



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	<ul style="list-style-type: none">• New data added to full data set New data added to full data set

Trial information

Trial identification

Sponsor protocol code	EMR 200136-532
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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
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Arm title	VigantOL oil interferon beta-1a (Rebif)
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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)
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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)
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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)
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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
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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
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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
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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
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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
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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
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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)
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End point description:

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

End point type	Secondary
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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
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End point description:

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

End point type	Secondary
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1
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Reporting groups

Reporting group title	Placebo interferon beta-1a (Rebif)
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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)
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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 occurrences causally related to treatment / all deaths causally related to treatment / all	6 / 116 (5.17%) 0 / 6 0 / 0	8 / 113 (7.08%) 0 / 8 0 / 0	
Vascular disorders Hypertension alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 116 (0.00%) 0 / 0 0 / 0	1 / 113 (0.88%) 0 / 1 0 / 0	
Cardiac disorders Cardiac failure alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 116 (0.00%) 0 / 0 0 / 0	1 / 113 (0.88%) 0 / 1 0 / 0	
Nervous system disorders Headache alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 116 (0.86%) 0 / 1 0 / 0	0 / 113 (0.00%) 0 / 0 0 / 0	
Syncope alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 116 (0.00%) 0 / 0 0 / 0	1 / 113 (0.88%) 0 / 1 0 / 0	
Gastrointestinal disorders Abdominal pain alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 116 (0.00%) 0 / 0 0 / 0	1 / 113 (0.88%) 0 / 1 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 occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Thyroid neoplasm subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Uterine leiomyoma subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Vascular disorders Circulatory collapse subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 2	0 / 113 (0.00%) 0	
Haematoma subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Haemorrhage subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Hypertension subjects affected / exposed occurrences (all)	4 / 116 (3.45%) 5	6 / 113 (5.31%) 7	
Surgical and medical procedures Endodontic procedure subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Hospitalisation subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Mammoplasty subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Parotidectomy subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Shoulder operation			

subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Tooth extraction subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Wisdom teeth removal subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 2	0 / 113 (0.00%) 0	
Pregnancy, puerperium and perinatal conditions Pregnancy subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	2 / 113 (1.77%) 2	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	2 / 113 (1.77%) 2	
Chest discomfort subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Chest pain subjects affected / exposed occurrences (all)	4 / 116 (3.45%) 4	0 / 113 (0.00%) 0	
Chills subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	13 / 116 (11.21%) 16	8 / 113 (7.08%) 8	
Feeling cold subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	2 / 113 (1.77%) 3	
Gait disturbance subjects affected / exposed occurrences (all)	2 / 116 (1.72%) 2	3 / 113 (2.65%) 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 occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Insomnia subjects affected / exposed occurrences (all)	4 / 116 (3.45%) 4	4 / 113 (3.54%) 5	
Loss of libido subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Mood swings subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	2 / 113 (1.77%) 2	
Panic attack subjects affected / exposed occurrences (all)	3 / 116 (2.59%) 3	0 / 113 (0.00%) 0	
Restlessness subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Sleep disorder subjects affected / exposed occurrences (all)	4 / 116 (3.45%) 5	1 / 113 (0.88%) 1	
Stress subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	2 / 113 (1.77%) 2	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Anti-thyroid antibody positive subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Antibody test positive subjects affected / exposed occurrences (all)	2 / 116 (1.72%) 2	0 / 113 (0.00%) 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 occurrences (all)	2 / 116 (1.72%) 2	2 / 113 (1.77%) 2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	3 / 113 (2.65%) 3	
Haematotoxicity			
subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Leukopenia			
subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	2 / 113 (1.77%) 4	
Lymph node pain			
subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Lymphadenopathy			
subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	1 / 113 (0.88%) 1	
Lymphopenia			
subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	2 / 113 (1.77%) 2	
Neutropenia			
subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 3	
Thrombocytopenia			
subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Tinnitus			
subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	1 / 113 (0.88%) 1	
Vertigo			

subjects affected / exposed occurrences (all)	2 / 116 (1.72%) 2	1 / 113 (0.88%) 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 occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Toothache subjects affected / exposed occurrences (all)	2 / 116 (1.72%) 2	3 / 113 (2.65%) 3	
Vomiting subjects affected / exposed occurrences (all)	4 / 116 (3.45%) 5	3 / 113 (2.65%) 3	
Vomiting in pregnancy subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	1 / 113 (0.88%) 1	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 2	2 / 113 (1.77%) 2	
Acne subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	1 / 113 (0.88%) 1	
Blister subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Dermatitis subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Dermatitis psoriasiform subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Eczema subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	1 / 113 (0.88%) 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 occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Skin ulcer subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Urticaria subjects affected / exposed occurrences (all)	4 / 116 (3.45%) 4	2 / 113 (1.77%) 2	
Renal and urinary disorders			
Bladder dysfunction subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	1 / 113 (0.88%) 2	
Dysuria subjects affected / exposed occurrences (all)	4 / 116 (3.45%) 4	2 / 113 (1.77%) 2	
Incontinence subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Micturition urgency subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Pollakiuria subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	2 / 113 (1.77%) 2	
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	2 / 113 (1.77%) 2	
Urinary tract pain subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Urinary retention subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 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 occurrences (all)	0 / 116 (0.00%) 0	2 / 113 (1.77%) 2	
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Metabolism and nutrition disorders			
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 0	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Iron deficiency subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	1 / 113 (0.88%) 1	
Vitamin B12 deficiency subjects affected / exposed occurrences (all)	0 / 116 (0.00%) 0	2 / 113 (1.77%) 2	
Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	0 / 113 (0.00%) 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	<p>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.</p> <p>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.</p> <p>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.</p> <p>Update of inclusion criterion 1: Males and females between 18 and 55 years of age.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported