Clinical trial results:
A multi-centre, open-label, non-randomised, parallel group clinical trial to assess the efficacy of fingolimod in naïve patients versus fingolimod in patients previously treated with interferons or glatiramer acetate, based on the presence of relapses in patients with relapsing-remitting multiple sclerosis. EARLIMS Study

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2011-003484-30
Trial protocol	ES
Global end of trial date	23 December 2015
Results information	
Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification	
Sponsor protocol code	CFTY720DES03
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01498887
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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether naïve treatment with 0.5 mg fingolimod in patients with short duration relapsing-remitting multiple sclerosis (less than five years) is superior in reducing the annual relapse rate, compared with treatment with 0.5 mg fingolimod in patients with the same disease and duration who have previously received first-line treatments.

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	21 December 2011
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: 61
Country: Number of subjects enrolled	Spain: 286
Worldwide total number of subjects	347
EEA total number of subjects	286

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)	0
From 65 to 84 years	347
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was an open-label, non-randomized, parallel group study.

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	Naive or de novo participants

Arm description:

Participants received 0.5 mg FTY720 (fingolimod) orally once daily for 12 months.

Arm type	Experimental
Investigational medicinal product name	Fingolimod
Investigational medicinal product code	FTY720
Other name	Gilenya
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 0.5 mg FTY720 (fingolimod) orally once daily for 12 months.

Arm title	Previously treated with first-line DMTs participants

Arm description:

Participants received 0.5 mg FTY720 (fingolimod) orally once daily for 12 months.

Arm type	Experimental
Investigational medicinal product name	Fingolimod
Investigational medicinal product code	FTY720
Other name	Gilenya
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 0.5 mg FTY720 (fingolimod) orally once daily for 12 months.

Number of subjects in period 1	Naive or de novo participants	Previously treated with first-line DMTs participants
Started	200	147
Safety set	200	147
Intent-to-treat	185	135 [1]
Completed	184	136
Not completed	16	11

Consent withdrawn by subject	1	-
Adverse event, non-fatal	4	1
Administrative problems	1	-
Abnormal laboratory value	2	2
Lost to follow-up	1	1
Protocol deviation	1	3
Lack of efficacy	5	3
Abnormal result from test procedure	1	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects reported in the milestone is correct.

Baseline characteristics

Reporting groups	
Reporting group title	Naive or de novo participants
Reporting group description:	
Participants received 0.5 mg FTY720 (fingolimod) orally once daily for 12 months.	
Reporting group title	Previously treated with first-line DMTs participants
Reporting group description:	
Participants received 0.5 mg FTY720 (fingolimod) orally once daily for 12 months.	

Reporting group values	Naive or de novo participants	Previously treated with first-line DMTs participants	Total
Number of subjects	200	147	347
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)	200	147	347
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender, Male/Female Units: Subjects			
Female	148	98	246
Male	52	49	101

End points

End points reporting groups

Reporting group title	Naive or de novo participants
Reporting group description: Participants received 0.5 mg FTY720 (fingolimod) orally once daily for 12 months.	
Reporting group title	Previously treated with first-line DMTs participants
Reporting group description: Participants received 0.5 mg FTY720 (fingolimod) orally once daily for 12 months.	

Primary: Annual Relapse Rate (ARR)

End point title	Annual Relapse Rate (ARR)
End point description: ARR = 365 days * number of relapses / total days taking the study medication.	
End point type	Primary
End point timeframe: 12 months	

End point values	Naive or de novo participants	Previously treated with first-line DMTs participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	135		
Units: Annual number of relapses per patient				
arithmetic mean (standard deviation)	0.29 (± 0.7399)	0.354 (± 0.8547)		

Statistical analyses

Statistical analysis title	Annual Relapse Rate
Comparison groups	Naive or de novo participants v Previously treated with first-line DMTs participants
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3118
Method	Wilcoxon (Mann-Whitney)

Secondary: Time to first relapse

End point title	Time to first relapse

End point description:

Time to first relapse was defined as the time from the first day of treatment to the first day of a new neurological symptom or worsening of an existing one.

End point type	Secondary

End point timeframe:

12 months

End point values	Naive or de novo participants	Previously treated with first-line DMTs participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	135		
Units: months				
median (confidence interval 95%)	9999 (-9999 to 9999)	9999 (-9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Expanded Disability Status Scale (EDSS) score

End point title	Change from baseline in Expanded Disability Status Scale (EDSS) score

End point description:

The EDSS is an ordinal clinical rating scale ranging from a total score of 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, 12 months

End point values	Naive or de novo participants	Previously treated with first-line DMTs participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	130		
Units: score on a scale				
arithmetic mean (standard deviation)	0 (± 0.804)	-0.077 (± 0.7911)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in cerebral volume

End point title	Change from baseline in cerebral volume

End point description:

Cerebral volume was assessed by magnetic resonance imaging (MRI). A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, 12 months

End point values	Naive or de novo participants	Previously treated with first-line DMTs participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	43		
Units: Percent				
number (not applicable)	-0.595	-0.387		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with mild, moderate or severe relapse

End point title	Percentage of participants with mild, moderate or severe relapse

End point description:

The investigator classified a relapse as moderate-severe if oral or intravenous (IV) treatment (according to the local clinical practice) with steroids and/or hospitalization was needed. If neither oral nor IV treatment with steroids nor hospitalization was needed, the relapse was considered as mild.

End point type	Secondary

End point timeframe:

12 months

End point values	Naive or de novo participants	Previously treated with first-line DMTs participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	39		
Units: Percent				
number (not applicable)				
Mild	42.55	38.46		
Moderate	57.45	56.41		
Severe	0	5.13		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of relapse-free participants

End point title	Percentage of relapse-free participants

End point description:

Relapse-free participants were defined as participants who experienced no new neurological symptom or worsening of an existing one (relapses) during the 12-month treatment period with 0.5 mg fingolimod.

End point type	Secondary

End point timeframe:

12 months

End point values	Naive or de novo participants	Previously treated with first-line DMTs participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	135		
Units: Percent				
number (not applicable)	71.89	66.67		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of T2 active lesions

End point title	Mean number of T2 active lesions

End point description:

The mean number of new or enlarged T2 active lesions was assessed by MRI.

End point type	Secondary

End point timeframe:

12 months

End point values	Naive or de novo participants	Previously treated with first-line DMTs participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	106		
Units: number of T2 lesions				
arithmetic mean (standard deviation)	2 (± 3.36)	1.6 (± 2.72)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Naive or de novo participants

Reporting group description:

Participants received 0.5 mg FTY720 (fingolimod) orally once daily for 12 months.

Reporting group title	Previously treated with first-line DMTs participants

Reporting group description:

Participants received 0.5 mg FTY720 (fingolimod) orally once daily for 12 months.

Reporting group title	All participants

Reporting group description: -

Serious adverse events	Naive or de novo participants	Previously treated with first-line DMTs participants	All participants
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 200 (5.50%)	4 / 147 (2.72%)	15 / 347 (4.32%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrioventricular block second degree			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	2 / 200 (1.00%)	1 / 147 (0.68%)	3 / 347 (0.86%)
occurrences causally related to treatment / all	2 / 2	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Naive or de novo participants	Previously treated with first-line DMTs participants	All participants
Total subjects affected by non-serious adverse events			
subjects affected / exposed	143 / 200 (71.50%)	114 / 147 (77.55%)	257 / 347 (74.06%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Basal cell carcinoma			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Fibroadenoma of breast			

subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Fibrous histiocytoma			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Melanocytic naevus			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Seborrhoeic keratosis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Skin papilloma			
subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	3	3
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	1 / 200 (0.50%)	3 / 147 (2.04%)	4 / 347 (1.15%)
occurrences (all)	1	3	4
Surgical and medical procedures			
Intraocular lens implant			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Skin lesion excision			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Tooth extraction			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
General disorders and administration site conditions			

Adverse drug reaction			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Chest discomfort			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Chest pain			
subjects affected / exposed	1 / 200 (0.50%)	3 / 147 (2.04%)	4 / 347 (1.15%)
occurrences (all)	1	3	4
Exercise tolerance decreased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	11 / 200 (5.50%)	9 / 147 (6.12%)	20 / 347 (5.76%)
occurrences (all)	11	9	20
Gait disturbance			
subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	2	2
Influenza like illness			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	2	1	3
Pain			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	1 / 200 (0.50%)	5 / 147 (3.40%)	6 / 347 (1.73%)
occurrences (all)	1	5	6
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Benign prostatic hyperplasia			

subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Cervical dysplasia			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Dysmenorrhoea			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Erectile dysfunction			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Menorrhagia			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Menstrual disorder			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Metrorrhagia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Sexual dysfunction			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 200 (0.50%)	4 / 147 (2.72%)	5 / 347 (1.44%)
occurrences (all)	1	4	5
Dyspnoea			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Epistaxis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Nasal dryness			

subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	3 / 200 (1.50%)	1 / 147 (0.68%)	4 / 347 (1.15%)
occurrences (all)	4	1	5
Psychiatric disorders			
Adjustment disorder with mixed anxiety and depressed mood			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Anxiety			
subjects affected / exposed	11 / 200 (5.50%)	6 / 147 (4.08%)	17 / 347 (4.90%)
occurrences (all)	11	6	17
Anxiety disorder			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Bruxism			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Confusional state			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Depressed mood			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Depression			
subjects affected / exposed	9 / 200 (4.50%)	6 / 147 (4.08%)	15 / 347 (4.32%)
occurrences (all)	9	6	15
Dysthymic disorder			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Generalised anxiety disorder			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Insomnia			

subjects affected / exposed	5 / 200 (2.50%)	3 / 147 (2.04%)	8 / 347 (2.31%)
occurrences (all)	5	3	8
Laziness			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Personality disorder			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences (all)	2	0	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 200 (1.00%)	5 / 147 (3.40%)	7 / 347 (2.02%)
occurrences (all)	2	5	7
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 200 (0.00%)	5 / 147 (3.40%)	5 / 347 (1.44%)
occurrences (all)	0	5	5
B-lymphocyte count decreased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Blood calcium decreased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Blood chloride increased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Blood cholesterol increased			
subjects affected / exposed	1 / 200 (0.50%)	2 / 147 (1.36%)	3 / 347 (0.86%)
occurrences (all)	1	2	3
Blood iron decreased			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Blood pressure increased			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Blood triglycerides increased			

subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	2	2
CD4 lymphocytes decreased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
CD8 lymphocytes decreased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 200 (0.00%)	3 / 147 (2.04%)	3 / 347 (0.86%)
occurrences (all)	0	3	3
Hepatic enzyme increased			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Liver function test abnormal			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Low density lipoprotein increased			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Lymphocyte count decreased			
subjects affected / exposed	1 / 200 (0.50%)	2 / 147 (1.36%)	3 / 347 (0.86%)
occurrences (all)	1	2	3
Micturition urgency			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
T-lymphocyte count decreased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Transaminases abnormal			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1

Weight decreased			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	2	3
Weight increased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Contusion			
subjects affected / exposed	3 / 200 (1.50%)	0 / 147 (0.00%)	3 / 347 (0.86%)
occurrences (all)	4	0	4
Fall			
subjects affected / exposed	1 / 200 (0.50%)	3 / 147 (2.04%)	4 / 347 (1.15%)
occurrences (all)	1	3	4
Foot fracture			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Ligament sprain			
subjects affected / exposed	2 / 200 (1.00%)	1 / 147 (0.68%)	3 / 347 (0.86%)
occurrences (all)	2	1	3
Maternal exposure during pregnancy			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Muscle injury			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Road traffic accident			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Congenital, familial and genetic disorders			
Retinal anomaly congenital			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Cardiac disorders			

Atrioventricular block first degree			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences (all)	2	0	2
Bradycardia			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Palpitations			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences (all)	2	0	2
Tachycardia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Aphonia			
subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	2	2
Balance disorder			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Burning sensation			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Carpal tunnel syndrome			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Cervicobrachial syndrome			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	5 / 200 (2.50%)	7 / 147 (4.76%)	12 / 347 (3.46%)
occurrences (all)	5	7	12
Dysaesthesia			

subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Epilepsy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Head discomfort			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Headache			
subjects affected / exposed	17 / 200 (8.50%)	17 / 147 (11.56%)	34 / 347 (9.80%)
occurrences (all)	25	23	48
Hemiparesis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Hyperreflexia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Hypersomnia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Hypoaesthesia			
subjects affected / exposed	1 / 200 (0.50%)	3 / 147 (2.04%)	4 / 347 (1.15%)
occurrences (all)	1	3	4
Lethargy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Migraine			
subjects affected / exposed	6 / 200 (3.00%)	6 / 147 (4.08%)	12 / 347 (3.46%)
occurrences (all)	6	6	12
Migraine with aura			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences (all)	2	0	2
Migraine without aura			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences (all)	3	0	3
Multiple sclerosis relapse			

subjects affected / exposed	2 / 200 (1.00%)	1 / 147 (0.68%)	3 / 347 (0.86%)
occurrences (all)	3	1	4
Neuralgia			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences (all)	2	0	2
Neurological symptom			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Neuropathy peripheral			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Optic neuritis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Paraesthesia			
subjects affected / exposed	3 / 200 (1.50%)	4 / 147 (2.72%)	7 / 347 (2.02%)
occurrences (all)	3	4	7
Partial seizures			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Presyncope			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	2	3
Restless legs syndrome			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Sciatica			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Sensorimotor disorder			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Sleep paralysis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Somnolence			

subjects affected / exposed	1 / 200 (0.50%)	2 / 147 (1.36%)	3 / 347 (0.86%)
occurrences (all)	1	2	3
Syncope			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Tension headache			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Typical aura without headache			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Uhthoff's phenomenon			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
VIIth nerve paralysis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 200 (1.50%)	0 / 147 (0.00%)	3 / 347 (0.86%)
occurrences (all)	3	0	3
Iron deficiency anaemia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Lymphadenitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Lymphadenopathy			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences (all)	2	0	2
Lymphocytosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Lymphopenia			
subjects affected / exposed	9 / 200 (4.50%)	7 / 147 (4.76%)	16 / 347 (4.61%)
occurrences (all)	9	9	18

Microcytic anaemia			
subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	2	2
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Ear pain			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Hypoacusis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Tinnitus			
subjects affected / exposed	2 / 200 (1.00%)	1 / 147 (0.68%)	3 / 347 (0.86%)
occurrences (all)	2	1	3
Vertigo			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Eye disorders			
Amblyopia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Astigmatism			
subjects affected / exposed	2 / 200 (1.00%)	1 / 147 (0.68%)	3 / 347 (0.86%)
occurrences (all)	2	1	3
Conjunctival haemorrhage			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Conjunctivitis			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Diplopia			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences (all)	2	0	2
Dry eye			

subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Erythema of eyelid			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Eye pain			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Eyelid oedema			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Macular oedema			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Myopia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Ocular hyperaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Optic atrophy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Pinguecula			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Presbyopia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Retinal pigment epitheliopathy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Strabismus			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Vision blurred			

subjects affected / exposed	2 / 200 (1.00%)	3 / 147 (2.04%)	5 / 347 (1.44%)
occurrences (all)	2	3	5
Visual impairment			
subjects affected / exposed	2 / 200 (1.00%)	2 / 147 (1.36%)	4 / 347 (1.15%)
occurrences (all)	2	2	4
Vitreous floaters			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 200 (1.50%)	1 / 147 (0.68%)	4 / 347 (1.15%)
occurrences (all)	3	4	7
Abdominal distension			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Abdominal pain			
subjects affected / exposed	1 / 200 (0.50%)	2 / 147 (1.36%)	3 / 347 (0.86%)
occurrences (all)	1	2	3
Abdominal pain upper			
subjects affected / exposed	5 / 200 (2.50%)	3 / 147 (2.04%)	8 / 347 (2.31%)
occurrences (all)	5	3	8
Constipation			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Dental caries			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Dental cyst			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	5 / 200 (2.50%)	9 / 147 (6.12%)	14 / 347 (4.03%)
occurrences (all)	5	10	15
Dyspepsia			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2

Gastritis			
subjects affected / exposed	3 / 200 (1.50%)	1 / 147 (0.68%)	4 / 347 (1.15%)
occurrences (all)	3	1	4
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Gingival bleeding			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Haemorrhoids			
subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	2	2
Hyperchlorhydria			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Mouth ulceration			
subjects affected / exposed	4 / 200 (2.00%)	1 / 147 (0.68%)	5 / 347 (1.44%)
occurrences (all)	4	1	5
Nausea			
subjects affected / exposed	7 / 200 (3.50%)	5 / 147 (3.40%)	12 / 347 (3.46%)
occurrences (all)	9	7	16
Odynophagia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Oesophagitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Oral discomfort			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Oral pain			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1

Stomatitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Toothache			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Vomiting			
subjects affected / exposed	2 / 200 (1.00%)	4 / 147 (2.72%)	6 / 347 (1.73%)
occurrences (all)	3	4	7
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Hepatic function abnormal			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Hepatomegaly			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Hypertransaminasaemia			
subjects affected / exposed	3 / 200 (1.50%)	0 / 147 (0.00%)	3 / 347 (0.86%)
occurrences (all)	3	0	3
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 200 (1.50%)	2 / 147 (1.36%)	5 / 347 (1.44%)
occurrences (all)	3	2	5
Actinic keratosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Alopecia			
subjects affected / exposed	4 / 200 (2.00%)	3 / 147 (2.04%)	7 / 347 (2.02%)
occurrences (all)	4	3	7
Dermatitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Dermatitis allergic			

subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Dermatitis atopic			
subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	2	2
Eczema			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences (all)	2	0	2
Eczema nummular			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Erythema			
subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	2	2
Hand dermatitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Hidradenitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Hyperhidrosis			
subjects affected / exposed	2 / 200 (1.00%)	0 / 147 (0.00%)	2 / 347 (0.58%)
occurrences (all)	2	0	2
Night sweats			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Pain of skin			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	4 / 200 (2.00%)	0 / 147 (0.00%)	4 / 347 (1.15%)
occurrences (all)	4	0	4
Rash macular			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Rash pruritic			

subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Seborrhoeic dermatitis			
subjects affected / exposed	2 / 200 (1.00%)	2 / 147 (1.36%)	4 / 347 (1.15%)
occurrences (all)	2	2	4
Skin depigmentation			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Skin discolouration			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Skin fissures			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Skin hypertrophy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Skin lesion			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Solar lentigo			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Lower urinary tract symptoms			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Micturition urgency			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Neurogenic bladder			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1

Pollakiuria			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Polyuria			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Renal colic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Renal pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Urinary incontinence			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Urinary retention			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 200 (0.50%)	3 / 147 (2.04%)	4 / 347 (1.15%)
occurrences (all)	2	3	5
Back pain			
subjects affected / exposed	12 / 200 (6.00%)	4 / 147 (2.72%)	16 / 347 (4.61%)
occurrences (all)	13	4	17
Bursitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Haemophilic arthropathy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Muscle contracture			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Muscle spasms			

subjects affected / exposed	0 / 200 (0.00%)	3 / 147 (2.04%)	3 / 347 (0.86%)
occurrences (all)	0	3	3
Muscular weakness			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 200 (0.50%)	3 / 147 (2.04%)	4 / 347 (1.15%)
occurrences (all)	1	3	4
Musculoskeletal stiffness			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Myokymia			
subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	2	2
Neck pain			
subjects affected / exposed	5 / 200 (2.50%)	6 / 147 (4.08%)	11 / 347 (3.17%)
occurrences (all)	5	7	12
Pain in extremity			
subjects affected / exposed	2 / 200 (1.00%)	2 / 147 (1.36%)	4 / 347 (1.15%)
occurrences (all)	2	2	4
Sjogren's syndrome			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Spondylolisthesis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Synovial cyst			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Tendonitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1

Bacterial vaginosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Bronchitis			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Conjunctivitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Conjunctivitis viral			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	4	0	4
Cystitis			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	4	5
Ear infection			
subjects affected / exposed	1 / 200 (0.50%)	2 / 147 (1.36%)	3 / 347 (0.86%)
occurrences (all)	1	2	3
Folliculitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Fungal skin infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Gastric infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Gastroenteritis			
subjects affected / exposed	9 / 200 (4.50%)	6 / 147 (4.08%)	15 / 347 (4.32%)
occurrences (all)	10	7	17
Gastroenteritis viral			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Genital herpes			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1

Genitourinary tract infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Herpes ophthalmic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Herpes simplex			
subjects affected / exposed	2 / 200 (1.00%)	1 / 147 (0.68%)	3 / 347 (0.86%)
occurrences (all)	2	1	3
Herpes zoster			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Influenza			
subjects affected / exposed	3 / 200 (1.50%)	3 / 147 (2.04%)	6 / 347 (1.73%)
occurrences (all)	4	5	9
Laryngitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Lower respiratory tract infection			
subjects affected / exposed	3 / 200 (1.50%)	0 / 147 (0.00%)	3 / 347 (0.86%)
occurrences (all)	3	0	3
Molluscum contagiosum			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Nasopharyngitis			
subjects affected / exposed	16 / 200 (8.00%)	8 / 147 (5.44%)	24 / 347 (6.92%)
occurrences (all)	22	9	31
Onychomycosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1

Oral herpes			
subjects affected / exposed	7 / 200 (3.50%)	5 / 147 (3.40%)	12 / 347 (3.46%)
occurrences (all)	7	5	12
Paronychia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Periodontitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Pertussis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Pharyngitis			
subjects affected / exposed	8 / 200 (4.00%)	4 / 147 (2.72%)	12 / 347 (3.46%)
occurrences (all)	9	4	13
Pharyngitis bacterial			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	2	2
Pharyngitis streptococcal			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Pharyngotonsillitis			
subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	2	2
Pneumonia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Respiratory tract infection			
subjects affected / exposed	4 / 200 (2.00%)	2 / 147 (1.36%)	6 / 347 (1.73%)
occurrences (all)	4	2	6
Rhinitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Sinusitis			
subjects affected / exposed	3 / 200 (1.50%)	2 / 147 (1.36%)	5 / 347 (1.44%)
occurrences (all)	3	3	6

Sinusitis bacterial			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Skin infection			
subjects affected / exposed	0 / 200 (0.00%)	3 / 147 (2.04%)	3 / 347 (0.86%)
occurrences (all)	0	3	3
Tinea versicolour			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Tonsillitis			
subjects affected / exposed	6 / 200 (3.00%)	3 / 147 (2.04%)	9 / 347 (2.59%)
occurrences (all)	8	4	12
Tonsillitis bacterial			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Tooth abscess			
subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	5	5
Tooth infection			
subjects affected / exposed	1 / 200 (0.50%)	2 / 147 (1.36%)	3 / 347 (0.86%)
occurrences (all)	1	2	3
Tracheobronchitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	15 / 200 (7.50%)	12 / 147 (8.16%)	27 / 347 (7.78%)
occurrences (all)	18	14	32
Urinary tract infection			
subjects affected / exposed	15 / 200 (7.50%)	15 / 147 (10.20%)	30 / 347 (8.65%)
occurrences (all)	16	23	39
Viral infection			
subjects affected / exposed	3 / 200 (1.50%)	0 / 147 (0.00%)	3 / 347 (0.86%)
occurrences (all)	3	0	3
Viral pharyngitis			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2

Vulvovaginal candidiasis			
subjects affected / exposed	2 / 200 (1.00%)	5 / 147 (3.40%)	7 / 347 (2.02%)
occurrences (all)	3	7	10
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	2	3
Wound infection bacterial			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Dyslipidaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Hypercholesterolaemia			
subjects affected / exposed	3 / 200 (1.50%)	4 / 147 (2.72%)	7 / 347 (2.02%)
occurrences (all)	3	4	7
Hypertriglyceridaemia			
subjects affected / exposed	1 / 200 (0.50%)	2 / 147 (1.36%)	3 / 347 (0.86%)
occurrences (all)	1	2	3
Hypocalcaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Hypokalaemia			
subjects affected / exposed	1 / 200 (0.50%)	1 / 147 (0.68%)	2 / 347 (0.58%)
occurrences (all)	1	1	2
Hypophosphataemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Lactose intolerance			
subjects affected / exposed	1 / 200 (0.50%)	0 / 147 (0.00%)	1 / 347 (0.29%)
occurrences (all)	1	0	1
Polydipsia			

subjects affected / exposed	0 / 200 (0.00%)	1 / 147 (0.68%)	1 / 347 (0.29%)
occurrences (all)	0	1	1
Vitamin D deficiency			
subjects affected / exposed	0 / 200 (0.00%)	2 / 147 (1.36%)	2 / 347 (0.58%)
occurrences (all)	0	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2011	Addition of Exclusion Criterion 14: "Patients with severe hepatic impairment (Child-Pugh class C)". Addition of Australian sites, leading to an increase in the recruitment.
01 December 2011	A secondary endpoint was modified adding: "Since not all participating centres have the SIENAX software, the analysis of all MRIs will be applicable only for a subpopulation of subjects". The window days between visits were modified: "The study will consist of 4 visits (Visit 0, Visit 1, Visit 2, and Visit 3) and a screening visit (Visit -1): Day -30 to -1, during which patients must be examined either at the scheduled visits or on the earliest day possible (day 0 for V0 and ±15 days for V1, V2 and V3). Inclusion criteria 6 was modified as follows: "Patients: a. Treatment-naïve: patients who have never been treated with a DMT or b. Previously treated with first-line DMT patients who have been treated with a first-line DMT continuously for at least a one year period (interferon β-1a [IM or SC], interferon-β-1b or glatiramer acetate)". • Exclusion criteria 7 was modified as follows: "Patients who test negative for IgG antibodies against the varicella-zoster virus at the screening visit. Patients may be vaccinated once it is established that they have IgG antibodies and could be included at least 1 month after vaccination". • It included laboratory analysis at Visit 1 of the study: "To assess safety, laboratory tests (haematology, biochemistry) will be conducted at the screening visit (Visit -1), Visit 2 (6 months) and Visit 3 (final study visit at 12 months or at early withdrawal from the study)".
23 January 2012	Due to a new security measure from EMA, it added an ECG before medication administration and after six hours of administration. Arterial pressure and pulse frequency will be taken each hour till 6 hours. It added laboratory analysis at first month and at month 9. It included a series of remarks in the protocol.
29 May 2012	It has been specified that the inclusion criteria No. 4 only applies to Spain. Added the inclusion criteria No. 5, which only applies to Australia. Added the exclusion criteria number 15 and 16.
01 October 2012	The centralization of MRI analysis of all patients in the trial in a central laboratory in Australia is included (Sydney Neuroimaging Analysis Centre, SNAC).
08 January 2013	Due to a security requirements from EMA, it adds the same monitoring process as for treatment initiation when treatment is interrupted for: 1 day or more during the first 2 weeks of treatment; more than 7 days during weeks 3 and 4 of treatment; more than 2 weeks after one month of treatment.
04 July 2013	Due to that several centres in Spain had difficulty adapting to the parameters of SNAC, SNAC analyse separately MRI of Australia and Spain. In addition, for patients in Spain, another MRI central analysis will be run at Institut de diagnòstic per la Imatge of Hospital Vall d'Hebron.
03 June 2014	The central analysis for patients in Spain at Institut de diagnòstic per la Imatge of Hospital Vall d'Hebron is deleted. Recruitment period is prolonged to December 2014.
10 June 2014	Clarification on compliance checks in Australia, aligned with standard of care.
30 October 2015	Notification that an Interim Analysis was done.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: