Clinical trial results:
A Three Arm, Randomized, Double Blind, Placebo Controlled, Multicenter, Phase II Study to Evaluate the Efficacy of Vigantol Oil as Add on Therapy in Subjects With Relapsing Remitting Multiple Sclerosis Receiving Treatment With 44mg Tiw of Rebif.

Summary

EudraCT number	2010-020328-23
Trial protocol	FI NL DE DK BE IT LT EE LV AT PT
Global end of trial date	19 May 2015

Results information

Result version number	v2 (current)
This version publication date	09 September 2016
First version publication date	07 June 2016
Version creation reason	• New data added to full data set New data added to full data set

Trial information

Trial identification

Sponsor protocol code	EMR 200136-532

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01285401
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Serono, a division of Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Merck KGaA Communication Center, Merck Serono, a division of Merck KGaA, service@merckgroup.com
Scientific contact	Merck KGaA Communication Center, Merck Serono, a division of Merck KGaA, 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	26 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The drug being tested is called VigantOL® oil - a very effective form of Vitamin D hormone supplement (cholecalciferol). Low levels of Vitamin D have been described to be associated with a higher risk of developing Multiple Sclerosis (MS), and it is known that up to 90% of patients with Multiple Sclerosis have Vitamin D deficiency.
Rebif® is known to be an effective treatment for slowing down the progression of MS. The purpose of this research trial is to evaluate if VigantOL® oil along with Rebif® has any benefit on the progression of MS compared to Rebif® and placebo.
Disease activity was assessed by clinical examination and Magnetic Resonance Imaging (MRI). The planned study treatment duration for each study subject is 48 weeks, and the study consists of a total of 8 visits. Study subjects who are already passed Week 48 at the time of approval of Protocol Amendment 5 had a study duration of 96 weeks and a total of 12 visits.

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	15 February 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 26
Country: Number of subjects enrolled	Estonia: 10
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Latvia: 7
Country: Number of subjects enrolled	Lithuania: 3
Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Netherlands: 65
Country: Number of subjects enrolled	Switzerland: 15
Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Italy: 30

Worldwide total number of subjects	232
EEA total number of subjects	217

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)	232
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Total 232 subject were randomised in the study was analyzed based on 229 subjects since 3 subjects of the 232 randomized subjects were excluded from analysis as they did not received any medication.

Pre-assignment

Screening details:

NA

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	VigantOL oil interferon beta-1a (Rebif)

Arm description:

Subjects with 25-hydroxyvitamin D [25(OH)D3] serum levels below 150 nano mol per liter (nmol/L) received Vigantol oil 6,670 international unit per day (IU/d) [167 microgram per day (mcg/d)] orally for 4 weeks followed by 14,007 IU/d (350 mcg/d) for 44 weeks along with Rebif 44 mcg administered subcutaneous three times a week (tiw).

Arm type	Experimental
Investigational medicinal product name	Vigantol oil
Investigational medicinal product code	
Other name	Cholecalciferol, Vitamin D3
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

Subjects received Vigantol oil 6,670 international unit per day (IU/d) [167 microgram per day (mcg/d)] orally for 4 weeks, followed by 14,007 IU/d (350 mcg/d) for 44 weeks.

Investigational medicinal product name	Rebif
Investigational medicinal product code	
Other name	Interferon beta-1a
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subject were administered Rebif 44 mcg administered subcutaneous three times a week (tiw).

Arm title	Placebo interferon beta-1a (Rebif)

Arm description:

Subjects with 25(OH)D3 serum levels below 150 nmol/L, received matching placebo for 48 weeks along with Rebif 44 mcg administered subcutaneous tiw.

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

Dosage and administration details:	
Subject received placebo matching Vigantol oil for 44 weeks.	
Investigational medicinal product name	Rebif
Investigational medicinal product code	
Other name	Interferon beta-1a
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received Rebif 44 mcg administered subcutaneous tiw.

Number of subjects in period 1	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)
Started	115	117
Treated	113	116
Completed	98	88
Not completed	17	29
Prematurely withdrawn from the study	17	29

Baseline characteristics

Reporting groups	
Reporting group title	VigantOL oil interferon beta-1a (Rebif)
Reporting group description:	
Subjects with 25-hydroxyvitamin D [25(OH)D3] serum levels below 150 nano mol per liter (nmol/L) received Vigantol oil 6,670 international unit per day (IU/d) [167 microgram per day (mcg/d)] orally for 4 weeks followed by 14,007 IU/d (350 mcg/d) for 44 weeks along with Rebif 44 mcg administered subcutaneous three times a week (tiw).	
Reporting group title	Placebo interferon beta-1a (Rebif)
Reporting group description:	
Subjects with 25(OH)D3 serum levels below 150 nmol/L, received matching placebo for 48 weeks along with Rebif 44 mcg administered subcutaneous tiw.	

Reporting group values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)	Total
Number of subjects	115	117	232
Age categorical Units: Subjects			
Age Continuous			
Baseline analysis set included all randomized subjects.			
Units: years			
arithmetic mean	34.2	33.6	
standard deviation	± 8.1	± 9.3	-
Gender, Male/Female Units: subjects			
Female	78	79	157
Male	37	38	75

End points

End points reporting groups

Reporting group title	VigantOL oil interferon beta-1a (Rebif)
Reporting group description:	
Subjects with 25-hydroxyvitamin D [25(OH)D3] serum levels below 150 nano mol per liter (nmol/L) received Vigantol oil 6,670 international unit per day (IU/d) [167 microgram per day (mcg/d)] orally for 4 weeks followed by 14,007 IU/d (350 mcg/d) for 44 weeks along with Rebif 44 mcg administered subcutaneous three times a week (tiw).	
Reporting group title	Placebo interferon beta-1a (Rebif)
Reporting group description:	
Subjects with 25(OH)D3 serum levels below 150 nmol/L, received matching placebo for 48 weeks along with Rebif 44 mcg administered subcutaneous tiw.	

Primary: Percentage of Subjects With Disease Activity Free Status up to Week 48

End point title	Percentage of Subjects With Disease Activity Free Status up to Week 48[1]
End point description:	
Disease activity free status was defined as absence of any of the clinical and imaging parameters related to the assessment of disease activity; no relapses, no expanded disability status scale (EDSS) progression and no new gadolinium (Gd)-enhancing or relaxation time 2 (T2) magnetic resonance imaging (MRI) lesions. ITT set included all randomised subjects who received at least 1 dose of the IMP.	
End point type	Primary
End point timeframe:	
Up to Week 48	

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: Since analysis is descriptive in nature, statistical data could not be provided.

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percentage of subjects				
number (not applicable)	37.2	35.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of relapse-free subjects at Week 48

End point title	Percentage of relapse-free subjects at Week 48
End point description:	
A relapse was defined as the development of new or the exacerbation of existing neurological symptoms or signs, in the absence of fever, lasting for 24 hours and with a previous period for more than 30 days with a stable or an improving condition. ITT set included all randomised subjects who received at least 1 dose of the IMP.	
End point type	Secondary

End point timeframe:

Week 48

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percentage of subjects				
number (not applicable)	78.8	75		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects free from any Expanded Disability Status Scale (EDSS) progression at Week 48

End point title	Percentage of subjects free from any Expanded Disability Status Scale (EDSS) progression at Week 48

End point description:

EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated. A confirmed EDSS progression was defined EDSS greater than or equal to 1.0 point confirmed during a visit performed 6 months later. An EDSS progression was defined as an increase of the EDSS score of at least 1.0 point compared to baseline (SD1) for subjects with a baseline EDSS ≤ 4.0. For subjects with an EDSS score of 0 at baseline (SD1), EDSS progression was defined as an increase of at least 1.5 points. A confirmed EDSS progression was defined as an EDSS progression confirmed after 24 weeks.

End point type	Secondary

End point timeframe:

Week 48

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percentage of subjects				
number (not applicable)	71.7	75		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Confirmed EDSS Progression

End point title	Number of Subjects With Confirmed EDSS Progression

End point description:

EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated. A confirmed EDSS progression was defined EDSS greater than or equal to 1.0 point confirmed during a visit performed 6 months later. An EDSS progression was defined as an increase of the EDSS score of at least 1.0 point compared to baseline (SD1) for subjects with a baseline EDSS ≤ 4.0. For subjects with an EDSS score of 0 at baseline (SD1), EDSS progression was defined as an increase of at least 1.5 points. A confirmed EDSS progression was defined as an EDSS progression confirmed after 24 weeks. ITT analysis set consisted of all randomized subjects who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

Baseline upto 48 Weeks

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: subjects				
number (not applicable)	8	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative number of Relaxation time 1 (T1) gadolinium enhancing lesions at Week 48

End point title	Cumulative number of Relaxation time 1 (T1) gadolinium enhancing lesions at Week 48

End point description:

ITT set included all randomised subjects who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

48 Weeks

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[2]	92[3]		
Units: lesions per subject per scan				
arithmetic mean (standard deviation)	0.36 (± 1.73)	0.25 (± 0.67)		

Notes:

[2] - Here "N" signifies number of subject analyzed for respective outcome measure.

[3] - Here "N" signifies number of subject analyzed for respective outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of combined unique active (CUA) lesions per subject per scan at Week 48

End point title	Mean number of combined unique active (CUA) lesions per subject per scan at Week 48

End point description:

CUA lesions was defined as new T1 (Gd enhancing) lesions, new Relaxation time 2 (T2) lesions, or enlarging T2 lesions. ITT set included all randomised subjects who received at least 1 dose of the IMP. Here "N" signifies number of subjects analyzed for respective outcome measure.

End point type	Secondary

End point timeframe:

48 Weeks

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: lesions per subject per scan				
arithmetic mean (standard deviation)	1.09 (± 3.84)	1.49 (± 4.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative number of new combined unique active (CUA) lesions at Week 48

End point title	Cumulative number of new combined unique active (CUA) lesions at Week 48

End point description:

CUA lesions was defined as new T1 (Gd enhancing) lesions, new T2 lesions, or enlarging T2 lesions. ITT set included all randomised subjects who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

48 Weeks

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: lesions per subject per scan				
arithmetic mean (standard deviation)	1.09 (± 3.84)	1.49 (± 4.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in the total volume of T2 lesions at Week 48 (T2 Burden of disease)

End point title	Mean change from baseline in the total volume of T2 lesions at Week 48 (T2 Burden of disease)
End point description:	
ITT set included all randomised subjects who received at least 1 dose of the IMP.	
End point type	Secondary
End point timeframe:	
Baseline, 48 Weeks	

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[4]	92[5]		
Units: millimeter^3 (mm^3)				
arithmetic mean (standard deviation)	130.38 (± 830.82)	95.75 (± 401.87)		

Notes:

[4] - Here "N" signifies number of subject analyzed for respective outcome measure.

[5] - Here "N" signifies number of subject analyzed for respective outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects free from T1 gadolinium enhancing lesions at Week 48

End point title	Percentage of subjects free from T1 gadolinium enhancing lesions at Week 48
End point description:	
ITT set included all randomised subjects who received at least 1 dose of the IMP.	
End point type	Secondary
End point timeframe:	
48 Weeks	

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percentage of subjects				
number (not applicable)	83.2	70.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects free from new T1 hypointense lesions (black holes) at Week 48

End point title	Percentage of subjects free from new T1 hypointense lesions (black holes) at Week 48

End point description:

ITT set included all randomised subjects who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

48 Weeks

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percentage of subjects				
number (not applicable)	78.8	63.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of new T1 hypointense lesions (black holes) at Week 48 within the subgroup of new or enlarging non-enhancing T2 lesions

End point title	Percentage of new T1 hypointense lesions (black holes) at Week 48 within the subgroup of new or enlarging non-enhancing T2 lesions

End point description:

ITT set included all randomised subjects who received at least 1 dose of the IMP. Here in the subgroup of subjects having new or enlarging T2 lesions.

End point type	Secondary

End point timeframe:

48 Weeks

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[6]	36[7]		
Units: percentage of new T1 hypointense lesions				
arithmetic mean (standard deviation)	20.11 (± 34.72)	27.7 (± 39.33)		

Notes:

[6] - Here "N" signifies number of subject analyzed for respective outcome measure.

[7] - Here "N" signifies number of subject analyzed for respective outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with relapse

End point title	Number of subjects with relapse

End point description:

Relapse was defined as neurological abnormality, either newly appearing or re-appearing, with abnormality specified by both as neurological abnormality separated by at least 30 days from onset of a preceding MS attack and Neurological abnormality lasting for at least 24 hours, absence of fever or known infection greater than 37.5 degree centigrade /99.5 degree fahrenheit , objective neurological impairment, correlating with the subject's reported symptoms, defined as either increase in at least one of the functional systems of the EDSS or increase of the total EDSS score and occurrence of paraesthesia, fatigue, mental symptoms, and/or vegetative symptoms without any additional symptom will not be classified as an MS attack. ITT set included all randomised subjects who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

Baseline upto 48 weeks

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: subjects				
number (not applicable)	24	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Relapse Rate at Week 48

End point title	Annualized Relapse Rate at Week 48

End point description:

Relapse was defined as neurological abnormality, either newly appearing or re-appearing, with abnormality specified by both as neurological abnormality separated by at least 30 days from onset of a preceding MS attack and Neurological abnormality lasting for at least 24 hours, absence of fever or known infection greater than 37.5 degree centigrade /99.5 degree fahrenheit , objective neurological impairment, correlating with the subject's reported symptoms, defined as either increase in at least one of the functional systems of the EDSS or increase of the total EDSS score and occurrence of paraesthesia, fatigue, mental symptoms, and/or vegetative symptoms without any additional symptom will not be classified as an MS attack. ITT set included all randomised subjects who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

48 weeks

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: relapse per year				
arithmetic mean (standard deviation)	0.28 (± 0.59)	0.41 (± 0.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Reported Relapses at all Time Points up to 48 Weeks

End point title	Total Number of Reported Relapses at all Time Points up to 48 Weeks

End point description:

Relapse was defined as neurological abnormality, either newly appearing or re-appearing, with abnormality specified by both as neurological abnormality separated by at least 30 days from onset of a preceding MS attack and Neurological abnormality lasting for at least 24 hours, absence of fever or known infection greater than 37.5 degree centigrade /99.5 degree fahrenheit , objective neurological impairment, correlating with the subject's reported symptoms, defined as either increase in at least one of the functional systems of the EDSS or increase of the total EDSS score and occurrence of paraesthesia, fatigue, mental symptoms, and/or vegetative symptoms without any additional symptom will not be classified as an MS attack. ITT set included all randomised subjects who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

48 weeks

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: number of relapse per subject				
arithmetic mean (standard deviation)	0.25 (± 0.53)	0.34 (± 0.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Treated With Glucocorticoids due to Relapses

End point title	Percentage of Subjects Treated With Glucocorticoids due to Relapses

End point description:

Relapse was defined as neurological abnormality, either newly appearing or re-appearing, with abnormality specified by both as neurological abnormality separated by at least 30 days from onset of a preceding MS attack and Neurological abnormality lasting for at least 24 hours, absence of fever or known infection greater than 37.5 degree centigrade /99.5 degree fahrenheit , objective neurological impairment, correlating with the subject's reported symptoms, defined as either increase in at least one of the functional systems of the EDSS or increase of the total EDSS score and occurrence of paraesthesia, fatigue, mental symptoms, and/or vegetative symptoms without any additional symptom will not be classified as an MS attack. ITT set included all randomised subjects who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

Baseline upto 48 weeks

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percentage of subjects				
number (not applicable)	15.9	20.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the Total Volume of T1 Hypo Intense Lesions at Week 48

End point title	Mean Change From Baseline in the Total Volume of T1 Hypo Intense Lesions at Week 48

End point description:

ITT set included all randomised subjects who received at least 1 dose of the IMP.

End point type	Secondary

End point timeframe:

Baseline, 48 Weeks

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: lesion per subject per scan				
arithmetic mean (standard deviation)	20.88 (± 140.56)	18.47 (± 68.08)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Percentage of Subjects With Disease Activity Free Status (Alternate Definition) at Week 48

End point title	Percentage of Subjects With Disease Activity Free Status (Alternate Definition) at Week 48

End point description:

Disease activity free (DAF) status was defined as absence of any of the clinical and imaging parameters related to the assessment of disease activity; no relapses, no confirmed expanded disability status scale (EDSS) progression and no new gadolinium (Gd)-enhancing or relaxation time 2 (T2) magnetic resonance imaging (MRI) lesions. Confirmed EDSS progression was defined as an EDSS progression confirmed after 24 weeks. ITT set included all randomised subjects who received at least 1 dose of the IMP.

End point type	Post-hoc

End point timeframe:

Week 48

End point values	VigantOL oil interferon beta-1a (Rebif)	Placebo interferon beta-1a (Rebif)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	116		
Units: percentage of subjects				
number (not applicable)	47.8	37.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to end of trial (EOT: 60 months)	
Adverse event reporting additional description:	
Safety Analysis Set: All randomised subjects who received at least 1 dose of the IMP	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups	
Reporting group title	Placebo interferon beta-1a (Rebif)
Reporting group description:	
Subjects with 25(OH)D3 serum levels below 150 nmol/L, received matching placebo for 48 weeks along with Rebif 44 mcg administered subcutaneous tiw.	
Reporting group title	VigantOL oil interferon beta-1a (Rebif)
Reporting group description:	
Subjects with 25(OH)D3 serum levels below 150 nmol/L received Vigantol oil 6,670 IU/d [167 mcg/d] orally for 4 weeks followed by 14,007 IU/d (350 mcg/d) for 44 weeks along with of Rebif 44 mcg administered subcutaneous tiw.	

Serious adverse events	Placebo interferon beta-1a (Rebif)	VigantOL oil interferon beta-1a (Rebif)	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 116 (6.90%)	18 / 113 (15.93%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian cancer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
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			

Overdose			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 116 (5.17%)	8 / 113 (7.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
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	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemorrhoids			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
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	Placebo interferon beta-1a (Rebif)	VigantOL oil interferon beta-1a (Rebif)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 116 (80.17%)	99 / 113 (87.61%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipofibroma			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Morton's neuroma			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Mycosis fungoides			

subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Thyroid neoplasm			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Uterine leiomyoma			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	2	0	
Haematoma			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Haemorrhage			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	4 / 116 (3.45%)	6 / 113 (5.31%)	
occurrences (all)	5	7	
Surgical and medical procedures			
Endodontic procedure			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Hospitalisation			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Mammoplasty			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Parotidectomy			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Shoulder operation			

subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Tooth extraction			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Wisdom teeth removal			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	2	0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Chest discomfort			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	4 / 116 (3.45%)	0 / 113 (0.00%)	
occurrences (all)	4	0	
Chills			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	13 / 116 (11.21%)	8 / 113 (7.08%)	
occurrences (all)	16	8	
Feeling cold			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	3	
Gait disturbance			
subjects affected / exposed	2 / 116 (1.72%)	3 / 113 (2.65%)	
occurrences (all)	2	3	
Inflammation			

subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	13 / 116 (11.21%)	12 / 113 (10.62%)	
occurrences (all)	18	14	
Injection site erythema			
subjects affected / exposed	0 / 116 (0.00%)	4 / 113 (3.54%)	
occurrences (all)	0	6	
Injection site induration			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Injection site inflammation			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Injection site irritation			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Injection site pain			
subjects affected / exposed	2 / 116 (1.72%)	2 / 113 (1.77%)	
occurrences (all)	2	2	
Injection site reaction			
subjects affected / exposed	3 / 116 (2.59%)	5 / 113 (4.42%)	
occurrences (all)	3	5	
Injection site pruritus			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Injection site swelling			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Injection site urticaria			
subjects affected / exposed	3 / 116 (2.59%)	0 / 113 (0.00%)	
occurrences (all)	3	0	
Irritability			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Malaise			

subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Pain			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	12 / 116 (10.34%)	7 / 113 (6.19%)	
occurrences (all)	24	9	
Sensation of foreign body			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Immune system disorders			
Multiple allergies			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Dysmenorrhoea			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	6	
Erectile dysfunction			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Menopausal symptoms			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Menstruation irregular			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Metrorrhagia			

subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Ovarian cyst			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Premenstrual syndrome			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Sexual dysfunction			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Uterine enlargement			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Vaginal discharge			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	6 / 116 (5.17%)	7 / 113 (6.19%)	
occurrences (all)	6	7	
Dysphonia			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	2	2	
Dyspnoea			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Oropharyngeal pain			

subjects affected / exposed	5 / 116 (4.31%)	7 / 113 (6.19%)	
occurrences (all)	7	9	
Paranasal sinus mucosal hypertrophy			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Pulmonary hilum mass			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	2 / 116 (1.72%)	0 / 113 (0.00%)	
occurrences (all)	2	0	
Alcohol abuse			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	5 / 116 (4.31%)	2 / 113 (1.77%)	
occurrences (all)	5	2	
Anxiety disorder			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Delusional perception			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	2 / 116 (1.72%)	4 / 113 (3.54%)	
occurrences (all)	2	4	
Fear of needles			

subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	4 / 116 (3.45%)	4 / 113 (3.54%)	
occurrences (all)	4	5	
Loss of libido			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Mood swings			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Panic attack			
subjects affected / exposed	3 / 116 (2.59%)	0 / 113 (0.00%)	
occurrences (all)	3	0	
Restlessness			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	4 / 116 (3.45%)	1 / 113 (0.88%)	
occurrences (all)	5	1	
Stress			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Anti-thyroid antibody positive			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Antibody test positive			
subjects affected / exposed	2 / 116 (1.72%)	0 / 113 (0.00%)	
occurrences (all)	2	0	
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 116 (0.86%)	3 / 113 (2.65%)	
occurrences (all)	2	4	
Blood creatinine decreased			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Blood folate decreased			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Blood glucose increased			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Blood iron decreased			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Blood parathyroid hormone increased			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Creatine urine abnormal			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Creatinine urine increased			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Drug specific antibody present			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram abnormal			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			

subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)		
occurrences (all)	0	3		
Liver function test abnormal				
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)		
occurrences (all)	0	1		
Lymphocyte count decreased				
subjects affected / exposed	2 / 116 (1.72%)	0 / 113 (0.00%)		
occurrences (all)	3	0		
Platelet count decreased				
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)		
occurrences (all)	2	0		
Thyroid function test abnormal				
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)		
occurrences (all)	1	0		
Urine calcium				
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)		
occurrences (all)	2	0		
Urine calcium/creatinine ratio increased				
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)		
occurrences (all)	0	1		
Vitamin B12 decreased				
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)		
occurrences (all)	1	2		
Weight decreased				
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)		
occurrences (all)	1	0		
Weight increased				
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)		
occurrences (all)	1	0		
White blood cell count increased				
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)		
occurrences (all)	0	1		
Blood thyroid stimulating hormone abnormal				

subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Arthropod bite			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Arthropod sting			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Concussion			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	2	
Epicondylitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	2	
Joint injury			
subjects affected / exposed	0 / 116 (0.00%)	3 / 113 (2.65%)	
occurrences (all)	0	3	
Joint sprain			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Limb injury			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Procedural headache			

subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Tendon injury			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Tooth injury			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Traumatic brain injury			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Whiplash injury			
subjects affected / exposed	2 / 116 (1.72%)	0 / 113 (0.00%)	
occurrences (all)	2	0	
Wrist fracture			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Atrioventricular block first degree			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Ventricular extrasystoles			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Balance disorder			

subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Burning sensation			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Carotid artery stenosis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Cervicobrachial syndrome			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Coordination abnormal			
subjects affected / exposed	2 / 116 (1.72%)	0 / 113 (0.00%)	
occurrences (all)	3	0	
Dizziness			
subjects affected / exposed	4 / 116 (3.45%)	5 / 113 (4.42%)	
occurrences (all)	4	6	
Dystonia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Facial neuralgia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	21 / 116 (18.10%)	20 / 113 (17.70%)	
occurrences (all)	33	36	
Hypoaesthesia			
subjects affected / exposed	2 / 116 (1.72%)	2 / 113 (1.77%)	
occurrences (all)	2	2	
Memory impairment			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Meralgia paraesthetica			

subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	2	
Migraine			
subjects affected / exposed	5 / 116 (4.31%)	6 / 113 (5.31%)	
occurrences (all)	6	6	
Migraine with aura			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Motor dysfunction			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Multiple sclerosis relapse			
subjects affected / exposed	2 / 116 (1.72%)	0 / 113 (0.00%)	
occurrences (all)	3	0	
Neuralgia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	4 / 116 (3.45%)	5 / 113 (4.42%)	
occurrences (all)	7	7	
Presyncope			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Restless legs syndrome			
subjects affected / exposed	3 / 116 (2.59%)	0 / 113 (0.00%)	
occurrences (all)	3	0	
Sciatica			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Sensory disturbance			
subjects affected / exposed	3 / 116 (2.59%)	4 / 113 (3.54%)	
occurrences (all)	3	4	
Syncope			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Tremor			

subjects affected / exposed	2 / 116 (1.72%)	2 / 113 (1.77%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 116 (0.00%)	3 / 113 (2.65%)	
occurrences (all)	0	3	
Haematotoxicity			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	4	
Lymph node pain			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Lymphadenopathy			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Lymphopenia			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Neutropenia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	3	
Thrombocytopenia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Vertigo			

subjects affected / exposed	2 / 116 (1.72%)	1 / 113 (0.88%)	
occurrences (all)	2	1	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 116 (1.72%)	1 / 113 (0.88%)	
occurrences (all)	2	1	
Diplopia			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Dry eye			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Eye irritation			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Eye pain			
subjects affected / exposed	3 / 116 (2.59%)	3 / 113 (2.65%)	
occurrences (all)	3	4	
Glaucoma			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Oscillopsia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Ulcerative keratitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	3 / 116 (2.59%)	3 / 113 (2.65%)	
occurrences (all)	4	3	
Visual impairment			
subjects affected / exposed	3 / 116 (2.59%)	1 / 113 (0.88%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Abdominal distension			

subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	4 / 116 (3.45%)	2 / 113 (1.77%)	
occurrences (all)	4	2	
Abdominal pain lower			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	3 / 116 (2.59%)	9 / 113 (7.96%)	
occurrences (all)	3	9	
Abdominal tenderness			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	2 / 116 (1.72%)	6 / 113 (5.31%)	
occurrences (all)	2	6	
Diarrhoea			
subjects affected / exposed	7 / 116 (6.03%)	10 / 113 (8.85%)	
occurrences (all)	7	11	
Dyspepsia			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Dysphagia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Food poisoning			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorder			

subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Gingivitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Lip swelling			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	4 / 116 (3.45%)	3 / 113 (2.65%)	
occurrences (all)	5	3	
Oral discomfort			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Paraesthesia oral			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Rectal haemorrhage			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Tooth impacted			

subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	2 / 116 (1.72%)	3 / 113 (2.65%)	
occurrences (all)	2	3	
Vomiting			
subjects affected / exposed	4 / 116 (3.45%)	3 / 113 (2.65%)	
occurrences (all)	5	3	
Vomiting in pregnancy			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	2	2	
Acne			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Blister			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Dermatitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Dermatitis psoriasiform			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Erythema nodosum			

subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Hyperhidrosis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Pain of skin			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Pigmentation disorder			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Pityriasis rosea			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Pruritus generalised			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Skin reaction			

subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	4 / 116 (3.45%)	2 / 113 (1.77%)	
occurrences (all)	4	2	
Renal and urinary disorders			
Bladder dysfunction			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	2	
Dysuria			
subjects affected / exposed	4 / 116 (3.45%)	2 / 113 (1.77%)	
occurrences (all)	4	2	
Incontinence			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Micturition urgency			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Urinary incontinence			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Urinary tract pain			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	

Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Hyperthyroidism			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Hypothyroidism			
subjects affected / exposed	3 / 116 (2.59%)	2 / 113 (1.77%)	
occurrences (all)	3	3	
Thyroid disorder			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 116 (4.31%)	4 / 113 (3.54%)	
occurrences (all)	6	5	
Back pain			
subjects affected / exposed	7 / 116 (6.03%)	10 / 113 (8.85%)	
occurrences (all)	7	15	
Bursitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Flank pain			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Growing pains			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Joint swelling			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Limb discomfort			

subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 116 (0.86%)	7 / 113 (6.19%)	
occurrences (all)	2	7	
Muscular weakness			
subjects affected / exposed	1 / 116 (0.86%)	3 / 113 (2.65%)	
occurrences (all)	1	3	
Musculoskeletal discomfort			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	2	
Musculoskeletal pain			
subjects affected / exposed	2 / 116 (1.72%)	2 / 113 (1.77%)	
occurrences (all)	2	2	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Myokymia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	3 / 116 (2.59%)	5 / 113 (4.42%)	
occurrences (all)	3	6	
Osteopenia			
subjects affected / exposed	5 / 116 (4.31%)	0 / 113 (0.00%)	
occurrences (all)	5	0	
Pain in extremity			
subjects affected / exposed	6 / 116 (5.17%)	13 / 113 (11.50%)	
occurrences (all)	10	18	
Pain in jaw			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Rheumatic fever			

subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	2 / 116 (1.72%)	1 / 113 (0.88%)	
occurrences (all)	2	1	
Tenosynovitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Muscle tightness			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Bacterial infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	2 / 116 (1.72%)	4 / 113 (3.54%)	
occurrences (all)	2	4	
Cystitis			
subjects affected / exposed	7 / 116 (6.03%)	3 / 113 (2.65%)	
occurrences (all)	9	5	
Ear infection			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Eye infection			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Eyelid infection			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	

Fungal infection			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Furuncle			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Gastric infection			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	5 / 116 (4.31%)	2 / 113 (1.77%)	
occurrences (all)	5	2	
Gastroenteritis viral			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Gastrointestinal infection			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Groin abscess			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Herpes simplex			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Herpes virus infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	2	
Herpes zoster			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Impetigo			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Infected cyst			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	

Infection			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	19 / 116 (16.38%)	13 / 113 (11.50%)	
occurrences (all)	29	17	
Injection site abscess			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Laryngitis			
subjects affected / exposed	2 / 116 (1.72%)	3 / 113 (2.65%)	
occurrences (all)	2	3	
Localised infection			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	17 / 116 (14.66%)	18 / 113 (15.93%)	
occurrences (all)	20	41	
Oral herpes			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Otitis media			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Pharyngitis			
subjects affected / exposed	2 / 116 (1.72%)	1 / 113 (0.88%)	
occurrences (all)	2	1	
Pneumonia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Pseudofolliculitis barbae			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	

Respiratory tract infection			
subjects affected / exposed	2 / 116 (1.72%)	4 / 113 (3.54%)	
occurrences (all)	2	5	
Rhinitis			
subjects affected / exposed	1 / 116 (0.86%)	5 / 113 (4.42%)	
occurrences (all)	1	5	
Sinusitis			
subjects affected / exposed	4 / 116 (3.45%)	5 / 113 (4.42%)	
occurrences (all)	4	5	
Skin infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Tinea pedis			
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Tonsillitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 116 (0.86%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	4 / 116 (3.45%)	3 / 113 (2.65%)	
occurrences (all)	6	3	
Urinary tract infection			
subjects affected / exposed	6 / 116 (5.17%)	12 / 113 (10.62%)	
occurrences (all)	6	16	
Vaginal infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	

Vulvovaginal candidiasis			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences (all)	0	1	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 116 (0.00%)	2 / 113 (1.77%)	
occurrences (all)	0	2	
Vitamin D deficiency			
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2011	The primary MRI endpoint was changed from the mean change from baseline in the total volume of T2 lesions to the mean number of CUA lesions at Week 48.
26 July 2011	The number of drops of Vigantol ® oil to be orally administered during the trial was changed from 14 drops to 10 drops during the first 4 weeks of the trial. If the treatment was well tolerated the subjects were to take 21 drops instead of 28 drops of Vigantol ® oil (corresponding to 7'000 IU/d (175 µg/d) from Week 5 and up to Week 92.
29 August 2011	The maximum allowed dose for Vitamin D supplementation was changed from 400 IU (10 µg) per day to 1000 IU (25 µg) per day.
08 May 2013	Update to Primary Endpoint: The primary endpoint is the proportion of subjects disease activity free (DAF), defined as absence of any of the clinical and imaging parameters related to the assessment of disease activity; namely no relapses, no EDSS progression and no new Gd-enhancing or T2 MRI lesions at Week 48. The duration of the trial period was reduced from 96 to 48 weeks and all trial procedures e.g. duration of treatment were updated accordingly. The sample size was reduced from 348 subjects (174 subjects per treatment arm) to 230 subjects (115 subjects per treatment arm) with 25-hydroxy-vitamin D serum levels <150 nmol/L and an unspecified number of subjects with 25-hydroxy-vitamin D serum levels ≥150 nmol/L. Update of inclusion criterion 1: Males and females between 18 and 55 years of age.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported