Clinical trial results:
A Multicentre, Randomised, Double-blind, Placebo-controlled Study of the Efficacy of Supplementary Treatment With Cholecalciferol (Vitamin D3) in Patients With Relapsing- Multiple Sclerosis (RMS) Treated With Subcutaneous Interferon Beta-1a 44 mcg 3 Times Weekly

Summary

EudraCT number	2009-013695-46
Trial protocol	FR
Global end of trial date	12 November 2015

Results information

Result version number	v1 (current)
This version publication date	21 January 2017
First version publication date	21 January 2017

Trial information

Trial identification

Sponsor protocol code	701068-524

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01198132
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.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?	Yes
Primary completion date	30 March 2015
Global end of trial reached?	Yes
Global end of trial date	12 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study the efficacy and safety of supplementary treatment with cholecalciferol (vitamin D3) in patients with relapsing multiple sclerosis (RMS) treated with subcutaneous interferon beta 1a 44 microgram (mcg) 3 times weekly.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 129
Worldwide total number of subjects	129
EEA total number of subjects	129

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)	129
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 129 subjects were randomized. Out of which 126 subjects treated in the study and 90 subjects completed the study.

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	Cholecalciferol

Arm description:

Subjects received Cholecalciferol 100,000 IU one dose fortnightly (equivalent to a daily dose of approximately 7142 IU) for 96 weeks treatment period along with subcutaneous Rebif 44 mcg 3 times a week.

Arm type	Experimental
Investigational medicinal product name	Cholecalciferol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects received Cholecalciferol 100,000 IU one dose fortnightly (equivalent to a daily dose of approximately 7142 IU) for 96 weeks treatment period along with subcutaneous Rebif 44 mcg 3 times a week.

Arm title	Placebo

Arm description:

Subjects received matching placebo to Cholecalciferol once every two weeks orally along with subcutaneous injection of Rebif 44 mcg 3 times weekly.

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

Dosage and administration details:

Subjects received matching placebo to Cholecalciferol once every two weeks orally along with subcutaneous injection of Rebif 44 mcg 3 times weekly.

Number of subjects in period 1	Cholecalciferol	Placebo
Started	63	66
Completed	45	45
Not completed	18	21
Physician decision	5	4
Consent withdrawn by subject	4	5
Sign/symptoms of underlying disease	2	1
Abnormal/clinically significant biologic	1	1
Other Un-specified	3	6
Adverse event, non-fatal	-	1
Lack of efficacy	2	3
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Cholecalciferol
Reporting group description:	
Subjects received Cholecalciferol 100,000 IU one dose fortnightly (equivalent to a daily dose of approximately 7142 IU) for 96 weeks treatment period along with subcutaneous Rebif 44 mcg 3 times a week.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo to Cholecalciferol once every two weeks orally along with subcutaneous injection of Rebif 44 mcg 3 times weekly.	

Reporting group values	Cholecalciferol	Placebo	Total
Number of subjects	63	66	129
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	38.5	36.9	
standard deviation	± 9.29	± 8.34	-
Gender, Male/Female			
Units: subjects			
Female	50	39	89
Male	13	27	40

End points

End points reporting groups

Reporting group title	Cholecalciferol

Reporting group description:

Subjects received Cholecalciferol 100,000 IU one dose fortnightly (equivalent to a daily dose of approximately 7142 IU) for 96 weeks treatment period along with subcutaneous Rebif 44 mcg 3 times a week.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo to Cholecalciferol once every two weeks orally along with subcutaneous injection of Rebif 44 mcg 3 times weekly.

Subject analysis set title	All Subjects
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received Cholecalciferol (Vitamin D3) 100 000 International units (IU) [1 IU - 1 IU biological equivalent of 0.025 microgram (mcg) cholecalciferol] one dose every two week orally (equivalent to a daily dose of approximately 7142 IU) for 96 weeks treatment period along with sub-cutaneous injection of Rebif 44 mcg 3 times a week and subjects received matching placebo to Cholecalciferol once every two weeks orally along with sub-cutaneous injection of Rebif 44 mcg 3 times weekly.

Primary: Reduction in Rate of Relapse

End point title	Reduction in Rate of Relapse[1]

End point description:

Relapse rate was expressed as rate ratio between the two groups. Relapse rate was calculated for each treatment group as follows: the number of relapses observed during the trial period divided by the number of subject years at risk. Intent-to-treat (ITT) set included all randomized subjects.

End point type	Primary

End point timeframe:

2 years post treatment (Investigational Medicinal product: IMP) administration

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: Due to database constraint, a separate document has been attached presenting the statistical analysis for this endpoint.

End point values	All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	129			
Units: ratio				
number (confidence interval 95%)	0.8 (0.48 to 1.32)			

Attachments (see zip file)	Statistical Analysis 1.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Documented Relapse

End point title	Time to First Documented Relapse

End point description:

Time to First Documented Relapse was calculated using Kaplan-Meier survival methods. ITT set included all randomized subjects. Here "Number of participant analyzed" signifies those subjects who were evaluable for this outcome measure. Here "99999" signifies Median and Confidence interval could not be calculated due to a limited number of events.

End point type	Secondary

End point timeframe:

2 years post treatment (IMP) administration

End point values	Cholecalciferol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	65		
Units: weeks				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (60.1 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Number of Relapses per Subject

End point title	Mean Number of Relapses per Subject

End point description:

Relapse rate was calculated for each treatment group as follows: the number of relapses observed during the trial period divided by the number of subject years at risk. ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

2 years post treatment (IMP) administration

End point values	Cholecalciferol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	66		
Units: relapses				
median (full range (min-max))	0 (0 to 3)	0 (0 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Relapse-Free (Documented) Subjects

End point title	Number of Relapse-Free (Documented) Subjects

End point description:

The relapse-free patients after 2 years of treatment was calculated using Cochran-Mantel-Haenszel test using the site as control variable. ITT set included all randomized subjects. Here "Number of subjects analysed" those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

2 years post treatment (IMP) administration

End point values	Cholecalciferol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	46		
Units: subjects				
number (not applicable)	35	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Probability of Progression of Disability

End point title	Cumulative Probability of Progression of Disability

End point description:

Disability progression was assessed using Expanded disability status scale (EDSS). EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated. A one-point increase on the EDSS scale was considered as a progression in disability. The time to disability progression was summarized using Kaplan-Meier survival methods. ITT set included all randomized subjects. Here "Number of subjects analysed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

2 years post treatment (IMP) administration

End point values	Cholecalciferol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	65		
Units: cumulative probability				
number (not applicable)	12.7	9.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of New or Extended Lesions by T1- and T2-Weighted Magnetic

Resonance Imaging (MRI)

End point title	Number of New or Extended Lesions by T1- and T2-Weighted Magnetic Resonance Imaging (MRI)

End point description:

ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

2 years post treatment (IMP) administration

End point values	Cholecalciferol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[2]	41[3]		
Units: lesions				
arithmetic mean (standard deviation)				
T1-weighted MRI	0.4 (± 0.76)	1.9 (± 3.76)		
T2-weighted MRI	0.5 (± 0.79)	2 (± 4.71)		

Notes:

[2] - Here "N" signifies number of participant analysed for this endpoint.

[3] - Here "N" signifies number of participant analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Measured Lesion Load (T2)

End point title	Changes From Baseline in Measured Lesion Load (T2)

End point description:

Baseline defined as last value recorded prior to first intake of study drug. ITT set included all randomized subjects. Here "n" signifies those subjects who were evaluable for this outcome measure at the specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Cholecalciferol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	66		
Units: cubic millimeter (mm^3)				
arithmetic mean (standard deviation)				
Baseline (n=49, 43)	5305.4 (± 10858.86)	3520.1 (± 4954.44)		
Change at Week 96 (n=44, 38)	-315 (± 2523.97)	596.3 (± 2034.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement and Evaluation of Cognitive Ability by Paced Auditory Serial Addition Task (PASAT)

End point title	Measurement and Evaluation of Cognitive Ability by Paced Auditory Serial Addition Task (PASAT)

End point description:

The Adapted Paced Auditory Serial Addition Task (PASAT) is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. The score for PASAT is the total number of correct answers (out of 60, for a total possible score ranging from 0-60 with higher score preferred as it indicates higher auditory processing speed) for each trial. The PASAT test score was summarized per treatment group at each visit. The variations compared to the baseline values was calculated and summarized. The variations between the baseline values and the values after 2 years between the treatment groups was compared using analysis of covariance methods including the baseline value as covariate. ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

2 years post treatment (IMP) administration

End point values	Cholecalciferol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	66		
Units: units on a scale				
arithmetic mean (standard deviation)	49.1 (± 10.88)	49.9 (± 10.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Euro Quality of Life Scale (EuroQol) 5-Dimension-3 Level (EQ-5D-3L)

End point title	Change from Baseline in Euro Quality of Life Scale (EuroQol) 5-Dimension-3 Level (EQ-5D-3L)

End point description:

The EQ-5D health questionnaire is a generic self-reported health-related quality of life instrument that includes a 100 mm Visual Analog Scale (VAS) to measure the general health state, as well as 5 items corresponding to one dimension each: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In this study, the VAS scale is not collected and the version 3L of the scale was used: Each dimension had 3 possible levels: 1 = no problem, 2 = some problems and 3 = extreme problems. EQ-5D-3L weighted health state index exists that combines the score of the 5 dimensions and ranges from 0 to 1 (full health). The variables for the 5 dimensions of the EQ-5D descriptive system was named 'mobility','selfcare', 'activity', 'pain', and 'anxiety'. The 5 variables contained the values for the

different dimensions in the EQ-5D health profile (i.e. 1, 2, or 3). ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

2 years post treatment (IMP) administration

End point values	Cholecalciferol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	66		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=60, 63)	0.7834 (± 0.2409)	0.7937 (± 0.21447)		
Change at Week 96 (n=43, 45)	-0.0051 (± 0.13742)	0.0043 (± 0.19654)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious TEAEs and Abnormal Clinical Laboratory

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious TEAEs and Abnormal Clinical Laboratory

End point description:

A serious TEAE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect. Clinical laboratory abnormalities are expected to be reported as adverse events if they met any criterion for seriousness, led to treatment discontinuation, required a medical intervention or were considered clinically significant by the investigator. Safety set included all subjects who receive at least one administration of trial medication.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment (week 96)

End point values	Cholecalciferol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	65		
Units: subjects				
number (not applicable)				
TEAEs	43	35		
Serious TEAEs	11	10		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline till the end of the study (week 96)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Cholecalciferol
Reporting group description:	
Subjects received Cholecalciferol 100,000 IU one dose fortnightly (equivalent to a daily dose of approximately 7142 IU) for 96 weeks treatment period along with subcutaneous Rebif 44 mcg 3 times a week.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo to Cholecalciferol once every two weeks orally along with subcutaneous injection of Rebif 44 mcg 3 times weekly.	

Serious adverse events	Cholecalciferol	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 61 (18.03%)	10 / 65 (15.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced complete			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plastic surgery to the face			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy on contraceptive			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy on oral contraceptive			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy after post coital contraception			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal death			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (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			
Foot fracture			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Stress cardiomyopathy			

subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal mass			

subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Psoriatic arthropathy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 61 (1.64%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
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: 0 %

Non-serious adverse events	Cholecalciferol	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 61 (65.57%)	31 / 65 (47.69%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Vascular disorders			
Arterial disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	1 / 61 (1.64%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 61 (6.56%)	2 / 65 (3.08%)	
occurrences (all)	4	3	
Cyst			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 61 (1.64%)	5 / 65 (7.69%)	
occurrences (all)	1	5	
Injection site erythema			
subjects affected / exposed	2 / 61 (3.28%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Injection site pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Injection site reaction			

subjects affected / exposed	1 / 61 (1.64%)	2 / 65 (3.08%)	
occurrences (all)	1	2	
Malaise			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Social circumstances			
Menopause			
subjects affected / exposed	3 / 61 (4.92%)	0 / 65 (0.00%)	
occurrences (all)	4	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Erectile dysfunction			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Menorrhagia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	2 / 61 (3.28%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Dyspnoea			
subjects affected / exposed	1 / 61 (1.64%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 61 (1.64%)	4 / 65 (6.15%)	
occurrences (all)	1	4	
Pulmonary hypertension			

subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	0 / 61 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Snoring			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 61 (3.28%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Depression			
subjects affected / exposed	5 / 61 (8.20%)	3 / 65 (4.62%)	
occurrences (all)	6	3	
Depressive symptom			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Stress			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Creatinine urine increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			

subjects affected / exposed	2 / 61 (3.28%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Normetanephrine urine increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Serum ferritin increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	2 / 61 (3.28%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Urine calcium/creatinine ratio increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
White blood cell count decreased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Breast injury			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	3 / 61 (4.92%)	0 / 65 (0.00%)	
occurrences (all)	4	0	
Head injury			
subjects affected / exposed	2 / 61 (3.28%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Ligament sprain			

subjects affected / exposed	1 / 61 (1.64%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Limb injury			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Road traffic accident			
subjects affected / exposed	0 / 61 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Skin abrasion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Spinal column injury			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Tooth fracture			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	4 / 61 (6.56%)	1 / 65 (1.54%)	
occurrences (all)	4	1	
Migraine			
subjects affected / exposed	3 / 61 (4.92%)	1 / 65 (1.54%)	
occurrences (all)	3	1	
Optic neuritis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Presyncope			

subjects affected / exposed	1 / 61 (1.64%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Radiculitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphopenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 61 (1.64%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Aphthous stomatitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	0 / 61 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Dental discomfort			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	

Gastritis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Gingival pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	2 / 61 (3.28%)	0 / 65 (0.00%)	
occurrences (all)	5	0	
Nausea			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	3	
Dry skin			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Erythema nodosum			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Skin necrosis			
subjects affected / exposed	2 / 61 (3.28%)	0 / 65 (0.00%)	
occurrences (all)	3	0	
Skin reaction			

subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 61 (1.64%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Articular calcification			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	2 / 61 (3.28%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Psoriatic arthropathy			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 61 (1.64%)	4 / 65 (6.15%)	
occurrences (all)	1	4	
Bronchitis viral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	2 / 61 (3.28%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	1 / 61 (1.64%)	4 / 65 (6.15%)	
occurrences (all)	1	4	
Gingivitis			
subjects affected / exposed	2 / 61 (3.28%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Hordeolum			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	3 / 61 (4.92%)	1 / 65 (1.54%)	
occurrences (all)	4	1	
Nasopharyngitis			
subjects affected / exposed	3 / 61 (4.92%)	4 / 65 (6.15%)	
occurrences (all)	4	6	
Oral candidiasis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	2	

Sinusitis			
subjects affected / exposed	1 / 61 (1.64%)	2 / 65 (3.08%)	
occurrences (all)	1	2	
Tooth abscess			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Tracheobronchitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	4 / 61 (6.56%)	4 / 65 (6.15%)	
occurrences (all)	4	5	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Metabolic syndrome			
subjects affected / exposed	1 / 61 (1.64%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	2 / 61 (3.28%)	2 / 65 (3.08%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2009	- Specified the equivalent daily dose of Uvedose in IU for the group A. - Specified that the number of new T1-weighted lesions and MRI variation parameters (brain volume, volume of T2 lesions, total number of Gd-enhanced lesions, volume of hypo-intense lesions) were summarized at visits V1 and V6 (week 96) by treatment group
30 October 2009	- Added "Patients with osteoporosis or known osteopenia" as an exclusion criterion
09 December 2009	- Replaced 25 Hydroxyvitamin-D3 (25(OH)D) by 25-hydroxyvitamin D (25(OH)D) - Removed spinal IRM, added a central review of the MRI, changed the text regarding the method of measuring the change in brain volume (defined as any change in normalized brain volume between baseline and final assessment parameters), described the MRI procedure (2 CD, anonymisation of the data, and 1 CD sent to the centralized reviewer).
08 June 2010	- Added changes requested by the Data Safety Monitoring Board (DSMB) on the safety assessments: Removed "measure of albumin in urine samples." - Added conditions for the premature discontinuation: lithiasis with clinical and/or radiological expression and adjustment of clinically significant laboratory abnormalities - Added renal lithiasis expressed clinically or discovered by accident, during an X-ray examination as AEs potentially related to Vitamin D overdose - Removed bony side events as a clinical events of hypercalcemia and replaced by the following General clinical signs: bilateral renal lithiasis with nephrocalcinosis; gastroduodenal ulcer; acute calcifying pancreatitis; hypertension; articular chondrocalcinosis; signs of chronic hypercalcemia, and add nausea, vomiting, anorexia
01 June 2011	- Changed to allow the 22mcg dose for Rebif in the clinical study (44mcg dose is the recommended dose however the 22mcg dose is recommended if the highest dose is not tolerated) and to increase the window time from 2 to 4 months for the subject selection in order to allow a better tolerance prior the randomization visit (V2) as flu-syndromes and tiredness are more important at the beginning of the treatment. The inclusion criteria was modified accordingly - Corrected exclusion criteria "Inadequate marrow reserves, defined as white blood cells inferior to 0.5 x lower limit of normal" and not "superior to" - Specified that Rebif has exception drug status requiring special monitoring during treatment and prescribed by a specialized physician (neurologist) - Added vitamin D-enriched food supplements without consulting the Investigator as prohibited medications - DSMB committee requested to add "corrected calcemia" in addition of "calcemia" for the clinically significant laboratory abnormalities. - Corrected to allow a biological re-test as needed prior the subject randomization and extension of the screening period from 8 to 17 weeks in case of biological re-tests.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported