Clinical trial results:
Effect of MD1003 in progressive multiple sclerosis: a randomized double-blind placebo-controlled study.

Summary

EudraCT number	2016-000700-29
Trial protocol	CZ SE DE ES HU BE PL IT
Global end of trial date	23 April 2020

Results information

Result version number	v1 (current)
This version publication date	07 October 2020
First version publication date	07 October 2020

Trial information

Trial identification

Sponsor protocol code	MD1003CT2016-01MS-SPI2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02936037
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov: NCT02936037

Notes:

Sponsors

Sponsor organisation name	Medday Pharmaceuticals
Sponsor organisation address	24-26 rue de la pépinière, Paris, France, 75008
Public contact	clinical trials information desk, Medday Pharmaceuticals, +33 1 80 40 14 40, frederic.sedel@medday-pharma.com
Scientific contact	clinical trials information desk, Medday Pharmaceuticals, +33 1 80 40 14 40, frederic.sedel@medday-pharma.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	15 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2019
Global end of trial reached?	Yes
Global end of trial date	23 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of MD1003, 300 mg/day, over placebo to clinically improve patients with not active progressive multiple sclerosis (MS).

Protection of trial subjects:

This protocol complied with the principal laid down by the 18th World Medical Assembly (Helsinki, 1964 an following amendments) and all applicable amendments laid down by the World Medical Assemblies, as well as the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. The trial complied with the laws and regulations of the country in which the study was performed, and any applicable guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Spain: 63
Country: Number of subjects enrolled	Sweden: 20
Country: Number of subjects enrolled	United Kingdom: 81
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Czech Republic: 60
Country: Number of subjects enrolled	Germany: 103
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Canada: 82
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	United States: 285
Worldwide total number of subjects	766
EEA total number of subjects	377

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)	745
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 766 subjects were screened and 642 were randomized into the study, of which 642 received at least one dose of placebo or biotin.

Period 1

Period 1 title	Double-Blind Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects with progressive multiple sclerosis received placebo matched to MD1003 (biotin) TID

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

Dosage and administration details:

Subjects received placebo matching MD1003 100 mg capsule TID

Arm title	MD1003

Arm description:

Subjects with progressive multiple sclerosis received MD1003 (100mg caps TID).

Arm type	Experimental
Investigational medicinal product name	MD1003
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received MD1003 100 mg capsule TID.

Number of subjects in period 1[1]	Placebo	MD1003
Started	316	326
Completed	267	261
Not completed	49	65
Adverse event, serious fatal	-	1

Consent withdrawn by subject	31	28
Suicidal risk	-	1
Adverse event, non-fatal	11	11
Other	2	7
Lost to follow-up	-	1
Lack of efficacy	4	12
Protocol deviation	1	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: For the worldwide number we included patients that were screened without taking account if they were randomized or screen failure (766 patients). For the baseline period, we included only randomized patients (642 patients).

Period 2

Period 2 title	Open label extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	MD1003

Arm description:

Subjects with progressive multiple sclerosis received MD1003 (100mg caps TID).

Arm type	Experimental
Investigational medicinal product name	MD1003
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received MD1003 100 mg capsule TID

Number of subjects in period 2	MD1003
Started	528
Completed	518
Not completed	10
Consent withdrawn by subject	4
Adverse event, non-fatal	3
not specified	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects with progressive multiple sclerosis received placebo matched to MD1003 (biotin) TID	
Reporting group title	MD1003
Reporting group description:	
Subjects with progressive multiple sclerosis received MD1003 (100mg caps TID).	

Reporting group values	Placebo	MD1003	Total
Number of subjects	316	326	642
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	52.8	52.6	
standard deviation	± 7.60	± 7.79	-
Gender categorical			
Units: Subjects			
Female	170	175	345
Male	146	151	297

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects with progressive multiple sclerosis received placebo matched to MD1003 (biotin) TID	
Reporting group title	MD1003
Reporting group description:	
Subjects with progressive multiple sclerosis received MD1003 (100mg caps TID).	
Reporting group title	MD1003
Reporting group description:	
Subjects with progressive multiple sclerosis received MD1003 (100mg caps TID).	
Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized subjects	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received at least one dose of study medication. Patients are summarised according to their randomized treatment group, except for the Safety Analysis Set, where subjects are summarised according to the actual treatment received	

Primary: Decreased EDSS or improved TW25 at M12 confirmed at M15

End point title	Decreased EDSS or improved TW25 at M12 confirmed at M15
End point description:	
The primary endpoint is a composite criterion which can be met in one of two ways: either through confirmed improvement in the EDSS score or in TW25. The composite criterion includes either • a decreased EDSS at M12 confirmed at M15 (decrease of at least 1 point if baseline EDSS is from 3.5 to 5.5 and of at least 0.5 point if baseline EDSS is from 6 to 6.5) compared to baseline EDSS or • an improved TW25 of at least 20% at M12 confirmed at M15 compared to baseline TW25. The baseline score for EDSS will be the lowest (best) value obtained during either the inclusion or randomization visits. For the TW25, the baseline value will be the best mean of the 2 values obtained at either the inclusion or randomization visits (the lowest mean value between these 2 visits). The TW25 value at visit M12 is defined as the mean of the two TW25 attempts at visit M12. The TW25 value at visit M15 is defined as the mean of the two TW25 attempts at visit M15.	
End point type	Primary
End point timeframe:	
The primary efficacy measure is the comparison of the proportion of patients achieving either composite criterion at M12 confirmed at M15 across treatment groups.	

End point values	Placebo	MD1003	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	316	326	642	
Units: percent				
number (not applicable)	9.2	12.0	10.6	

Statistical analyses

Statistical analysis title	Improved EDSS or TW25 at M12 confirmed at M15

Statistical analysis description:

A logistic regression will be fitted to estimate the treatment effect (odd-ratio of improved patients) using treatment, disease history (SPMS/PPMS) and geographical region as fixed factors (referred as the main logistic model in the following parts).
The main logistic model will then be used for each component of the composite outcome (EDSS and TW25 responses), to complement the analysis of the main endpoint.

Comparison groups	Placebo v MD1003
Number of subjects included in analysis	642
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1537
Method	t-test, 1-sided

Secondary: Time to 12-weeks confirmed EDSS progression

End point title	Time to 12-weeks confirmed EDSS progression

End point description:

12-weeks EDSS progression is defined as an increase of at least 1 point for baseline EDSS up to 5.5 and of at least 0.5 point for baseline EDSS 6 to 6.5 with respective confirmation 12 weeks later

End point type	Secondary

End point timeframe:

time to increase of baseline EDSS confirmed 12 weeks later

End point values	Placebo	MD1003	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	316	326	642	
Units: weeks				
median (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

Statistical analysis title	Time to 12-weeks confirmed EDSS progression

Statistical analysis description:

Timeto12-weeksconfirmedEDSSprogressionwillbecalculatedasdateof12-weeksconfirmedEDSSprogression(orcensoring)minusdateofrandomizationplus1;itwillbeexpressedinweeks

Comparison groups	Placebo v MD1003

Number of subjects included in analysis	642
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4348
Method	Regression, Logistic
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.385

Secondary: Clinical Global Impression of Improvement (CGI-I) at Visit M15

End point title	Clinical Global Impression of Improvement (CGI-I) at Visit M15

End point description:

End point type	Secondary

End point timeframe:

Mean difference between treatment arms in clinician global impression at M15

End point values	Placebo	MD1003	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	316	326	642	
Units: percentage				
number (not applicable)				
Very much improved	0	0	0	
Much improved	1.4	3.2	2.3	
Minimally improved	14.3	12.9	13.6	
No change	48.0	48.6	48.3	
Minimally worse	25.8	26.1	25.9	
Much worse	9.7	8.6	9.1	
Very much worse	0.7	0.7	0.7	

Statistical analyses

Statistical analysis title	Clinical Global Impression of Improvement (CGI-I)

Statistical analysis description:

One-sided Van Elteren test stratified for disease history (SPMS/PPMS) and geographical region (North America-Australia/Europe) comparing the two study treatment groups

Comparison groups	Placebo v MD1003

Number of subjects included in analysis	642
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5796
Method	Van Elteren

Secondary: Subject Global Impression of Improvement (SGI-I) at Visit M15

End point title	Subject Global Impression of Improvement (SGI-I) at Visit M15

End point description:

End point type	Secondary

End point timeframe:

15 months

End point values	Placebo	MD1003	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	316	326	642	
Units: percent				
number (not applicable)				
Very much improved	0	0	0	
Much improved	4.0	4.3	4.1	
Minimally improved	14.0	15.6	14.8	
No change	34.5	33.0	33.8	
Minimally worse	31.7	36.9	34.3	
Much worse	14.0	8.9	11.4	
Very much worse	1.8	1.4	1.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in TW25 at visit M15

End point title	Mean Change from Baseline in TW25 at visit M15

End point description:

End point type	Secondary

End point timeframe:

Mean change in TW25 score between M0 and M15

End point values	Placebo	MD1003	ITT analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	316	326	0[1]	
Units: Percentage				
arithmetic mean (confidence interval 95%)	22.5 (-46 to 343)	20.7 (-75 to 465)	(to)	

Notes:

[1] - This was only analyzed by reporting group and not as a total.

Statistical analyses

Statistical analysis title	Main analysis of percentage change from baseline

Statistical analysis description:

Main analysis of percentage change from baseline in TW25 at M15

Comparison groups	Placebo v MD1003
Number of subjects included in analysis	642
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.524
Method	t-test, 1-sided

Secondary: ECG at M0 and M15

End point title	ECG at M0 and M15

End point description:

End point type	Secondary

End point timeframe:

Month 0 and month 15

End point values	Placebo	MD1003	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	316	326	642	
Units: percent				
number (not applicable)				
Baseline abnormal CS	3.3	3.1	3.2	
M15 abnormal CS	3.8	3.3	3.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Brain MRI at M15 - New or enlarging T2

End point title	Brain MRI at M15 - New or enlarging T2

End point description:

End point type	Secondary

End point timeframe:
Month 15

End point values	Placebo	MD1003	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	316	326	642	
Units: percent				
number (not applicable)				
At least new	25.5	24.7	25.1	

Statistical analyses

No statistical analyses for this end point

Secondary: C-SSRS score at M15

End point title	C-SSRS score at M15

End point description:

End point type	Secondary

End point timeframe:
Month 15

End point values	Placebo	MD1003	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	316	326	642	
Units: percent				
number (not applicable)				
-4 points	0.3	0.0	0.2	
-2 points	0.0	0.3	0.2	
-1 point	1.0	1.8	1.4	
0 point	85.2	84.3	84.7	
1 point	1.6	0.6	1.1	
2 points	0.3	0.3	0.3	
3 points	0.6	0.0	0.3	
4 points	0.0	0.3	0.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Brain MRI at M0 and M15 - Gd+ lesion

End point title	Brain MRI at M0 and M15 - Gd+ lesion

End point description:

End point type	Secondary

End point timeframe:

Month 0 and month 15

End point values	Placebo	MD1003	Safety analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	316	326	642	
Units: percent				
number (not applicable)				
Baseline Gd+	5.8	4.5	5.3	
M15 Gd+	6.3	6.8	5.6	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the whole study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	MD1003
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	MD1003	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 331 (26.28%)	82 / 311 (26.37%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystadenocarcinoma ovary			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ovarian cancer metastatic			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenoma			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testis cancer			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 331 (0.60%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Elective procedure			
subjects affected / exposed	1 / 331 (0.30%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological rehabilitation			
subjects affected / exposed	1 / 331 (0.30%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastric banding reversal			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rehabilitation therapy			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 331 (0.60%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 331 (0.30%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (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			
Cervical dysplasia			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			

subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 331 (0.60%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 331 (0.60%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 331 (0.30%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Suicide attempt			
subjects affected / exposed	2 / 331 (0.60%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar I disorder			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breathing-related sleep disorder			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device failure			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
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			
Femoral neck fracture			

subjects affected / exposed	1 / 331 (0.30%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 331 (0.30%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 331 (0.30%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 331 (0.00%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat stroke			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			

subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lumbar vertebral fracture			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sunburn			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Factor V Leiden mutation			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	3 / 331 (0.91%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 331 (0.30%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Silent myocardial infarction			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	29 / 331 (8.76%)	31 / 311 (9.97%)	
occurrences causally related to treatment / all	3 / 36	1 / 37	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	4 / 331 (1.21%)	6 / 311 (1.93%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	1 / 331 (0.30%)	4 / 311 (1.29%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasticity			

subjects affected / exposed	3 / 331 (0.91%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uhthoff's phenomenon			
subjects affected / exposed	1 / 331 (0.30%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	2 / 331 (0.60%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory loss			
subjects affected / exposed	1 / 331 (0.30%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataplexy			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial spasm			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Narcolepsy			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			

subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyramidal tract syndrome			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transverse sinus thrombosis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eyelid ptosis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia, obstructive			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvi-ureteric obstruction			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			

subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	4 / 331 (1.21%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 331 (0.30%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint stiffness			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 331 (0.60%)	6 / 311 (1.93%)	
occurrences causally related to treatment / all	0 / 3	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 331 (0.91%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urosepsis			
subjects affected / exposed	2 / 331 (0.60%)	3 / 311 (0.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 331 (0.00%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 331 (0.30%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			

subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic pneumonia			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human anaplasmosis			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site inflammation			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme disease			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 331 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 331 (0.30%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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	MD1003	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	277 / 331 (83.69%)	264 / 311 (84.89%)	
Investigations			
Laboratory test interference			
subjects affected / exposed	25 / 331 (7.55%)	1 / 311 (0.32%)	
occurrences (all)	28	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	44 / 331 (13.29%)	37 / 311 (11.90%)	
occurrences (all)	84	60	
Contusion			
subjects affected / exposed	13 / 331 (3.93%)	23 / 311 (7.40%)	
occurrences (all)	20	26	
Nervous system disorders			

Multiple sclerosis relapse			
subjects affected / exposed	29 / 331 (8.76%)	31 / 311 (9.97%)	
occurrences (all)	36	37	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	24 / 331 (7.25%)	26 / 311 (8.36%)	
occurrences (all)	26	28	
Gait disturbance			
subjects affected / exposed	22 / 331 (6.65%)	17 / 311 (5.47%)	
occurrences (all)	28	21	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 331 (4.83%)	12 / 311 (3.86%)	
occurrences (all)	23	13	
Constipation			
subjects affected / exposed	18 / 331 (5.44%)	16 / 311 (5.14%)	
occurrences (all)	19	16	
Psychiatric disorders			
Depression			
subjects affected / exposed	17 / 331 (5.14%)	12 / 311 (3.86%)	
occurrences (all)	23	12	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	25 / 331 (7.55%)	26 / 311 (8.36%)	
occurrences (all)	29	31	
Muscular weakness			
subjects affected / exposed	20 / 331 (6.04%)	24 / 311 (7.72%)	
occurrences (all)	27	33	
Back pain			
subjects affected / exposed	19 / 331 (5.74%)	21 / 311 (6.75%)	
occurrences (all)	25	21	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	48 / 331 (14.50%)	50 / 311 (16.08%)	
occurrences (all)	74	94	
Nasopharyngitis			

subjects affected / exposed	39 / 331 (11.78%)	58 / 311 (18.65%)	
occurrences (all)	53	76	
Upper respiratory tract infection			
subjects affected / exposed	25 / 331 (7.55%)	27 / 311 (8.68%)	
occurrences (all)	33	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2018	Addition of an open-label extension for 39 additional months (up to M66). Change of the calculation method of the TW25 – part of the composite primary endpoint. Decided to take the best of the mean instead of the best value. Clarifications and minor logistic changes (i.e. Sponsor change of address, correct number of coutries and sites...). Addition of safety laboratory testings for thyroid panel testing related to laboratory interferences. Addition of Neurofilament blood level testing. Addition of the Patient Alert Card (alerting of the possibility that patient is taking biotin and it may interfere with laboratory test results).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported