Clinical trial results:
A double-blind, randomized, multicenter, placebo controlled, parallel group study to evaluate the efficacy and safety of fingolimod 0.5 mg administered orally once daily versus placebo in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

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	2011-005280-24
Trial protocol	BE NL DE ES GB IT GR PL CZ
Global end of trial date	01 September 2016
Results information	
Result version number	v1 (current)
This version publication date	08 July 2018
First version publication date	08 July 2018

Trial information

Trial identification	
Sponsor protocol code	CFTY720I2201
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01625182
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	01 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of fingolimod 0.5 mg daily compared with placebo on delaying disability progression in patients with CIDP, measured by the time to the first confirmed worsening on the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Scale. A confirmed worsening was defined as an increase by 1 point or more on the adjusted INCAT Disability Scale from the value at baseline.

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.

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	24 January 2014
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	Australia: 4
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Netherlands: 4

Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	106
EEA total number of subjects	63

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)	87
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were assigned randomly to each treatment group in a 1:1 ratio.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Fingolimod (FTY720)

Arm description:

Participants received Fingolimod 0.5 mg orally once daily.

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

Dosage and administration details:

Participants received fingolimod 0.5 mg orally once daily.

Arm title	Placebo

Arm description:

Participants received matching placebo to Fingolimod orally once daily.

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

Dosage and administration details:

Participants received matching placebo to fingolimod orally once daily.

Number of subjects in period 1	Fingolimod (FTY720)	Placebo
Started	54	52
Completed	34	41
Not completed	20	11
Consent withdrawn by subject	5	1
Adverse event, non-fatal	2	-

Protocol deviation	-	2
Administrative problems	1	-
Lack of efficacy	12	8

Baseline characteristics

Reporting groups	
Reporting group title	Fingolimod (FTY720)
Reporting group description:	
Participants received Fingolimod 0.5 mg orally once daily.	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo to Fingolimod orally once daily.	

Reporting group values	Fingolimod (FTY720)	Placebo	Total
Number of subjects	54	52	106
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)	43	44	87
From 65-84 years	11	8	19
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	54.3	54.6	
standard deviation	± 13.32	± 11.68	-
Gender, Male/Female Units: Subjects			
Female	17	22	39
Male	37	30	67

End points

End points reporting groups

Reporting group title	Fingolimod (FTY720)
Reporting group description:	
Participants received Fingolimod 0.5 mg orally once daily.	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo to Fingolimod orally once daily.	

Primary: Time to first confirmed worsening on the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Scale

End point title	Time to first confirmed worsening on the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Scale
End point description:	
Confirmed worsening in CIDP was measured by the adjusted INCAT Disability Scale. The adjusted INCAT disability scale measures arm disability and leg disability. For arm disability the scale ranges from 0 (no upper limb problems) to 5 (inability to use either arm for any purposeful movement). The leg disability scale ranges from 0 (walking not affected) to 5 (restricted to wheelchair, unable to stand and walk a few steps with help). The total adjusted INCAT disability score is calculated s the sum of the arm and leg disability scores where the total score ranges from 0 to 10. A confirmed worsening was defined as an increase by 1 or more points on the adjusted INCAT disability scale from the value at baseline.	
End point type	Primary
End point timeframe:	
Month 12	

End point values	Fingolimod (FTY720)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	52		
Units: Days				
median (confidence interval 95%)	721 (159 to 9999)	540 (183 to 9999)		

Statistical analyses

Statistical analysis title	Time to first confirmed worsening event
Statistical analysis description:	
Survival analysis of time to first confirmed worsening event by adjusted INCAT disability scale	
Comparison groups	Fingolimod (FTY720) v Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9838
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.7

Secondary: Change from Baseline for grip strength, dominant hand

End point title	Change from Baseline for grip strength, dominant hand

End point description:

Grip strength measurements were done using a vigorimeter. With this device, the pressure in the bulb exercised by the participant was registered on a manometer via a rubber junction tube. Both the dominant and non-dominant hands were tested. A negative change from baseline indicates deterioration.

End point type	Secondary

End point timeframe:

Month 6, Month 12

End point values	Fingolimod (FTY720)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: kPa				
least squares mean (confidence interval 95%)				
Month 6	-2.6 (-8.09 to 2.8)	-3.8 (-9.37 to 1.7)		
Month 12	-0.8 (-6.47 to 4.96)	-3.9 (-9.68 to 1.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline for grip strength, non-dominant hand

End point title	Change from Baseline for grip strength, non-dominant hand

End point description:

Grip strength measurements were done using a vigorimeter. With this device, the pressure in the bulb exercised by the participant was registered on a manometer via a rubber junction tube. Both the dominant and non-dominant hands were tested. A negative change from baseline indicates deterioration.

End point type	Secondary
End point timeframe: Month 6, Month 12	

End point values	Fingolimod (FTY720)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: kPa				
least squares mean (confidence interval 95%)				
Month 6	-2.7 (-8.13 to 2.66)	-6.1 (-11.59 to -0.66)		
Month 12	-1.2 (-6.69 to 4.37)	-5 (-10.57 to 0.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline for Rasch-Built Linearly Weighted Overall Disability Scale (R-ODS)

End point title	Change from Baseline for Rasch-Built Linearly Weighted Overall Disability Scale (R-ODS)

End point description:

This questionnaire was constructed using the patients' perception of their ability to perform daily and social activities. The questionnaire comprises 24 items ranging from ability to read a book or newspaper (as the easiest item to accomplish) to ability to run (most difficult item to accomplish). The obtained raw summed score was translated subsequently to a convenient centile metric score ranging from 0 (most severe disability) to 100 (no disability at all). A higher score indicated a better health status. A negative change from baseline indicates deterioration.

End point type	Secondary
End point timeframe: Month 6, Month 12	

End point values	Fingolimod (FTY720)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	51		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Month 6	-6.4 (-9.57 to -3.15)	-5.5 (-8.89 to -2.21)		
Month 12	-5.7 (-9.07 to -2.37)	-5.1 (-8.54 to -1.57)		

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:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Fingolimod 0.5 mg
Reporting group description:	
Fingolimod 0.5 mg	
Reporting group title	All@patients
Reporting group description:	
All@patients	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	Fingolimod 0.5 mg	All@patients	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 54 (16.67%)	13 / 106 (12.26%)	4 / 52 (7.69%)
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)			
Breast cancer			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal cancer			

subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Vasculitis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cauda equina syndrome			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic inflammatory demyelinating polyradiculoneuropathy			
subjects affected / exposed	2 / 54 (3.70%)	3 / 106 (2.83%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	1 / 2	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
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	Fingolimod 0.5 mg	All@patients	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 54 (74.07%)	82 / 106 (77.36%)	42 / 52 (80.77%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Fibrous histiocytoma			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Haemangioma			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Haemangioma of skin			

subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Malignant melanoma in situ			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Melanocytic naevus			
subjects affected / exposed	2 / 54 (3.70%)	3 / 106 (2.83%)	1 / 52 (1.92%)
occurrences (all)	2	4	2
Seborrhoeic keratosis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Skin papilloma			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Uterine leiomyoma			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	10 / 54 (18.52%)	11 / 106 (10.38%)	1 / 52 (1.92%)
occurrences (all)	10	11	1
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Asthenia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Chest discomfort			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Discomfort			

subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Fatigue			
subjects affected / exposed	4 / 54 (7.41%)	10 / 106 (9.43%)	6 / 52 (11.54%)
occurrences (all)	4	10	6
Influenza like illness			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Local swelling			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Oedema peripheral			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Pain			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Peripheral swelling			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Pyrexia			
subjects affected / exposed	2 / 54 (3.70%)	3 / 106 (2.83%)	1 / 52 (1.92%)
occurrences (all)	2	4	2
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Reproductive system and breast disorders			
Breast cyst			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Breast pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Breast swelling			

subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Cough			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Dyspnoea			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Dyspnoea exertional			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Epistaxis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Nasal congestion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	1 / 54 (1.85%)	4 / 106 (3.77%)	3 / 52 (5.77%)
occurrences (all)	1	4	3
Rhinitis allergic			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Psychiatric disorders			

Abnormal dreams			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Anxiety			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Hallucination			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Insomnia			
subjects affected / exposed	1 / 54 (1.85%)	5 / 106 (4.72%)	4 / 52 (7.69%)
occurrences (all)	1	6	5
Irritability			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 54 (3.70%)	3 / 106 (2.83%)	1 / 52 (1.92%)
occurrences (all)	2	4	2
Amylase increased			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Blood cholesterol increased			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Blood urine present			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Carbon monoxide diffusing capacity decreased			

subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Cardiac murmur			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 54 (5.56%)	3 / 106 (2.83%)	0 / 52 (0.00%)
occurrences (all)	3	3	0
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Grip strength decreased			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Heart rate increased			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Hepatic enzyme increased			
subjects affected / exposed	2 / 54 (3.70%)	2 / 106 (1.89%)	0 / 52 (0.00%)
occurrences (all)	2	2	0
Hepatitis A virus test positive			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Occult blood			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Optic nerve cup/disc ratio increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Pulmonary function test decreased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Serum ferritin decreased			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0

Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Concussion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Excoriation			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Fall			
subjects affected / exposed	4 / 54 (7.41%)	5 / 106 (4.72%)	1 / 52 (1.92%)
occurrences (all)	4	5	1
Foot fracture			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Hand fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Infusion related reaction			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Joint dislocation			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Joint injury			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Ligament sprain			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Limb injury			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Muscle hernia			

subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Muscle strain			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Post-traumatic pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	2	2
Procedural headache			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Procedural pain			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Tooth fracture			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Wound			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Wrist fracture			
subjects affected / exposed	0 / 54 (0.00%)	2 / 106 (1.89%)	2 / 52 (3.85%)
occurrences (all)	0	2	2
Congenital, familial and genetic disorders			
Ventricular septal defect			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Tachycardia			
subjects affected / exposed	0 / 54 (0.00%)	2 / 106 (1.89%)	2 / 52 (3.85%)
occurrences (all)	0	2	2
Nervous system disorders			

Amnesia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Coordination abnormal			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Dizziness			
subjects affected / exposed	3 / 54 (5.56%)	5 / 106 (4.72%)	2 / 52 (3.85%)
occurrences (all)	5	8	3
Dysgeusia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Headache			
subjects affected / exposed	12 / 54 (22.22%)	20 / 106 (18.87%)	8 / 52 (15.38%)
occurrences (all)	13	22	9
Hypoaesthesia			
subjects affected / exposed	2 / 54 (3.70%)	4 / 106 (3.77%)	2 / 52 (3.85%)
occurrences (all)	2	4	2
Memory impairment			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Meningism			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Migraine			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Neuralgia			
subjects affected / exposed	0 / 54 (0.00%)	2 / 106 (1.89%)	2 / 52 (3.85%)
occurrences (all)	0	2	2
Neuropathy peripheral			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Paraesthesia			
subjects affected / exposed	5 / 54 (9.26%)	5 / 106 (4.72%)	0 / 52 (0.00%)
occurrences (all)	6	6	0

Parkinsonism			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Sciatica			
subjects affected / exposed	2 / 54 (3.70%)	3 / 106 (2.83%)	1 / 52 (1.92%)
occurrences (all)	4	5	1
Somnolence			
subjects affected / exposed	1 / 54 (1.85%)	3 / 106 (2.83%)	2 / 52 (3.85%)
occurrences (all)	1	3	2
Syncope			
subjects affected / exposed	2 / 54 (3.70%)	3 / 106 (2.83%)	1 / 52 (1.92%)
occurrences (all)	2	3	1
Tremor			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	2	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Leukopenia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	2	2	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Tinnitus			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Vertigo			
subjects affected / exposed	3 / 54 (5.56%)	6 / 106 (5.66%)	3 / 52 (5.77%)
occurrences (all)	3	7	4
Eye disorders			
Blepharitis			
subjects affected / exposed	2 / 54 (3.70%)	2 / 106 (1.89%)	0 / 52 (0.00%)
occurrences (all)	2	2	0
Cataract			

subjects affected / exposed	1 / 54 (1.85%)	4 / 106 (3.77%)	3 / 52 (5.77%)
occurrences (all)	1	4	3
Diplopia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Eye pain			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Eye pruritus			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Iritis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Macular oedema			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Meibomianitis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Metamorphopsia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Retinal disorder			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Retinoschisis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Subretinal fluid			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Vision blurred			
subjects affected / exposed	2 / 54 (3.70%)	2 / 106 (1.89%)	0 / 52 (0.00%)
occurrences (all)	2	2	0
Visual acuity reduced			

subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Visual impairment			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Vitreous detachment			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Vitreous floaters			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Abdominal distension			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Abdominal mass			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Abdominal pain			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Abdominal pain upper			
subjects affected / exposed	2 / 54 (3.70%)	3 / 106 (2.83%)	1 / 52 (1.92%)
occurrences (all)	2	3	1
Change of bowel habit			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Chronic gastritis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1

Diarrhoea			
subjects affected / exposed	3 / 54 (5.56%)	5 / 106 (4.72%)	2 / 52 (3.85%)
occurrences (all)	3	5	2
Dry mouth			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Dyspepsia			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Dysphagia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Food poisoning			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Gastrointestinal disorder			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Gingival cyst			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Gingival hyperplasia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	2 / 54 (3.70%)	8 / 106 (7.55%)	6 / 52 (11.54%)
occurrences (all)	2	8	6
Oesophagitis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Periodontal disease			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1

Tooth disorder			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Tooth loss			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Liver disorder			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 54 (1.85%)	4 / 106 (3.77%)	3 / 52 (5.77%)
occurrences (all)	4	7	3
Alopecia			
subjects affected / exposed	2 / 54 (3.70%)	3 / 106 (2.83%)	1 / 52 (1.92%)
occurrences (all)	2	3	1
Chloasma			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Dermatitis			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Dermatitis allergic			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Dermatitis contact			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Dry skin			
subjects affected / exposed	1 / 54 (1.85%)	3 / 106 (2.83%)	2 / 52 (3.85%)
occurrences (all)	1	3	2
Eczema			

subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	2	4	2
Erythema			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Idiopathic urticaria			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Ingrowing nail			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Intertrigo			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Lentigo			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Night sweats			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Onycholysis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Petechiae			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	2	2	0
Pityriasis rosea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Pruritus			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	2 / 54 (3.70%)	5 / 106 (4.72%)	3 / 52 (5.77%)
occurrences (all)	2	5	3
Rash erythematous			

subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	2	2	0
Rash generalised			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Rash pruritic			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Rosacea			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 54 (0.00%)	3 / 106 (2.83%)	3 / 52 (5.77%)
occurrences (all)	0	3	3
Skin fissures			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Skin lesion			
subjects affected / exposed	2 / 54 (3.70%)	4 / 106 (3.77%)	2 / 52 (3.85%)
occurrences (all)	2	4	2
Urticaria			
subjects affected / exposed	2 / 54 (3.70%)	3 / 106 (2.83%)	1 / 52 (1.92%)
occurrences (all)	2	3	1
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	2	2
Dysuria			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Urinary tract inflammation			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Endocrine disorders			
Cushingoid			

subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Hypothyroidism			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 54 (1.85%)	3 / 106 (2.83%)	2 / 52 (3.85%)
occurrences (all)	1	3	2
Arthritis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Arthropathy			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Back pain			
subjects affected / exposed	4 / 54 (7.41%)	7 / 106 (6.60%)	3 / 52 (5.77%)
occurrences (all)	4	8	4
Bursitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Exostosis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Joint swelling			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Monarthritis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Muscle spasms			
subjects affected / exposed	2 / 54 (3.70%)	3 / 106 (2.83%)	1 / 52 (1.92%)
occurrences (all)	2	3	1
Muscle twitching			

subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Muscular weakness			
subjects affected / exposed	2 / 54 (3.70%)	4 / 106 (3.77%)	2 / 52 (3.85%)
occurrences (all)	4	7	3
Musculoskeletal pain			
subjects affected / exposed	2 / 54 (3.70%)	3 / 106 (2.83%)	1 / 52 (1.92%)
occurrences (all)	2	3	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Neck mass			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Neck pain			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Osteoarthritis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	7 / 54 (12.96%)	10 / 106 (9.43%)	3 / 52 (5.77%)
occurrences (all)	7	12	5
Rheumatoid arthritis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Spinal column stenosis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Synovial cyst			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Tendon pain			

subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Tendonitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Torticollis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 54 (5.56%)	4 / 106 (3.77%)	1 / 52 (1.92%)
occurrences (all)	4	5	1
Candida infection			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Catheter site infection			
subjects affected / exposed	0 / 54 (0.00%)	2 / 106 (1.89%)	2 / 52 (3.85%)
occurrences (all)	0	2	2
Diverticulitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Ear infection			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Folliculitis			
subjects affected / exposed	2 / 54 (3.70%)	5 / 106 (4.72%)	3 / 52 (5.77%)
occurrences (all)	2	5	3
Gastroenteritis			
subjects affected / exposed	0 / 54 (0.00%)	2 / 106 (1.89%)	2 / 52 (3.85%)
occurrences (all)	0	2	2
Gastroenteritis viral			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Herpes zoster			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1

Influenza			
subjects affected / exposed	2 / 54 (3.70%)	2 / 106 (1.89%)	0 / 52 (0.00%)
occurrences (all)	3	3	0
Laryngitis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Meningitis aseptic			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	6 / 54 (11.11%)	13 / 106 (12.26%)	7 / 52 (13.46%)
occurrences (all)	16	33	17
Onychomycosis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Oral herpes			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	4	4	0
Parasitic gastroenteritis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Periodontitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Pharyngitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Pharyngotonsillitis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Sinusitis			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Tinea cruris			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1

Tinea infection			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Tonsillitis bacterial			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Tooth infection			
subjects affected / exposed	0 / 54 (0.00%)	2 / 106 (1.89%)	2 / 52 (3.85%)
occurrences (all)	0	2	2
Upper respiratory tract infection			
subjects affected / exposed	1 / 54 (1.85%)	3 / 106 (2.83%)	2 / 52 (3.85%)
occurrences (all)	1	4	3
Urinary tract infection			
subjects affected / exposed	3 / 54 (5.56%)	4 / 106 (3.77%)	1 / 52 (1.92%)
occurrences (all)	4	5	1
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 54 (1.85%)	2 / 106 (1.89%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Wound infection			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Dyslipidaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Fluid retention			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 106 (0.94%)	0 / 52 (0.00%)
occurrences (all)	1	1	0
Increased appetite			

subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1
Vitamin D deficiency			
subjects affected / exposed	0 / 54 (0.00%)	1 / 106 (0.94%)	1 / 52 (1.92%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2013	Additional randomization stratification was introduced within 2 regions (Japan and countries outside Japan) to ensure balance of treatment assignments within Japan and globally; Clarification on the CIDP diagnosis was included in inclusion criteria to specify the European Federation of Neurological Societies/Peripheral Nerve Society criteria; A minimum glomerular filtration rate value was added to exclude patients with severe renal impairment. For assessments during the study the following key clarifications were provided: during ophthalmologic examination an OCT was to be performed at Screening to detect macular edema. The lower limits for clinically notable high values for SBP and DBP were updated. Clarification and guidance were provided for the management of patients with elevated liver function tests and lymphopenia.
06 September 2013	Directions were added that patients receiving corticosteroids were to be administered antiviral prophylaxis during corticosteroid taper period and for 4 weeks after the end of the taper period; Confirmation was added that if medically appropriate, corticosteroid treatment was to be initiated 6 or more weeks after stopping study drug. If treatment was needed during the first 6 weeks following study drug discontinuation, antiviral prophylaxis was to be initiated and continued until at least 6 weeks after the last dose of study drug. Information regarding antiviral prophylactic treatment in the "Risks and benefits" section was updated; Inclusion and exclusion criteria were updated to allow patients to enter the study who had a documented history of clinically meaningful deterioration within 1 year prior to Screening during therapy or following interruption or reduction of therapy. Exclusion criteria were updated to clarify that patients who presented with a current diagnosis of diabetes (including steroid-induced diabetes) were excluded but that patients with a history of diabetes (steroid-induced diabetes or gestational diabetes) were eligible if diabetes was controlled. The list of excluded treatments was updated. New text was added to update the criteria for liver events and management of patients with lymphopenia.
10 October 2013	The term multiple sclerosis was corrected and replaced by CIDP in one exclusion criterion.
22 July 2014	Exclusion criterion was updated to allow enrollment of patients with controlled diabetes mellitus who met electrophysiological criteria for demyelinating neuropathy and had documented clinically meaningful response to treatment with steroids, IVIg, or PE within the previous year.
05 May 2015	The time required to reach the minimum number of events was re-estimated, based on the current recruitment rate thus the maximum duration of the study was modified from 3 to approximately 4.5 years. The guidance of monitoring patients with infections was updated with additional guidance for early diagnosis and treatment of cryptococcal meningitis, should it have occurred. Guidance on study drug administration was updated to align with the current fingolimod prescribing information. Minor clarifications of exclusion criteria were provided; Criterion referring to CIDP history was revised: history of documented clinically meaningful deterioration, was revised from 1 year to 18 months. Inclusion criterion referring to stable CIDP symptoms before randomization without significant change in treatment regimen, was revised from 2 months to 6 weeks.

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.

The pre-planned interim analysis for futility revealed an unsatisfactory therapeutic effect of fingolimod in patients with CIDP. Therefore, the DMC recommended an early termination of this study and patients were brought in for a close-out visit.

Notes: