Clinical trial results:
A 3-year, multi-center study to evaluate optical coherence tomography as an outcome measure in patients with multiple sclerosis

Summary

EudraCT number	2011-001437-16
Trial protocol	DE
Global end of trial date	07 August 2017

Results information

Result version number	v1 (current)
This version publication date	28 January 2021
First version publication date	28 January 2021

Trial information

Trial identification

Sponsor protocol code	CFTY720D2319

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02907281
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	24 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate optical coherence tomography (OCT) as a technique to detect and longitudinally follow the degeneration of retinal axons by measuring change in retinal nerve fiber layer (RNFL) thickness and overall average macular ganglion cell layer (mGCL) thickness in patients with relapsing-remitting multiple sclerosis (RRMS) followed for up to 36 months compared to a group of reference subjects (without neurologic or ophthalmic disease).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 38
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Czechia: 32
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	Germany: 56
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Spain: 77
Country: Number of subjects enrolled	Switzerland: 30
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	United States: 79
Worldwide total number of subjects	422
EEA total number of subjects	236

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)	422
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 28 investigative sites in 12 countries.

Pre-assignment

Screening details:

The trial had an screening period of up to one month.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	MS patients

Arm description:

Patients with a diagnosis of multiple sclerosis

Arm type	Test
Investigational medicinal product name	Multiple sclerosis disease-modifying therapies
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients with MS could have been untreated or treated with a commercially available MS disease-modifying therapies (DMTs). The most common prior DMTs were interferon and glatiramer and the most common route of administration was subcutaneous injection. The purpose of the trial was not to evaluate the efficacy or security of these therapies.

Arm title	Reference subjects

Arm description:

Volunteer subjects without neurological or ophthalmic disease

Arm type	Reference

No investigational medicinal product assigned in this arm

Number of subjects in period 1	MS patients	Reference subjects
Started	353	69
Completed	302	57
Not completed	51	12
Consent withdrawn by subject	23	6
Adverse event, non-fatal	2	-
Protocol deviation	2	-
Administrative problems	3	1
Unknown	1	-

Lost to follow-up	19	5
Abnormal test procedure result(s)	1	-

Baseline characteristics

Reporting groups	
Reporting group title	MS patients
Reporting group description:	
Patients with a diagnosis of multiple sclerosis	
Reporting group title	Reference subjects
Reporting group description:	
Volunteer subjects without neurological or ophthalmic disease	

Reporting group values	MS patients	Reference subjects	Total
Number of subjects	353	69	422
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	353	69	422
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	39.1	35.3	
standard deviation	± 8.57	± 9.66	-
Gender Categorical Units: Subjects			
Female	248	47	295
Male	105	22	127
Race Units: Subjects			
Caucasian	332	66	398
Black	6	0	6
Asian	5	2	7
Other	10	1	11

End points

End points reporting groups

Reporting group title	MS patients
Reporting group description:	
Patients with a diagnosis of multiple sclerosis	
Reporting group title	Reference subjects
Reporting group description:	
Volunteer subjects without neurological or ophthalmic disease	
Subject analysis set title	MS patients
Subject analysis set type	Full analysis
Subject analysis set description:	
All MS subjects who gave written informed consent to participate in the study, satisfied all eligibility criteria at screening, and provided a valid baseline and at least one post-baseline RNFL measurement in at least one eye.	
Subject analysis set title	MS patients – Left eye
Subject analysis set type	Full analysis
Subject analysis set description:	
MS patients with valid measurements in the left eye for a given endpoint.	
Subject analysis set title	MS patients – Right eye
Subject analysis set type	Full analysis
Subject analysis set description:	
MS patients with valid measurements in the right eye for a given endpoint.	
Subject analysis set title	MS patients – All eyes
Subject analysis set type	Full analysis
Subject analysis set description:	
MS patients with valid measurements in the left and/or right eye for a given endpoint.	
Subject analysis set title	Reference subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
All reference subjects who gave written informed consent to participate in the study, satisfied all eligibility criteria at screening, and provided a valid baseline and at least one post-baseline RNFL measurement in at least one eye.	
Subject analysis set title	Reference subjects – Left eye
Subject analysis set type	Full analysis
Subject analysis set description:	
Reference subjects with valid measurements in the left eye for a given endpoint.	
Subject analysis set title	Reference subjects – Right eye
Subject analysis set type	Full analysis
Subject analysis set description:	
Reference subjects with valid measurements in the right eye for a given endpoint.	
Subject analysis set title	Reference Subjects – All eyes
Subject analysis set type	Full analysis
Subject analysis set description:	
Reference subjects with valid measurements in the left and/or right eye for a given endpoint.	

Primary: Change from baseline in the RNFL thickness at Month 36 measured by OCT

End point title	Change from baseline in the RNFL thickness at Month 36 measured by OCT
End point description:	
Change from baseline in retinal nerve fiber layer (RNFL) thickness, measured by optical coherence tomography (OCT), was investigated using the global score for RNFL thickness, which was calculated as	

the mean of the measurements of fields 1 to 8 from the circular scan of the optic nerve head (ONH). If at least one result from fields 1 to 8 was missing then the global score for RNFL thickness was not calculated. The change from baseline was derived as "measurement at post-baseline visit – measurement at baseline".

End point type	Primary

End point timeframe:

Baseline, Month 36

End point values	MS patients – Left eye	MS patients – Right eye	MS patients – All eyes	Reference subjects – Left eye
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	283	277	284[1]	55
Units: microns				
arithmetic mean (standard deviation)	-1.90 (± 3.490)	-1.32 (± 5.499)	-1.61 (± 4.600)	-0.17 (± 3.002)

Notes:

[1] - A total of 560 eyes were assessed.

End point values	Reference subjects – Right eye	Reference Subjects – All eyes		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56[2]		
Units: microns				
arithmetic mean (standard deviation)	-0.02 (± 2.988)	-0.09 (± 2.982)		

Notes:

[2] - A total of 110 eyes were assessed.

Statistical analyses

Statistical analysis title	Change from baseline to Month 36 in RNFL thickness
Comparison groups	Reference Subjects – All eyes v MS patients – All eyes
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed-model repeated measures (MMRM)
Parameter estimate	Least Squares (LS) mean difference
Point estimate	-1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	-1.17

Secondary: Correlation of change from baseline in global score for RNFL thickness

(microns) for the most affected eye at baseline with percentage change from baseline in brain volume (%)

End point title	Correlation of change from baseline in global score for RNFL thickness (microns) for the most affected eye at baseline with percentage change from baseline in brain volume (%)

End point description:

The RNFL thickness was measured by OCT and the brain volume was measured by magnetic resonance imaging (MRI). The relationship between change from baseline in global score for RNFL thickness (microns) for the most affected eye at baseline and percentage change from baseline in brain volume (%) was assessed graphically. Scatter plots at Month 36 were produced for MS patients and reference subjects separately, showing change in RNFL thickness on the x-axis and change in brain volume on the y-axis. To aid interpretation of these relationships, the Pearson product-moment correlation coefficient (r) was calculated and it is reported in this record for each group of participants.

End point type	Secondary

End point timeframe:

Baseline, Month 36

End point values	MS patients	Reference subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	284[3]	56[4]		
Units: no units				
number (not applicable)	0.020235	0.026099		

Notes:

[3] - approximate number of participants analyzed.

[4] - approximate number of participants analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of change from baseline in mGCL thickness (microns) for the most affected eye at baseline with percentage change from baseline in brain volume (%)

End point title	Correlation of change from baseline in mGCL thickness (microns) for the most affected eye at baseline with percentage change from baseline in brain volume (%)

End point description:

The macular ganglion cell layer (mGCL) thickness was measured by OCT and the brain volume was measured by magnetic resonance imaging (MRI). The relationship between change from baseline in mGCL thickness (microns) for the most affected eye at baseline and percentage change from baseline in brain volume (%) was assessed graphically. Scatter plots at Month 36 were produced for MS patients and reference subjects separately, showing change in RNFL thickness on the x-axis and change in brain volume on the y-axis. To aid interpretation of these relationships, the Pearson product-moment correlation coefficient (r) was calculated and it is reported in this record for each group of participants.

End point type	Secondary

End point timeframe:

Baseline, Month 36

End point values	MS patients	Reference subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	285[5]	55[6]		
Units: no units				
number (not applicable)	0.111615	-0.09672		

Notes:

[5] - approximate number of participants analyzed.

[6] - approximate number of participants analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of change from baseline in global score for RNFL thickness (microns) for the most affected eye at baseline with change from baseline in Expanded Disability Status Scale (EDSS) score

End point title	Correlation of change from baseline in global score for RNFL thickness (microns) for the most affected eye at baseline with change from baseline in Expanded Disability Status Scale (EDSS) score

End point description:

The RNFL thickness was measured by OCT and the disability was measured for MS patients only by the EDSS score, ranging from 0 (normal) to 10 (death due to multiple sclerosis). The relationship between change from baseline in global score for RNFL thickness (microns) for the most affected eye at baseline and change from baseline in EDSS score was assessed graphically. Scatter plots at Month 36 were produced for MS patients only, showing change in RNFL thickness on the x-axis and change in EDSS score on the y-axis. To aid interpretation of these relationships, the Pearson product-moment correlation coefficient (r) was calculated and it is reported in this record for MS patients.

End point type	Secondary

End point timeframe:

Baseline, Month 36

End point values	MS patients			
Subject group type	Subject analysis set			
Number of subjects analysed	284[7]			
Units: no units				
number (not applicable)	0.005841			

Notes:

[7] - approximate number of participants analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of change from baseline in mGCL thickness (microns) for the most affected eye at baseline with change from baseline in Expanded Disability Status Scale (EDSS)

End point title	Correlation of change from baseline in mGCL thickness (microns) for the most affected eye at baseline with change from baseline in Expanded Disability Status Scale (EDSS)

End point description:

The mGCL thickness was measured by OCT and the disability was measured for MS patients only by the EDSS score, ranging from 0 (normal) to 10 (death due to multiple sclerosis). The relationship between change from baseline in mGCL thickness (microns) for the most affected eye at baseline and change from baseline in EDSS score was assessed graphically. Scatter plots at Month 36 were produced for MS patients only, showing change in RNFL thickness on the x-axis and change in EDSS score on the y-axis. To aid interpretation of these relationships, the Pearson product-moment correlation coefficient (r) was calculated and it is reported in this record for MS patients.

End point type	Secondary

End point timeframe:

Baseline, Month 36

End point values	MS patients			
Subject group type	Subject analysis set			
Number of subjects analysed	285[8]			
Units: no units				
number (not applicable)	-0.00425			

Notes:

[8] - approximate number of participants analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of change from baseline in global score for RNFL thickness (microns) with change from baseline in visual acuity (total number of letters correct)

End point title	Correlation of change from baseline in global score for RNFL thickness (microns) with change from baseline in visual acuity (total number of letters correct)

End point description:

The RNFL thickness was measured by OCT and visual acuity was evaluated by the total number of letters correct from high-contrast and low-contrast tests. The relationship between change from baseline in global score for RNFL thickness (microns) and change from baseline in visual acuity (total number of letters correct) from high-contrast and low-contrast tests was assessed graphically. Scatter plots at Month 36 were produced for MS patients and reference subjects separately, showing change in RNFL thickness on the x-axis and change in visual acuity on the y-axis for both eyes separately. To aid interpretation of these relationships, the Pearson product-moment correlation coefficient (r) was calculated and it is reported in this record for each group of participants.

End point type	Secondary

End point timeframe:

Baseline, Month 36

End point values	MS patients – Left eye	MS patients – Right eye	Reference subjects – Left eye	Reference subjects – Right eye
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	283[9]	277[10]	55[11]	55[12]
Units: no units				
number (not applicable)				

High-contrast visual test	0.039801	-0.00911	-0.12477	0.125906
Low-contrast visual test	-0.04888	-0.00212	-0.13731	0.11323

Notes:

[9] - approximate number of participants analyzed.

[10] - approximate number of participants analyzed.

[11] - approximate number of participants analyzed.

[12] - approximate number of participants analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Short-term reproducibility (ICC) of the mGCL thickness measure based on within-subject measures obtained between baseline and Month 1

End point title	Short-term reproducibility (ICC) of the mGCL thickness measure based on within-subject measures obtained between baseline and Month 1

End point description:

The intraclass correlation coefficient (ICC) can range from 0 to 1 with a value closer to 1 indicating better reproducibility. ICC was determined by fitting a 1-way ANOVA model with mGCL thickness as the response and subject as a random effect. ICC was then calculated by dividing (MSB–MSW) by (MSB+MSW), where MSB = between-subject mean square and MSW = within-subject mean square.

End point type	Secondary

End point timeframe:

Baseline, Month 1

End point values	MS patients – Left eye	MS patients – Right eye	Reference subjects – Left eye	Reference subjects – Right eye
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	296	288	61	60
Units: no units				
number (confidence interval 95%)	0.974 (0.967 to 0.979)	0.971 (0.963 to 0.977)	0.835 (0.741 to 0.897)	0.904 (0.845 to 0.941)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the mGCL thickness at Month 36 measured by OCT

End point title	Change from baseline in the mGCL thickness at Month 36 measured by OCT

End point description:

Change from baseline in the mGCL thickness was investigated using the overall average mGCL thickness, which was calculated as the average of the 16 individual subfield areas measured using OCT. If at least one result was missing from any of the 16 individual subfields then the average was not calculated. The change from baseline was derived as "measurement at post-baseline visit – measurement at baseline".

End point type	Secondary

End point timeframe:
Baseline, Month 36

End point values	MS patients – Left eye	MS patients – Right eye	MS patients – All eyes	Reference subjects – Left eye
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	283	284	285[13]	55
Units: microns				
arithmetic mean (standard deviation)	-0.30 (± 3.832)	-0.42 (± 3.990)	-0.36 (± 3.909)	-0.50 (± 3.823)

Notes:
[13] - A total of 567 eyes were assessed.

End point values	Reference subjects – Right eye	Reference Subjects – All eyes		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	55[14]		
Units: microns				
arithmetic mean (standard deviation)	-1.20 (± 4.004)	-0.85 (± 3.911)		

Notes:
[14] - A total of 109 eyes were assessed.

Statistical analyses

Statistical analysis title	Change from baseline to Month 36 in mGCL thickness
Comparison groups	MS patients – All eyes v Reference Subjects – All eyes
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3829
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	1.15

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from signature of informed consent until 30 days after the patient/subject had stopped study participation.	
Adverse event reporting additional description:	
Any sign or symptom that occurs from signature of informed consent until 30 days after the patient/subject had stopped study participation.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	MS patients
Reporting group description:	
MS patients	
Reporting group title	Reference subjects
Reporting group description:	
Reference subjects	

Serious adverse events	MS patients	Reference subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 353 (7.08%)	1 / 69 (1.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Uterine leiomyoma			
subjects affected / exposed	0 / 353 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral venous disease			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	6 / 353 (1.70%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			

subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (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			
Cervix disorder			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			

subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypoparathyroidism			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	1 / 353 (0.28%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MS patients	Reference subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 353 (20.11%)	15 / 69 (21.74%)	
Nervous system disorders			
Migraine			
subjects affected / exposed	3 / 353 (0.85%)	4 / 69 (5.80%)	
occurrences (all)	3	4	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	17 / 353 (4.82%)	6 / 69 (8.70%)	
occurrences (all)	18	6	
Eye disorders			
Optic atrophy			
subjects affected / exposed	24 / 353 (6.80%)	1 / 69 (1.45%)	
occurrences (all)	26	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	21 / 353 (5.95%)	2 / 69 (2.90%)	
occurrences (all)	32	2	
Viral upper respiratory tract infection			
subjects affected / exposed	18 / 353 (5.10%)	6 / 69 (8.70%)	
occurrences (all)	31	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2011	The main changes incorporated in this protocol amendment were the changes in Section 7 (Safety monitoring) of the protocol, which was modified to require all AEs, SAEs, and pregnancies to be reported and not just those reported in connection to a Novartis licensed pharmaceutical product.
17 June 2013	The primary objective was modified to remove reference to assessing RNFL thickness "to be useful as a monitoring tool". In some countries, this monitoring with OCT devices was already part of medical practice for monitoring patients with MS. The investigational plan and study population were modified to clarify that healthy volunteers (control) group were to be enrolled in selected countries only, in addition to selected sites.
07 August 2017	The statistical methodology sections of the protocol were updated to align with the planned statistical analysis following input from advisors and steering committee members overseeing the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported