 new/enlarged T2 lesions; change in volume of T2 lesions, change in volume of T1 hypointense lesions, number of new T1 hypointense lesions, and brain atrophy were added and grouped as MRI endpoints; addition of immunoglobulin (IgG, IgM, and IgA) measurements at Baseline and every 24 weeks, aimed to provide additional information on a potential, although not expected, effect of teriflunomide on the immune system in this age group; poisson regression model changed in negative binomial model for the analysis of the number of new or enlarged T2-lesions and the number of T1 Gd-enhancing lesions per MRI scan. Reduced the impact of potential outliers, ordinal logistic regression model including treatment group, region, pubertal status, and age were also used to analyse these endpoints. The Poisson regression model with a robust error variance was to be used in sensitivity analyses.
26 June 2014	Following changes were made: Extension of the open-label period up to 192 weeks after randomisation; one MRI timepoint added at Week 72; addition of a criterion for switch into open-label period taking this additional MRI scan into account as follows: at least 5 new/enlarged T2 lesions on each of the 2 consecutive MRI scans of Week 48 and Week 72; change in exclusion criteria: the required minimum washout period duration for previous multiple sclerosis (MS) treatment was modified; addition of exclusion criteria: previous treatment with alemtuzumab; addition of a note about the content of teriflunomide tablets (lactose) and that therefore, investigators were to consider whether history of lactose intolerance could affect treatment tolerability; addition of a note about contraception and the association of local additional requirements (United Kingdom) to be followed, e.g., spermicidal foam/gel/film/cream/suppository, as per medicines and healthcare products regulatory agency rules; addition of endpoints: proportion of subjects free of new or enlarged MRI T2-lesions at Weeks 48 and 96. It was specified that the main MRI endpoints were the number of new/newly enlarged T2 lesions and the number of T1 Gd-enhancing T1 lesions; proportion of disease-free subjects as an exploratory endpoint; addition of text to introduce the rationale for placebo-controlled design; addition of endocrine function evaluation consisting of measurement of thyroid stimulating hormone (TSH) every 24 weeks and at end of treatment (EOT); addition of text to specify that local anesthetic was to be offered for blood draws to minimise pain and discomfort; correction of text: Pre-defined adverse events and laboratory abnormalities for specific reporting to restore the instructions that were included in the initial protocol but had been inadvertently taken out in Amended protocol 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported