



Clinical trial results:

A 1-week, open-label, multi-center study to explore conduction abnormalities during first dose administration of fingolimod in patients with relapsing-remitting multiple sclerosis (START)

Summary

EudraCT number	2012-000653-32
Trial protocol	DE
Global end of trial date	12 December 2016

Results information

Result version number	v1 (current)
This version publication date	23 December 2017
First version publication date	23 December 2017

Trial information

Trial identification

Sponsor protocol code	CFTY720DDE17
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01585298
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 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 December 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the incidence of patients with bradycardia (heart rate < 45 beats per min) and bradyarrhythmic ECG events during 6-hour monitoring period as measured by heart rate and second and third-degree AV blocks after treatment initiation of fingolimod 0.5 mg.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2012
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	Germany: 6998
Worldwide total number of subjects	6998
EEA total number of subjects	6998

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)	6957
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All participants received open-label fingolimod.

Period 1

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

Arms

Arm title	Fingolimod
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Arm description:

Fingolimod 0.5 mg by mouth once daily for 7 days.

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:

Fingolimod 0.5 mg by mouth once daily for 7 days.

Number of subjects in period 1	Fingolimod
Started	6998
Completed	6961
Not completed	37
Consent withdrawn by subject	4
Abnormal test procedure results	1
Study completion was not documented.	1
Adverse event, non-fatal	24
Protocol deviation	1
Administrative problems	4
Lost to follow-up	2

Baseline characteristics

Reporting groups

Reporting group title	Fingolimod
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Reporting group description:

Fingolimod 0.5 mg by mouth once daily for 7 days.

Reporting group values	Fingolimod	Total	
Number of subjects	6998	6998	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	6957	6957	
From 65-84 years	41	41	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	39.2		
standard deviation	± 10.52	-	
Gender, Male/Female			
Units: Subjects			
Female	4924	4924	
Male	2074	2074	

End points

End points reporting groups

Reporting group title	Fingolimod
Reporting group description: Fingolimod 0.5 mg by mouth once daily for 7 days.	

Primary: Number of participants with 2nd or 3rd degree AV block

End point title	Number of participants with 2nd or 3rd degree AV block ^[1]
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End point description:

Number of participants with 2nd or 3rd degree AV block in ECG during first dose observation. Participants can simultaneously experience both types of AV blocks. Two patients of the safety analysis set discontinued the study without having received treatment, but safety information was collected on these two patients.

End point type	Primary
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End point timeframe:

baseline during 6 hour monitoring post dose

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis does not apply to this end point.

End point values	Fingolimod			
Subject group type	Reporting group			
Number of subjects analysed	6998			
Units: Participants				
Any AV block II degree or higher	120			
AV block II degree: Mobitz type I degree	117			
AV block II degree: Mobitz type II degree	0			
AV block II degree: 2:1	43			
AV block III degree	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with heart rate below 45 beats per minute (BPM)

End point title	Number of patients with heart rate below 45 beats per minute (BPM) ^[2]
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End point description:

Number of patients with heart rate below 45 beats bpm in ECG during first dose observation. Two patients of the safety analysis set discontinued the study without having received treatment, but safety information was collected on these two patients.

End point type	Primary
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End point timeframe:

baseline during 6 hour monitoring post dose

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis does not apply to this end point.

End point values	Fingolimod			
Subject group type	Reporting group			
Number of subjects analysed	6998			
Units: Participants	63			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with prolonged QTc interval (Friderica)

End point title	Number of participants with prolonged QTc interval (Friderica)
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End point description:

Number of patients with conduction abnormalities such as QT prolongation, first degree AV block during treatment initiation. Two patients of the safety analysis set discontinued the study without having received treatment, but safety information was collected on these two patients.

End point type	Secondary
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End point timeframe:

baseline post-dose

End point values	Fingolimod			
Subject group type	Reporting group			
Number of subjects analysed	6844			
Units: Participants				
Female, QTcFridericia Interval > 470 ms (n=4808)	7			
Male, QTcF Interval > 450 ms (n=2036)	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with bradyarrhythmic electrocardiogram (ECG) events

End point title	Number of participants with bradyarrhythmic electrocardiogram (ECG) events
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End point description:

The number of participants with bradyarrhythmic electrocardiogram (ECG) events was assessed. Bradyarrhythmic ECG events are defined as QTc Fridericia time > 450 ms for males and > 470 ms for females. Two patients of the safety analysis set discontinued the study without having received treatment, but safety information was collected on these two patients.

End point type	Secondary
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End point timeframe:

up to day 7

End point values	Fingolimod			
Subject group type	Reporting group			
Number of subjects analysed	6998			
Units: Participants	26			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with cardiac adverse events

End point title	Number of patients with cardiac adverse events
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End point description:

The number of participants with the occurrence of subsequent cardiac adverse events (AEs) and serious cardiac AEs during study was assessed. Cardiac events were defined as the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms: angina pectoris, chest discomfort, dizziness, dyspnoea, dyspnoea exertional, fatigue, palpitations, syncope, vertigo, vertigo positional and vision blurred. Two patients of the safety analysis set discontinued the study without having received treatment, but safety information was collected on these two patients.

End point type	Secondary
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End point timeframe:

7 days

End point values	Fingolimod			
Subject group type	Reporting group			
Number of subjects analysed	6998			
Units: Participants				
Cardiac events	489			
Serious cardiac AEs	9			

Statistical analyses

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.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Fingolimod 0.5 mg
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Reporting group description:

Fingolimod 0.5 mg

Serious adverse events	Fingolimod 0.5 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	160 / 6998 (2.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm benign			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Blood pressure fluctuation			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Unintended pregnancy			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Painful respiration			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract inflammation			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Borderline personality disorder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression suicidal			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental fatigue			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Panic attack			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
CD4/CD8 ratio decreased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram QT prolonged			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Heart rate decreased			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

Atrioventricular block complete subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block second degree subjects affected / exposed	49 / 6998 (0.70%)		
occurrences causally related to treatment / all	47 / 49		
deaths causally related to treatment / all	0 / 0		
Bradycardia subjects affected / exposed	24 / 6998 (0.34%)		
occurrences causally related to treatment / all	24 / 24		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease subjects affected / exposed	2 / 6998 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ischaemic cardiomyopathy subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction subjects affected / exposed	2 / 6998 (0.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia subjects affected / exposed	2 / 6998 (0.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Supraventricular extrasystoles subjects affected / exposed	2 / 6998 (0.03%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Ataxia				
subjects affected / exposed	1 / 6998 (0.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Central nervous system lesion				
subjects affected / exposed	1 / 6998 (0.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	3 / 6998 (0.04%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Embolic cerebral infarction				
subjects affected / exposed	1 / 6998 (0.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	2 / 6998 (0.03%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 6998 (0.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	1 / 6998 (0.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial aneurysm				
subjects affected / exposed	1 / 6998 (0.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple sclerosis relapse				

subjects affected / exposed	26 / 6998 (0.37%)		
occurrences causally related to treatment / all	0 / 26		
deaths causally related to treatment / all	0 / 0		
Optic neuritis			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Partial seizures			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Restless legs syndrome			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural hygroma			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukopenia			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphopenia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Macular oedema			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Visual acuity reduced			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal fistula			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Dysphagia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth haemorrhage			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin irritation			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus urethral			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myalgia			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral herpes			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Fingolimod 0.5 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2179 / 6998 (31.14%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Pharyngeal neoplasm benign			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Vascular disorders			
Blood pressure fluctuation			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Circulatory collapse			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Diastolic hypertension			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Haematoma			

subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Hot flush subjects affected / exposed occurrences (all)	3 / 6998 (0.04%) 3		
Hypertension subjects affected / exposed occurrences (all)	64 / 6998 (0.91%) 64		
Hypotension subjects affected / exposed occurrences (all)	12 / 6998 (0.17%) 12		
Pallor subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Peripheral coldness subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Varicose vein subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Pregnancy, puerperium and perinatal conditions Pregnancy subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Pregnancy of unknown location subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Unintended pregnancy subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
General disorders and administration site conditions Application site reaction subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Asthenia			

subjects affected / exposed	10 / 6998 (0.14%)		
occurrences (all)	10		
Chest discomfort			
subjects affected / exposed	24 / 6998 (0.34%)		
occurrences (all)	25		
Chest pain			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	11 / 6998 (0.16%)		
occurrences (all)	11		
Chronic fatigue syndrome			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Discomfort			
subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
Face oedema			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	227 / 6998 (3.24%)		
occurrences (all)	227		
Feeling abnormal			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Feeling cold			
subjects affected / exposed	8 / 6998 (0.11%)		
occurrences (all)	8		
Feeling drunk			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
Gait disturbance			

subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
Inflammation			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	19 / 6998 (0.27%)		
occurrences (all)	19		
Infusion site inflammation			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Infusion site necrosis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Local swelling			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	11 / 6998 (0.16%)		
occurrences (all)	11		
Mucosal dryness			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	31 / 6998 (0.44%)		
occurrences (all)	31		
Oedema peripheral			
subjects affected / exposed	7 / 6998 (0.10%)		
occurrences (all)	7		
Pain			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Peripheral swelling			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Pyrexia			

subjects affected / exposed occurrences (all)	17 / 6998 (0.24%) 17		
Secretion discharge subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Sensation of foreign body subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Sense of oppression subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Temperature intolerance subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Thirst subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Immune system disorders Food allergy subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Hypersensitivity subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Seasonal allergy subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Social circumstances Walking disability subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Reproductive system and breast disorders Breast discomfort subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Breast disorder			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Breast pain			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	3		
Breast tenderness			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Cervical dysplasia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Dysmenorrhoea			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Metrorrhagia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Ovulation pain			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Priapism			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Uterine haemorrhage			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Vulvovaginal burning sensation			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Allergic bronchitis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Asthma			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	20 / 6998 (0.29%)		
occurrences (all)	20		
Dysphonia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	18 / 6998 (0.26%)		
occurrences (all)	18		
Dyspnoea exertional			
subjects affected / exposed	6 / 6998 (0.09%)		
occurrences (all)	6		
Epistaxis			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Increased bronchial secretion			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Nasal oedema			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	27 / 6998 (0.39%)		
occurrences (all)	27		
Painful respiration			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Pleurisy			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Respiratory distress			

subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Rhinitis allergic			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Sinus disorder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Throat irritation			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Throat tightness			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Adjustment disorder with depressed mood			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Affective disorder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Aggression			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Agitation			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Anxiety			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	19 / 6998 (0.27%)		
occurrences (all)	19		
Dyssomnia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Emotional disorder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Initial insomnia			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	12 / 6998 (0.17%)		
occurrences (all)	12		
Irritability			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Laziness			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Listless			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Mental disorder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Mental fatigue			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Middle insomnia			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Mood altered			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Mood swings			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Nervousness			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Nightmare			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Panic attack			
subjects affected / exposed	7 / 6998 (0.10%)		
occurrences (all)	7		
Persistent depressive disorder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	8 / 6998 (0.11%)		
occurrences (all)	8		
Sleep disorder			
subjects affected / exposed	18 / 6998 (0.26%)		
occurrences (all)	18		
Product issues			
Device defective			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Hyperbilirubinaemia			

subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
Liver disorder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	21 / 6998 (0.30%)		
occurrences (all)	21		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Basophil count increased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	11 / 6998 (0.16%)		
occurrences (all)	11		
Blood chloride decreased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Blood glucose decreased			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Blood glucose increased			
subjects affected / exposed	9 / 6998 (0.13%)		
occurrences (all)	10		
Blood pressure decreased			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Blood pressure diastolic decreased			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Blood pressure diastolic increased			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Blood pressure increased			
subjects affected / exposed	10 / 6998 (0.14%)		
occurrences (all)	10		
Blood pressure systolic increased			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Blood urea increased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Electrocardiogram P wave abnormal			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Electrocardiogram QRS complex prolonged			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	9 / 6998 (0.13%)		
occurrences (all)	9		
Electrocardiogram ST segment abnormal			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Electrocardiogram ST segment depression			

subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Electrocardiogram abnormal			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Eosinophil count decreased			
subjects affected / exposed	13 / 6998 (0.19%)		
occurrences (all)	13		
Eosinophil count increased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 6998 (0.11%)		
occurrences (all)	9		
Haematocrit decreased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Haematocrit increased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Haemoglobin increased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Heart rate abnormal			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Heart rate decreased			
subjects affected / exposed	13 / 6998 (0.19%)		
occurrences (all)	13		

Heart rate increased subjects affected / exposed occurrences (all)	7 / 6998 (0.10%) 7		
Hepatic enzyme increased subjects affected / exposed occurrences (all)	14 / 6998 (0.20%) 14		
Liver function test increased subjects affected / exposed occurrences (all)	3 / 6998 (0.04%) 3		
Lymphocyte count abnormal subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	36 / 6998 (0.51%) 36		
Lymphocyte count increased subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Monocyte count decreased subjects affected / exposed occurrences (all)	3 / 6998 (0.04%) 3		
Monocyte count increased subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Neutrophil count decreased subjects affected / exposed occurrences (all)	6 / 6998 (0.09%) 6		
Neutrophil count increased subjects affected / exposed occurrences (all)	7 / 6998 (0.10%) 7		
Platelet aggregation subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		

Pulse abnormal			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Red blood cell count decreased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Weight increased			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
White blood cell count decreased			
subjects affected / exposed	18 / 6998 (0.26%)		
occurrences (all)	18		
White blood cell count increased			
subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
White blood cells urine			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Animal scratch			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Chest injury			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Fall			

subjects affected / exposed occurrences (all)	6 / 6998 (0.09%) 6		
Foot fracture subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Laceration subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Ligament sprain subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Limb injury subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Meniscus injury subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Post procedural complication subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Skin abrasion subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Thermal burn subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Congenital, familial and genetic disorders Corneal dystrophy subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)	11 / 6998 (0.16%) 11		
Arrhythmia			

subjects affected / exposed	7 / 6998 (0.10%)		
occurrences (all)	7		
Atrioventricular block first degree			
subjects affected / exposed	116 / 6998 (1.66%)		
occurrences (all)	117		
Atrioventricular block second degree			
subjects affected / exposed	74 / 6998 (1.06%)		
occurrences (all)	74		
Bradycardia			
subjects affected / exposed	48 / 6998 (0.69%)		
occurrences (all)	48		
Bundle branch block right			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Cardiac discomfort			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Cardiovascular disorder			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Coronary artery stenosis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Extrasystoles			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Palpitations			
subjects affected / exposed	26 / 6998 (0.37%)		
occurrences (all)	26		
Pericardial effusion			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Sinus arrhythmia			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Sinus bradycardia			

subjects affected / exposed	8 / 6998 (0.11%)		
occurrences (all)	8		
Sinus tachycardia			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Supraventricular extrasystoles			
subjects affected / exposed	10 / 6998 (0.14%)		
occurrences (all)	10		
Tachycardia			
subjects affected / exposed	6 / 6998 (0.09%)		
occurrences (all)	6		
Ventricular extrasystoles			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Ventricular pre-excitation			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Ventricular tachycardia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Ataxia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Balance disorder			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Carpal tunnel syndrome			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Disturbance in attention			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		

Dizziness			
subjects affected / exposed	126 / 6998 (1.80%)		
occurrences (all)	126		
Dizziness exertional			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Dizziness postural			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Dysaesthesia			
subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
Dysgeusia			
subjects affected / exposed	21 / 6998 (0.30%)		
occurrences (all)	21		
Epilepsy			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Facial spasm			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Head discomfort			
subjects affected / exposed	6 / 6998 (0.09%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	316 / 6998 (4.52%)		
occurrences (all)	325		
Hemiparesis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Hyperaesthesia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Hypertonia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		

Hypoaesthesia			
subjects affected / exposed	14 / 6998 (0.20%)		
occurrences (all)	14		
Lhermitte's sign			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Migraine			
subjects affected / exposed	17 / 6998 (0.24%)		
occurrences (all)	18		
Migraine with aura			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Monoparesis			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Multiple sclerosis			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Multiple sclerosis relapse			
subjects affected / exposed	70 / 6998 (1.00%)		
occurrences (all)	70		
Muscle spasticity			
subjects affected / exposed	6 / 6998 (0.09%)		
occurrences (all)	6		
Neuralgia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Optic neuritis			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Orthostatic intolerance			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		

Paraesthesia			
subjects affected / exposed	29 / 6998 (0.41%)		
occurrences (all)	29		
Peroneal nerve palsy			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Psychogenic pseudosyncope			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Radial nerve compression			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Restless legs syndrome			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Sciatica			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Sensory disturbance			
subjects affected / exposed	7 / 6998 (0.10%)		
occurrences (all)	7		
Somnolence			
subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
Syncope			
subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
Tension headache			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Tremor			
subjects affected / exposed	9 / 6998 (0.13%)		
occurrences (all)	9		

Trigeminal neuralgia subjects affected / exposed occurrences (all)	3 / 6998 (0.04%) 3		
Visual field defect subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	4 / 6998 (0.06%) 4		
Eosinopenia subjects affected / exposed occurrences (all)	7 / 6998 (0.10%) 7		
Eosinophilia subjects affected / exposed occurrences (all)	12 / 6998 (0.17%) 12		
Granulocytosis subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Haemoglobinaemia subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Leukocytosis subjects affected / exposed occurrences (all)	11 / 6998 (0.16%) 11		
Leukopenia subjects affected / exposed occurrences (all)	68 / 6998 (0.97%) 68		
Lymphadenopathy subjects affected / exposed occurrences (all)	5 / 6998 (0.07%) 5		
Lymphopenia subjects affected / exposed occurrences (all)	119 / 6998 (1.70%) 119		
Microcytic anaemia			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Monocytopenia			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Monocytosis			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	9 / 6998 (0.13%)		
occurrences (all)	9		
Neutrophilia			
subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
Pancytopenia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	7 / 6998 (0.10%)		
occurrences (all)	7		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Ear discomfort			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Ear pain			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
External ear inflammation			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Sudden hearing loss			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		

Tinnitus			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Vertigo			
subjects affected / exposed	68 / 6998 (0.97%)		
occurrences (all)	69		
Vertigo positional			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Eye disorders			
Amblyopia			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Blepharospasm			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Cataract			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Diplopia			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Eye irritation			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Eye pain			
subjects affected / exposed	11 / 6998 (0.16%)		
occurrences (all)	12		
Eye swelling			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Eyelid oedema			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Foreign body sensation in eyes			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Iridocyclitis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Macular oedema			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Ocular discomfort			
subjects affected / exposed	6 / 6998 (0.09%)		
occurrences (all)	6		
Photopsia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Retinal vein thrombosis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	20 / 6998 (0.29%)		
occurrences (all)	20		
Visual acuity reduced			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Visual impairment			
subjects affected / exposed	6 / 6998 (0.09%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	9 / 6998 (0.13%)		
occurrences (all)	9		
Abdominal distension			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	9 / 6998 (0.13%)		
occurrences (all)	10		

Abdominal pain lower subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Abdominal pain upper subjects affected / exposed occurrences (all)	53 / 6998 (0.76%) 53		
Anal incontinence subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Bowel movement irregularity subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Constipation subjects affected / exposed occurrences (all)	13 / 6998 (0.19%) 13		
Diarrhoea subjects affected / exposed occurrences (all)	96 / 6998 (1.37%) 96		
Dry mouth subjects affected / exposed occurrences (all)	7 / 6998 (0.10%) 7		
Dyspepsia subjects affected / exposed occurrences (all)	11 / 6998 (0.16%) 11		
Dysphagia subjects affected / exposed occurrences (all)	2 / 6998 (0.03%) 2		
Enteritis subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		
Eructation subjects affected / exposed occurrences (all)	1 / 6998 (0.01%) 1		

Faeces soft			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	9 / 6998 (0.13%)		
occurrences (all)	9		
Frequent bowel movements			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Gastric disorder			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Gastrointestinal disorder			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Gastrointestinal erosion			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Haemorrhoids			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	143 / 6998 (2.04%)		
occurrences (all)	143		
Odynophagia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Oral dysaesthesia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		

Oral pain			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Oral pruritus			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Paraesthesia oral			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Tongue blistering			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Tooth disorder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	6 / 6998 (0.09%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	13 / 6998 (0.19%)		
occurrences (all)	13		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	8 / 6998 (0.11%)		
occurrences (all)	8		
Alopecia			
subjects affected / exposed	15 / 6998 (0.21%)		
occurrences (all)	15		
Blister			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Dermatitis			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Dermatitis allergic			

subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Dermatitis contact			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Dermatitis exfoliative			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Dermatosis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Drug eruption			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Dyshidrotic eczema			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Erythema			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Hand dermatitis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	14 / 6998 (0.20%)		
occurrences (all)	15		
Night sweats			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Photosensitivity reaction			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Pigmentation disorder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Pityriasis rosea			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	24 / 6998 (0.34%)		
occurrences (all)	24		
Pruritus generalised			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	15 / 6998 (0.21%)		
occurrences (all)	15		
Rash pruritic			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Rash vesicular			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Rosacea			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Skin burning sensation			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Skin disorder			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Skin exfoliation			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Skin irritation			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Skin odour abnormal			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Skin reaction			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Swelling face			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Renal and urinary disorders			
Bladder dysfunction			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Micturition urgency			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Nephritis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Neurogenic bladder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Nocturia			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		

Pollakiuria			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Renal pain			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Urge incontinence			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 6998 (0.23%)		
occurrences (all)	17		
Arthritis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	46 / 6998 (0.66%)		
occurrences (all)	46		
Bone pain			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Bursitis			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Coccydynia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Groin pain			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Intervertebral disc protrusion			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Joint stiffness			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Limb discomfort			
subjects affected / exposed	6 / 6998 (0.09%)		
occurrences (all)	6		
Mobility decreased			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Muscle fatigue			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Muscle rigidity			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Muscle tightness			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Muscle twitching			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	8 / 6998 (0.11%)		
occurrences (all)	8		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Musculoskeletal stiffness			

subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	16 / 6998 (0.23%)		
occurrences (all)	17		
Myofascial pain syndrome			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	19 / 6998 (0.27%)		
occurrences (all)	19		
Spinal disorder			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Anorectal infection			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Bacterial infection			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	7 / 6998 (0.10%)		
occurrences (all)	7		
Chronic sinusitis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		

Cystitis			
subjects affected / exposed	6 / 6998 (0.09%)		
occurrences (all)	6		
Dysentery			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Erysipelas			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Febrile infection			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Fungal infection			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Gastroenteritis viral			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
Genital herpes			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Genitourinary tract infection			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Helminthic infection			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		

Herpes simplex			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Herpes virus infection			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Herpes zoster			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Hordeolum			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Infected bite			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	23 / 6998 (0.33%)		
occurrences (all)	23		
Laryngitis			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Mastoiditis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Myelitis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	137 / 6998 (1.96%)		
occurrences (all)	137		
Onychomycosis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		

Oral herpes			
subjects affected / exposed	27 / 6998 (0.39%)		
occurrences (all)	27		
Pharyngitis			
subjects affected / exposed	3 / 6998 (0.04%)		
occurrences (all)	3		
Pyelonephritis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	7 / 6998 (0.10%)		
occurrences (all)	7		
Rhinitis			
subjects affected / exposed	12 / 6998 (0.17%)		
occurrences (all)	12		
Sialoadenitis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	6 / 6998 (0.09%)		
occurrences (all)	6		
Tinea versicolour			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	12 / 6998 (0.17%)		
occurrences (all)	12		
Urinary tract infection			
subjects affected / exposed	15 / 6998 (0.21%)		
occurrences (all)	15		
Vaginal abscess			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		

Viral infection			
subjects affected / exposed	2 / 6998 (0.03%)		
occurrences (all)	2		
Viral rhinitis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Vulvovaginal mycotic infection			
subjects affected / exposed	5 / 6998 (0.07%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 6998 (0.13%)		
occurrences (all)	9		
Food craving			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Gluten sensitivity			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	4 / 6998 (0.06%)		
occurrences (all)	4		
Hyperkalaemia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Increased appetite			

subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 6998 (0.01%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	6 / 6998 (0.09%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2012	change of inclusion and exclusion criteria with regards to cardiac risk patients and inclusion of further criteria for study drug discontinuation; inclusion of the most recent recommendations from EMA in terms of cardiac response monitoring following the first dose of fingolimod (April 20, 2012)
26 March 2013	implementation of an update to the Gilenya® (fingolimod) label in the EU approved by the CHMP; as the incidence of cardiac events after enrolling 1000 patients was found to be significantly lower than the incidence from recent studies which was the basis for the initial sample size calculation, the sample size needed to be increased from 2000 to a flexible sample size ranging from 3800 to 7000 patients with a fixed study termination by end of 2015
20 March 2014	implementation of a further update to the Gilenya® (fingolimod) label regarding interruption and restart of fingolimod real-life data: inter-patient regarding the incidence of bradycardia and bradyarrhythmic ECG events of patients who paused fingolimod treatment in comparison to fingolimod-naïve patients, treated for the first time in the START study, as well as within-patient comparisons for patients formerly treated with fingolimod within the START study.
24 April 2014	Correction of minor errors in version 3
20 July 2014	Clarification of the handling of safety cases for patients participating in both the interventional study START and the non-interventional study PASSAGE, thereby ensuring compliance with both the GCP regulations (START) and the modified regulations of the good pharmacovigilance practices module (specifically VI).
11 May 2015	Addition of the same procedure as defined in amendment 5 for the PASSAGE study for patients participating in the PANGAEA 2.0 study; Change of the definition of bradycardia from <40 bpm to <45 beats per minute to harmonize with the current Gilenya® label in the EU; Removal of the exploratory endpoints regarding a sub-population of patients receiving a 24-hour monitoring due to low recruitment in this subgroup; Extension of fixed recruitment end to June 2016 to enroll approximately 7000 patients.
11 November 2015	implementation of an update to the Gilenya® (fingolimod) label in the EU approved by the CHMP. The CHMP adopted a change to the existing indication to reflect a modification in the criteria for disease activity that needed to be fulfilled in order to enable a switch from a first line disease modifying therapy to Gilenya®. Hence, inclusion criterion #3 was adapted accordingly

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported