Clinical trial results:
Exploratory Open Label Study to Investigate the Effect of Teriflunomide on Immune Cell Subsets in the Blood of subjects With Relapsing Forms of Multiple Sclerosis

Summary

EudraCT number	2012-005324-16
Trial protocol	BE NL DE
Global end of trial date	22 January 2015

Results information

Result version number	v1 (current)
This version publication date	16 April 2016
First version publication date	16 April 2016

Trial information

Trial identification

Sponsor protocol code	LPS13539

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01863888
WHO universal trial number (UTN)	U1111-1139-8802

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	500 Kendall Street, Cambridge, MA, 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)	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	30 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To measure the effect of teriflunomide on lymphocytes subsets in subjects with relapsing forms of multiple sclerosis (RMS) as compared with baseline values and those of a reference population of untreated healthy subjects.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Germany: 41
Worldwide total number of subjects	70
EEA total number of subjects	70

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)	70
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 centers in 3 countries (for RMS subjects) and at a single site in Germany (for healthy subjects). A total of 87 subjects (56 RMS subjects and 31 healthy subjects) were screened between 10 October 2013 and 24 June 2014.

Pre-assignment

Screening details:

Of 56 RMS subjects screened, 50 were included and treated in the treatment arm. Of 31 healthy subjects screened, 20 were included in the healthy subjects' arm. 17 subjects (6 RMS subjects and 11 healthy subjects) were screen failure due to unmet inclusion criteria.

Period 1

Period 1 title	Main Study Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	RMS Subjects

Arm description:

Subjects with RMS received teriflunomide 14 mg once daily for 24 weeks.

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

Dosage and administration details:

Teriflunomide 14 mg administered orally once daily.

Arm title	Healthy Subjects

Arm description:

Untreated Healthy subjects followed for 24 weeks.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	RMS Subjects	Healthy Subjects
Started	50	20
Completed	43	20
Not completed	7	0
Consent withdrawn by subject	1	-
Adverse event	1	-
Other than specified	2	-
Lack of efficacy	3	-

Period 2

Period 2 title	Optional Extension Period (RMS Subjects)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	RMS Subjects

Arm description:

Subjects who could not receive the commercial drug due to unavailability at the time of completion of 24 week treatment period, were proposed the extension study and received teriflunomide 14 mg once daily till the availability of commercial teriflunomide.

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

Dosage and administration details:

Teriflunomide 14 mg administered orally once daily.

Number of subjects in period 2[1]	RMS Subjects
Started	20
Completed	19
Not completed	1
Adverse event	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only subjects who could not receive the commercial drug due to unavailability at the time of completion of 24 weeks treatment period, were proposed to continue in the extension study.

Baseline characteristics

Reporting groups	
Reporting group title	RMS Subjects
Reporting group description:	
Subjects with RMS received teriflunomide 14 mg once daily for 24 weeks.	
Reporting group title	Healthy Subjects
Reporting group description:	
Untreated Healthy subjects followed for 24 weeks.	

Reporting group values	RMS Subjects	Healthy Subjects	Total
Number of subjects	50	20	70
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	40.7	42.2	
standard deviation	± 9.4	± 8	-
Gender categorical Units: Subjects			
Female	35	14	49
Male	15	6	21

End points

End points reporting groups

Reporting group title	RMS Subjects
Reporting group description:	
Subjects with RMS received teriflunomide 14 mg once daily for 24 weeks.	
Reporting group title	Healthy Subjects
Reporting group description:	
Untreated Healthy subjects followed for 24 weeks.	
Reporting group title	RMS Subjects
Reporting group description:	
Subjects who could not receive the commercial drug due to unavailability at the time of completion of 24 week treatment period, were proposed the extension study and received teriflunomide 14 mg once daily till the availability of commercial teriflunomide.	

Primary: Change From Baseline In Lymphocytes Subsets

End point title	Change From Baseline In Lymphocytes Subsets[1]
End point description:	
Least square (LS) mean was estimated using mixed effect model with repeated measures (MMRM) approach adjusted on baseline. Analysis was performed on Per Protocol (PP) population consisted of all RMS subjects and healthy subjects with no major pharmacodynamics -related protocol deviations who had at the very minimum pharmacodynamics evaluations at baseline and week 24. Number of subjects analyzed=subjects with available data for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline, Week 12, Week 24.	
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: Only descriptive statistics were performed, treated and untreated arms were not compared.	

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	19		
Units: Percentage of Lymphocytes (in % PBMCs)				
least squares mean (standard error)				
At Week 12	-3.32 (± 1.3)	3.36 (± 1.07)		
At Week 24	-3.05 (± 1.43)	2.04 (± 1.38)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in T-Cells Subset Parameters

End point title	Change from Baseline in T-Cells Subset Parameters[2]

End point description:

Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint. Here 'n' signifies number of subjects with available data for T-cells subset parameters.

End point type	Primary

End point timeframe:

Baseline, Week 12, Week 24.

Notes:

[2] - 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: Only descriptive statistics were performed, treated and untreated arms were not compared.

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	19		
Units: Percentage of T cell subsets				
median (full range (min-max))				
CD4+ (in % of CD3+) at Week 12 (n=38,19)	1.9 (-8 to 10)	-0.8 (-21 to 2)		
CD4+ (in % of CD3+) at Week 24 (n=38,19)	1.6 (-15 to 6)	-0.8 (-25 to 4)		
HLADR+(in % CD4+) at Week 12 (n=38,19)	1 (-3 to 5)	0.9 (0 to 7)		
HLADR+(in % CD4+) at Week 24 (n=38,19)	0 (-5 to 6)	0.4 (-4 to 6)		
CD69+ (in % of CD4+) at Week 12 (n=38,19)	0.2 (-5 to 5)	0.2 (0 to 1)		
CD69+ (in % of CD4+) at Week 24 (n=38,19)	0.2 (-6 to 2)	0.2 (-1 to 3)		
Th17 (in % CD4+) at Week 12 (n=32,19)	0 (0 to 1)	0 (0 to 0)		
Th17 (in % CD4+) at Week 24 (n=32,19)	0 (0 to 1)	0 (0 to 0)		
Th1 (in % CD4+) at Week 12 (n=32,19)	-0.5 (-3 to 3)	0.8 (-3 to 2)		
Th1 (in % CD4+) at Week 24 (n=32,19)	-0.4 (-5 to 2)	0.7 (-2 to 3)		
CD8+ (in % of CD3+) at Week 12 (n=38,19)	-1.5 (-9 to 5)	0.9 (-2 to 21)		
CD8+ (in % of CD3+) at Week 24 (n=38,19)	-1 (-6 to 16)	0.6 (-4 to 24)		
HLADR+ (in % CD8+) at Week 12 (n=38,19)	-2.2 (-21 to 12)	3.3 (-1 to 62)		
HLADR+ (in % CD8+) at Week 24 (n=38,19)	-4.8 (-22 to 18)	1.4 (-9 to 21)		
CD69+ (in % of CD8+) at Week 12 (n=38,19)	2.4 (-21 to 30)	3.5 (-35 to 10)		
CD69+ (in % of CD8+) at Week 24 (n=38,19)	7 (-28 to 44)	4.7 (-33 to 18)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in T-Cells Subset Parameters (Continued)

End point title	Change from Baseline in T-Cells Subset Parameters (Continued)[3]

End point description:

LS mean was estimated using a MMRM approach adjusted on baseline. Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 12, Week 24

Notes:

[3] - 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: Only descriptive statistics were performed, treated and untreated arms were not compared.

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	19		
Units: Percentage of T cell subsets				
least squares mean (standard error)				
FoxP3+ (in % of CD4+) at Week 12	0.28 (± 0.28)	0.03 (± 0.14)		
FoxP3+ (in % of CD4+) at Week 24	0.31 (± 0.26)	-0.35 (± 0.19)		
Helios+FoxP3+ (in % of CD4) at Week 12	0.1 (± 0.22)	-0.15 (± 0.15)		
Helios+FoxP3+ (in % of CD4) at Week 24	0.01 (± 0.19)	-0.25 (± 0.15)		
Helios-FoxP3+ (in % of CD4+) at Week 12	0.18 (± 0.08)	0.19 (± 0.14)		
Helios-FoxP3+ (in % of CD4+) at Week 24	0.29 (± 0.1)	-0.08 (± 0.08)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in T-cells Subset Parameters [CD4+/CD8+ Ratio]

End point title	Change from Baseline in T-cells Subset Parameters [CD4+/CD8+ Ratio][4]

End point description:

A CD4+ (in % of CD3+)/CD8+ (in % of CD3+) ratio was performed. Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 12, Week 24

Notes:

[4] - 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: Only descriptive statistics were performed, treated and untreated arms were not compared.

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	19		
Units: Ratio				
median (full range (min-max))				
At Week 12	0.9 (-8 to 9)	-0.3 (-15 to 2)		
At Week 24	0.6 (-6 to 24)	-0.3 (-15 to 3)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in NK Cells Subset Parameters

End point title	Change from Baseline in NK Cells Subset Parameters[5]

End point description:

Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 12, Week 24.

Notes:

[5] - 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: Only descriptive statistics were performed, treated and untreated arms were not compared.

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	19		
Units: Percentage of NK cells				
median (full range (min-max))				
NK cells (in % of lymphocytes) at Week 12	-0.2 (-12 to 11)	0.3 (-6 to 10)		
NK cells (in % of lymphocytes) at Week 24	0.3 (-22 to 9)	1.1 (-10 to 10)		
CD56dimCD16+ (in % of NK cells) at Week 12	0.1 (-39 to 23)	4.1 (-6 to 22)		
CD56dimCD16+ (in % of NK cells) at Week 24	0.4 (-27 to 35)	8.1 (-5 to 21)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in NK Cells Subset Parameters (Continued)

End point title	Change from Baseline in NK Cells Subset Parameters (Continued)[6]

End point description:

LS mean was estimated using a MMRM approach adjusted on baseline. Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 12, Week 24

Notes:

[6] - 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: Only descriptive statistics were performed, treated and untreated arms were not compared.

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	19		
Units: Percentage of NK cells				
least squares mean (standard error)				
CD56brightCD16/ dim (in % of NK cells) at Week 12	0.13 (± 0.86)	-0.9 (± 0.52)		
CD56brightCD16/ dim (in % of NK cells) at Week 24	1.9 (± 0.95)	-0.37 (± 0.61)		
CD69+ (in % of CD56brightCD16/ dim) at Week 12	3.37 (± 1.29)	1.7 (± 1.28)		
CD69+ (in % of CD56brightCD16/ dim) at Week 24	3.5 (± 0.93)	5.5 (± 1.64)		
CD69+ (in % of CD56dimCD16+) at Week 12	7.14 (± 2.46)	1.9 (± 1.67)		
CD69+ (in % of CD56dimCD16+) at Week 24	2.48 (± 1.58)	8.85 (± 3.54)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in NKT Cells Subset Parameters

End point title	Change from Baseline in NKT Cells Subset Parameters[7]

End point description:

Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 12, Week 24

Notes:

[7] - 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: Only descriptive statistics were performed, treated and untreated arms were not compared.

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	19		
Units: Percentage of NKT cells				
median (full range (min-max))				
CD3+CD56+ (in % of lymphocytes) at Week 12	-0.1 (-2 to 1)	0 (-1 to 3)		
CD3+CD56+ (in % of lymphocytes) at Week 24	-0.1 (-4 to 2)	0.2 (0 to 1)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in B Cells Subset Parameters

End point title	Change from Baseline in B Cells Subset Parameters[8]

End point description:

Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 12, Week 24

Notes:

[8] - 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: Only descriptive statistics were performed, treated and untreated arms were not compared.

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	19		
Units: Percentage of B cells				
median (full range (min-max))				
CD19+ (in % of lymphocytes) at Week 12	-1.8 (-23 to 14)	-1.8 (-7 to 1)		
CD19+ (in % of lymphocytes) at Week 24	-2 (-25 to 13)	-1.3 (-8 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total Number of Different CD8+ T-Cell Clones

End point title	Change from Baseline in Total Number of Different CD8+ T-Cell Clones

End point description:

Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24.

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: Number of clones				
median (full range (min-max))				
At Week 12	-280001 (-1621815 to 424421)	500907.5 (-191690 to 2455942)		
At Week 24	-592877 (-1333858 to 527410)	814545 (-266108 to 2422501)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total Number of Unique CD8+ T-Cell Clones

End point title	Change from Baseline in Total Number of Unique CD8+ T-Cell Clones

End point description:

LS mean was estimated using a MMRM approach adjusted on baseline. Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24.

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	10		
Units: Number of clones				
least squares mean (standard error)				
At Week 12	-30177 (± 15416.73)	21400.8 (± 9996.99)		
At Week 24	-28535.6 (± 9172.9)	27884.1 (± 11043.98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proliferating CD8+ T Cells

End point title	Change from Baseline in Proliferating CD8+ T Cells

End point description:

LS mean was estimated using a MMRM approach adjusted on baseline. Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24.

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	18		
Units: Percentage of T cells				
least squares mean (standard error)				
At Week 12	-0.86 (± 1.13)	-2.01 (± 1.31)		
At Week 24	-1.53 (± 1.01)	-1.29 (± 0.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proliferating CD8+ T Cells Upon in-vitro Exposure to 100µM Teriflunomide

End point title	Change from Baseline in Proliferating CD8+ T Cells Upon in-vitro Exposure to 100µM Teriflunomide

End point description:

LS mean was estimated using a MMRM approach adjusted on baseline. Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, in-vitro exposure.

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	17		
Units: Percentage of T cells				
least squares mean (standard error)	-32.15 (± 2.15)	-34.5 (± 1.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Cytokine Production Interleukin-2 (IL-2) Upon anti-CD3/CD28 Induction for 24 hours

End point title	Change from Baseline in Cytokine Production Interleukin-2 (IL-2) Upon anti-CD3/CD28 Induction for 24 hours

End point description:

Induction of cytokine production by anti- CD3/CD28 was assessed from samples of subjects at baseline, week 12 and week 24. Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	13		
Units: pg/mL				
median (full range (min-max))				
At Week 12	-93 (-894 to 724)	-29 (-434 to 4013)		
At Week 24	-147 (-2758 to 715)	-165 (-718 to 525)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Cytokine Production Tumor Necrosis Factor (TNFα) Upon anti-CD3/CD28 Induction for 24 hours

End point title	Change from Baseline in Cytokine Production Tumor Necrosis Factor (TNFα) Upon anti-CD3/CD28 Induction for 24 hours

End point description:

LS mean was estimated using a MMRM approach adjusted on baseline. Analysis was performed on PP population. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24

End point values	RMS Subjects	Healthy Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	13		
Units: pg/mL				
least squares mean (standard error)				
At Week 12	-216.21 (± 135.15)	-674.46 (± 243.56)		
At Week 24	-459.64 (± 106.84)	-1361.38 (± 117.16)		

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 informed consent form up to final visit of the subject regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths were AEs developed/worsened and deaths occurred during 'treatment-emergent period'(time from administration of first investigational study drug to last dose of study drug in extension period for those who entered in extension or to last data[lab,vital signs or AE] available for those who did not enter in extension period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	RMS Subjects

Reporting group description:

Subjects with RMS who received at least one dose of teriflunomide 14 mg once daily during the study period (safety population). (Median exposure for main study period is 168 days and for extension period is 140 days)

Reporting group title	Healthy Subjects

Reporting group description:

Untreated healthy subjects followed for 24 weeks.

Serious adverse events	RMS Subjects	Healthy Subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 50 (8.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-Reactive Protein Increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine Leiomyoma			

subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Tendon Rupture			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic Steatosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	RMS Subjects	Healthy Subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 50 (72.00%)	0 / 20 (0.00%)	
Investigations			
Lipase Increased			
subjects affected / exposed	3 / 50 (6.00%)	0 / 20 (0.00%)	
occurrences (all)	4	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 50 (6.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 50 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	5	0	
Paraesthesia			
subjects affected / exposed	7 / 50 (14.00%)	0 / 20 (0.00%)	
occurrences (all)	8	0	
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	7 / 50 (14.00%)	0 / 20 (0.00%)	
occurrences (all)	7	0	
Diarrhoea			
subjects affected / exposed	10 / 50 (20.00%)	0 / 20 (0.00%)	
occurrences (all)	11	0	
Nausea			

subjects affected / exposed	6 / 50 (12.00%)	0 / 20 (0.00%)	
occurrences (all)	7	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	15 / 50 (30.00%)	0 / 20 (0.00%)	
occurrences (all)	15	0	
Pruritus			
subjects affected / exposed	3 / 50 (6.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 50 (6.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Pain In Extremity			
subjects affected / exposed	3 / 50 (6.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 50 (14.00%)	0 / 20 (0.00%)	
occurrences (all)	7	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2013	-Inclusion criteria was changed to define a wash-out period before switching to the study treatment teriflunomide.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported