Clinical trial results:
A single arm, open-label, multicenter study evaluating the long-term, safety and tolerability of 0.5 mg fingolimod (FTY) administered orally once daily in patients with relapsing form of multiple sclerosis

Summary

EudraCT number	2010-020515-37
Trial protocol	FI DE PT CZ ES SK HU GB SE FR EE IT AT GR NL IE BE DK NO
Global end of trial date	19 October 2018

Results information

Result version number	v1 (current)
This version publication date	31 October 2019
First version publication date	31 October 2019

Trial information

Trial identification

Sponsor protocol code	CFTY720D2399

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01201356
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate long-term safety and tolerability of fingolimod 0.5 mg/day in patients with Multiple Sclerosis for the duration of the study.

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	13 September 2010
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	Argentina: 37
Country: Number of subjects enrolled	Australia: 114
Country: Number of subjects enrolled	Austria: 42
Country: Number of subjects enrolled	Belgium: 89
Country: Number of subjects enrolled	Brazil: 65
Country: Number of subjects enrolled	Canada: 198
Country: Number of subjects enrolled	Czech Republic: 154
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	Egypt: 23
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	Finland: 43
Country: Number of subjects enrolled	France: 85
Country: Number of subjects enrolled	Germany: 1229
Country: Number of subjects enrolled	United Kingdom: 204
Country: Number of subjects enrolled	Greece: 59
Country: Number of subjects enrolled	Guatemala: 17
Country: Number of subjects enrolled	Hungary: 73
Country: Number of subjects enrolled	Ireland: 18
Country: Number of subjects enrolled	Israel: 14

Country: Number of subjects enrolled	Italy: 323
Country: Number of subjects enrolled	Jordan: 2
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Malaysia: 14
Country: Number of subjects enrolled	Netherlands: 92
Country: Number of subjects enrolled	Norway: 15
Country: Number of subjects enrolled	Panama: 10
Country: Number of subjects enrolled	Peru: 23
Country: Number of subjects enrolled	Poland: 232
Country: Number of subjects enrolled	Portugal: 72
Country: Number of subjects enrolled	Romania: 18
Country: Number of subjects enrolled	Russian Federation: 135
Country: Number of subjects enrolled	Slovakia: 27
Country: Number of subjects enrolled	South Africa: 15
Country: Number of subjects enrolled	Sweden: 58
Country: Number of subjects enrolled	Switzerland: 79
Country: Number of subjects enrolled	Turkey: 80
Country: Number of subjects enrolled	United States: 221
Country: Number of subjects enrolled	Spain: 211
Worldwide total number of subjects	4125
EEA total number of subjects	3066

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)	1
Adults (18-64 years)	4121
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open-label, multi-center, single treatment arm design allowing patients participating in the fingolimod MS clinical development program to enroll in order to collect additional long-term safety, tolerability, efficacy, and health outcomes data.

Pre-assignment

Screening details:

This study had two parts: Part 1, collecting long-term safety, tolerability, efficacy and health outcomes data until all Part 1 end of study (EOS) visits and last follow-up visit; Part 2, collecting limited safety and tolerability data, in a subset of patients who participated in Part 1, and other eligible patients from ongoing fingolimod trials.

Period 1

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

Arms

Arm title	Fingolimod 0.5 mg/day

Arm description:

Open-label fingolimod 0.5 mg, taken orally once daily

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

Dosage and administration details:

0.5 mg taken orally once daily

Number of subjects in period 1	Fingolimod 0.5 mg/day
Started	4125
Safety Set	4083
Fingolimod Full Analysis Set	4046
Completed	3481
Not completed	644
Abnormal laboratory value(s)	51
Adverse event, serious fatal	16
Consent withdrawn by subject	144
Adverse event, non-fatal	170
Unsatisfactory therapeutic effect	112
Condition no longer requires study drug	12

administrative problems	74
Lost to follow-up	50
Abnormal test procedure result(s)	3
Protocol deviation	12

Baseline characteristics

Reporting groups	
Reporting group title	Fingolimod 0.5 mg/day
Reporting group description:	
Open-label fingolimod 0.5 mg, taken orally once daily	

Reporting group values	Fingolimod 0.5 mg/day	Total	
Number of subjects	4125	4125	
Age, Customized Units: Subjects			
< 18 years	1	1	
18 - 30 years	951	951	
31 - 40 years	1497	1497	
41 - 55 years	1605	1605	
> 55 years	71	71	
Age Continuous Units: years			
arithmetic mean	37.8		
standard deviation	± 9.05	-	
Sex: Female, Male Units: Subjects			
Female	2933	2933	
Male	1192	1192	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	3927	3927	
Black	38	38	
Asian	35	35	
Native American	11	11	
Other	114	114	

End points

End points reporting groups

Reporting group title	Fingolimod 0.5 mg/day
Reporting group description:	
Open-label fingolimod 0.5 mg, taken orally once daily	

Primary: Parts I and II: Number of Participants with Adverse Events, Serious Adverse Event, and Death

End point title	Parts I and II: Number of Participants with Adverse Events, Serious Adverse Event, and Death[1]
End point description:	
Analysis of absolute and relative frequencies for Adverse Event (AE), Serious Adverse Event (SAE) and Deaths by primary System Organ Class (SOC) to demonstrate that Fingolimod 0.5 mg/day is safe in patients with relapsing forms of Multiple Sclerosis (MS) through the monitoring of relevant clinical and laboratory safety parameters. Only descriptive analysis performed.	
End point type	Primary
End point timeframe:	
Baseline (Part I) to Month 6 Follow-up (Part II), up to 8 years	
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: Only descriptive analysis performed.	

End point values	Fingolimod 0.5 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	4083			
Units: Participants				
number (not applicable)				
Adverse Event (AEs)	2125			
Serious Adverse Events (SAEs)	515			
Deaths	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Part I: Aggregate annualized Relapse Rates (ARR) from first dose of Fingolimod

End point title	Part I: Aggregate annualized Relapse Rates (ARR) from first dose of Fingolimod
End point description:	
Annualized relapse rate (ARR) is defined as the number of all relapses (including both confirmed and unconfirmed relapses) experienced during a specific period of time adjusted to a one-year period. ARR is calculated as follows: (total number of all relapses) / (total number of days in the study for all patients for that specific period of time) x 365.25. Month 0 is the first dose of fingolimod study drug among all studies in which patient participated. Only descriptive analysis performed.	
End point type	Secondary

End point timeframe:

Month 0 (Core Baseline) to End of Follow-up Visit (an average of 162 months)

End point values	Fingolimod 0.5 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	4046			
Units: Annual number of relapses per patient				
number (not applicable)				
Month 0 to Month 6	0.325			
Month 0 to Month 12	0.273			
Month 0 to Month 24	0.237			
Month 0 to Month 36	0.217			
Month 0 to Month 48	0.208			
Month 0 to Month 60	0.197			
Month 0 to Month 72	0.190			
Month 0 to Month 84	0.182			
Month 0 to Month 96	0.177			
Month 0 to Month 108	0.172			
Month 0 to Month 120	0.170			
Month 0 to Month 132	0.170			
Month 0 to Month 144	0.169			
Month 0 to Month 156	0.169			
Month 0 to end of Study	0.166			
Month 0 to end of Follow-up	0.169			

Statistical analyses

No statistical analyses for this end point

Secondary: Part I: Number of Participants with relapses (confirmed and unconfirmed) from first dose of Fingolimod

End point title	Part I: Number of Participants with relapses (confirmed and unconfirmed) from first dose of Fingolimod

End point description:

A relapse is defined as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. The abnormality must be present for at least 24 hours and occur in the absence of fever (<37.5°C) or infection. In Study Part One, a relapse must be confirmed by an Expanded Disability Status Scale (EDSS) certified Physician within 7 days of the onset of symptoms. A relapse is confirmed when it is accompanied by an increase of at least half a step (0.5) on the EDSS or an increase of 1 point on two different Functional Systems (FS) of the EDSS or 2 points on one of the FS (excluding Bowel/Bladder or Cerebral FS). Month 0 is the first dose of fingolimod study drug among all studies in which patient participated. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Month 0 (Core Baseline) to End of Follow-up Visit (an average of 162 months)

End point values	Fingolimod 0.5 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	4046			
Units: Participants				
number (not applicable)				
Month 0 to Month 6	655			
Month 0 to Month 12	992			
Month 0 to Month 24	1461			
Month 0 to Month 36	1794			
Month 0 to Month 48	2127			
Month 0 to Month 60	2383			
Month 0 to Month 72	2616			
Month 0 to Month 84	2793			
Month 0 to Month 96	2944			
Month 0 to Month 108	3036			
Month 0 to Month 120	3063			
Month 0 to Month 132	3072			
Month 0 to Month 144	3075			
Month 0 to Month 156	3079			
Month 0 to end of Study	2970			
Month 0 to end of Follow-up	3079			

Statistical analyses

No statistical analyses for this end point

Secondary: Part I: Annualized rates of new or newly enlarging T2 lesions (ARneT2) compared with first dose of Fingolimod

End point title	Part I: Annualized rates of new or newly enlarging T2 lesions (ARneT2) compared with first dose of Fingolimod

End point description:

Annualized rate of new/newly enlarging T2 lesions (ARneT2) is defined as the number of new or newly enlarging T2 lesions experienced during a specific period of time adjusted to a one-year period. ARneT2 was calculated as follows: (total number of new/newly enlarging T2 lesions) / (total number of days in the study for all patients for that specific period of time) x 365.25.Month 0 is the first dose of fingolimod study drug among all studies in which patient participated. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Month 0 (Core Baseline) to End of Study (an average of Month 156)

End point values	Fingolimod 0.5 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	4046			
Units: Annual number of T2 lesions per patient				
number (not applicable)				
Month 0 to Month 3	12.324			
Month 0 to Month 6	2.073			
Month 0 to Month 12	1.360			
Month 0 to Month 24	1.042			
Month 0 to Month 36	1.011			
Month 0 to Month 48	1.008			
Month 0 to Month 60	0.957			
Month 0 to Month 72	0.963			
Month 0 to Month 84	0.906			
Month 0 to Month 96	0.813			
Month 0 to Month 108	0.713			
Month 0 to Month 120	0.702			
Month 0 to Month 132	0.659			
Month 0 to Month 144	0.681			
Month 0 to Month 156	0.637			
Month 0 to end of study	0.751			

Statistical analyses

No statistical analyses for this end point

Secondary: Part I: Change from first dose of Fingolimod in Total T2 Lesions volume

End point title	Part I: Change from first dose of Fingolimod in Total T2 Lesions volume

End point description:

Total volume of T2 lesions was summarized by presenting descriptive statistics for change from first dose of fingolimod baseline values by visit.

End point type	Secondary

End point timeframe:

Month 3 to End of Study (Study Completion Visit)

End point values	Fingolimod 0.5 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	4046			
Units: mm^3				
arithmetic mean (standard deviation)				
T2 volume change at Month 3	-749.5 (± 5269.04)			
T2 volume change at Month 6	-207.0 (± 1385.64)			

T2 volume change at Month 12	-55.0 (± 1700.16)			
T2 volume change at Month 24	16.2 (± 2009.87)			
T2 volume change at Month 36	235.8 (± 2519.39)			
T2 volume change at Month 48	875.1 (± 4145.99)			
T2 volume change at Month 60	1546.3 (± 4556.51)			
T2 volume change at Month 72	1719.2 (± 5184.27)			
T2 volume change at Month 84	1635.8 (± 5075.13)			
T2 volume change at Month 96	1303.9 (± 4712.78)			
T2 volume change at Month 108	1562.0 (± 4654.67)			
T2 volume change at Month 120	1393.1 (± 4908.76)			
T2 volume change at Month 132	905.9 (± 3960.94)			
T2 volume change at Month 144	702.7 (± 3765.80)			
T2 volume change at Month 156	274.0 (± 5784.85)			
T2 volume change at End of Study	1588.5 (± 5157.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part I: Change from first dose of Fingolimod in Total T1 Hypointense Lesions volume

End point title	Part I: Change from first dose of Fingolimod in Total T1 Hypointense Lesions volume

End point description:

T1 hypointense lesion (black hole) volume was summarized by presenting descriptive statistics for change from first dose of fingolimod baseline values by visit.

End point type	Secondary

End point timeframe:

Month 3 to End of Study (Study Completion Visit)

End point values	Fingolimod 0.5 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	4046			
Units: mm^3				
arithmetic mean (standard deviation)				
T1 volume change at Month 3	-519.8 (± 1339.62)			

T1 volume change at Month 12	49.1 (± 718.77)			
T1 volume change at Month 24	64.1 (± 786.02)			
T1 volume change at Month 36	151.08 (± 1001.28)			
T1 volume change at Month 48	524.8 (± 1706.26)			
T1 volume change at Month 60	853.6 (± 1957.74)			
T1 volume change at Month 72	975.7 (± 2637.67)			
T1 volume change at Month 84	930.1 (± 2471.70)			
T1 volume change at Month 96	753.4 (± 1845.63)			
T1 volume change at Month 108	628.7 (± 1922.45)			
T1 volume change at Month 120	817.3 (± 2198.58)			
T1 volume change at Month 132	726.7 (± 999)			
T1 volume change at End of Study	800.6 (± 2247.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part I: Percent brain volume change (PBVC) relative to first dose of Fingolimod

End point title	Part I: Percent brain volume change (PBVC) relative to first dose of Fingolimod

End point description:

Descriptive statistics on normalized brain volume at core baseline and percent brain volume change from first dose of fingolimod baseline were presented by visit. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Month 0 (Core Baseline) to End of Study (an average of Month 156)

End point values	Fingolimod 0.5 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	4046			
Units: cc				
arithmetic mean (standard deviation)				
Normalized brain volume at Core Baseline	1519.63 (± 81.193)			
Percent volume change at Month 3	-0.19 (± 0.660)			
Percent volume change at Month 6	-0.20 (± 0.801)			

Percent volume change at Month 12	-0.36 (± 0.901)			
Percent volume change at Month 24	-0.74 (± 1.209)			
Percent volume change at Month 36	-1.03 (± 1.541)			
Percent volume change at Month 48	-1.44 (± 1.851)			
Percent volume change at Month 60	-1.65 (± 2.196)			
Percent volume change at Month 72	-2.02 (± 2.514)			
Percent volume change at Month 84	-2.38 (± 2.638)			
Percent volume change at Month 96	-2.41 (± 2.607)			
Percent volume change at Month 108	-2.91 (± 2.863)			
Percent volume change at Month 120	-3.42 (± 2.911)			
Percent volume change at Month 132	-4.61 (± 2.511)			
Percent volume change at Month 144	-4.21 (± 2.778)			
Percent volume change at Month 156	-4.33 (± 3.146)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part I: Annualized Rate of Brain Atrophy (ARBA) relative to first dose of Fingolimod

End point title	Part I: Annualized Rate of Brain Atrophy (ARBA) relative to first dose of Fingolimod

End point description:

The annualized rate of brain volume change is an "averaged annual percentage change" in brain volume. ARBA was calculated as: ARBA = [(SIENA/100+1) ^ (365.25/#days)-1]*100 where SIENA=(Vk/V0-1)*100 and Vk is the brain volume at time k, V0 is the brain volume at time 0 and k is the total number of days in the study for all patients for that specific period of time) × 365.25. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Month 3 to Month 156

End point values	Fingolimod 0.5 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	4046			
Units: Ratio				
arithmetic mean (standard deviation)				
Month 3	-0.73 (± 2.834)			

Month 6	-0.39 (± 1.590)			
Month 12	-0.35 (± 0.891)			
Month 24	-0.37 (± 0.615)			
Month 36	-0.35 (± 0.522)			
Month 48	-0.37 (± 0.480)			
Month 60	-0.34 (± 0.451)			
Month 72	-0.35 (± 0.433)			
Month 84	-0.35 (± 0.395)			
Month 96	-0.31 (± 0.340)			
Month 108	-0.33 (± 0.326)			
Month 120	-0.36 (± 0.308)			
Month 132	-0.43 (± 0.240)			
Month 144	-0.36 (± 0.244)			
Month 156	-0.35 (± 0.256)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part I: Number of Participants with confirmed 6-month disability progression after first dose of Fingolimod

End point title	Part I: Number of Participants with confirmed 6-month disability progression after first dose of Fingolimod

End point description:

Disability progression was defined based on an increase in the EDSS score by 1.5 point for patients with a first dose of fingolimod (FDF) baseline EDSS score of 0, 1 point for patients with FDF baseline EDSS of >=1 and <=5.5, and by 0.5 points for patients with an FDF baseline EDSS>5.5, confirmed after 6 months and all intermediate EDSS assessments. A 6-month confirmed disability progression was defined as a 6-month sustained increase from the reference (potential onset of progression) value in the EDSS scores. i.e., every EDSS score (scheduled or unscheduled) within a 6-month duration after the first progression should meet the progression criteria as specified above. The confirmation could only happen at a scheduled visit and in the absence of a relapse. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Month 12 to Month 156

End point values	Fingolimod 0.5 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	4046			
Units: Participants				
number (not applicable)				
Month 12	212			
Month 24	336			
Month 36	434			
Month 48	519			
Month 60	590			
Month 72	659			
Month 84	714			
Month 96	753			
Month 108	767			
Month 120	772			
Month 132	775			
Month 144	776			
Month 156	777			

Statistical analyses

No statistical analyses for this end point

Secondary: Part I: Number of Participants with categorized change from first dose of Fingolimod in Expanded Disability Status Scale (EDSS) overall score

End point title	Part I: Number of Participants with categorized change from first dose of Fingolimod in Expanded Disability Status Scale (EDSS) overall score

End point description:

The EDSS is a scale for assessing neurological impairment in MS (Kurtzke 1983) including (1) a series of scores in each of eight functional systems, and (2) the EDSS steps (ranging from 0 (normal) to 10 (death due to MS). The functional systems are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel and Bladder, Cerebral and Other functions. Based on the assessment of each FS, the participant's overall score is categorized as Improvement, Stable or Deterioration. If baseline EDSS score is <=5, improvement is indicated by an EDSS score change of <= -1, stable is indicated by an EDSS score change of > -1 and <= 0.5, deterioration is indicated by an EDSS score change of > 0.5; if baseline EDSS score is > 5, improvement is indicated by an EDSS score change of <= -0.5, stable is indicated by an EDSS score change of > -0.5 and <= 0, deterioration is indicated by an EDSS score change of > 0. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Month 3 to Month 6 Follow-up

End point values	Fingolimod 0.5 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	4046			
Units: Participants				
number (not applicable)				
Month 3|Improvement	374			
Month 6|Improvement	508			
Month 9|Improvement	482			
Month 12|Improvement	422			
Month 15|Improvement	405			
Month 18|Improvement	345			
Month 21|Improvement	376			
Month 24|Improvement	320			
Month 27|Improvement	313			
Month 30|Improvement	305			
Month 33|Improvement	326			
Month 36|Improvement	309			
Month 39|Improvement	284			
Month 42|Improvement	282			
Month 45|Improvement	244			
Month 48|Improvement	250			
Month 51|Improvement	244			
Month 54|Improvement	256			
Month 57|Improvement	201			
Month 60|Improvement	175			
Month 63|Improvement	182			
Month 66|Improvement	165			
Month 69|Improvement	156			
Month 72|Improvement	143			
Month 75|Improvement	156			
Month 78|Improvement	136			
Month 81|Improvement	150			
Month 84|Improvement	132			
Month 87|Improvement	147			
Month 90|Improvement	120			
Month 93|Improvement	143			
Month 96|Improvement	117			
Month 99|Improvement	110			
Month 102|Improvement	94			
Month 105|Improvement	103			
Month 108|Improvement	87			
Month 111|Improvement	74			
Month 114|Improvement	45			
Month 117|Improvement	31			
Month 120|Improvement	19			
Month 123|Improvement	9			
Month 126|Improvement	14			
Month 129|Improvement	6			
Month 132|Improvement	11			
Month 135|Improvement	5			
Month 138|Improvement	10			

Month 141|Improvement	6			
Month 144|Improvement	7			
Month 147|Improvement	6			
Month 150|Improvement	7			
Month 153|Improvement	8			
Month 156|Improvement	3			
Month 159|Improvement	1			
Month 162|Improvement	0			
End of study|Improvement	610			
Month 3 follow-up|Improvement	203			
Month 6 follow-up|Improvement	29			
Month 3|Stable	3126			
Month 6|Stable	2900			
Month 9|Stable	2425			
Month 12|Stable	1930			
Month 15|Stable	1764			
Month 18|Stable	1361			
Month 21|Stable	1524			
Month 24|Stable	1299			
Month 27|Stable	1271			
Month 30|Stable	1204			
Month 33|Stable	1172			
Month 36|Stable	1065			
Month 39|Stable	1015			
Month 42|Stable	948			
Month 45|Stable	875			
Month 48|Stable	838			
Month 51|Stable	784			
Month 54|Stable	788			
Month 57|Stable	694			
Month 60|Stable	577			
Month 63|Stable	540			
Month 66|Stable	499			
Month 69|Stable	503			
Month 72|Stable	440			
Month 75|Stable	437			
Month 78|Stable	398			
Month 81|Stable	456			
Month 84|Stable	407			
Month 87|Stable	450			
Month 90|Stable	413			
Month 93|Stable	386			
Month 96|Stable	375			
Month 99|Stable	325			
Month 102|Stable	283			
Month 105|Stable	261			
Month 108|Stable	287			
Month 111|Stable	198			
Month 114|Stable	181			
Month 117|Stable	94			
Month 120|Stable	88			
Month 123|Stable	36			

Month 126|Stable	45			
Month 129|Stable	18			
Month 132|Stable	36			
Month 135|Stable	19			
Month 138|Stable	39			
Month 141|Stable	18			
Month 144|Stable	30			
Month 147|Stable	21			
Month 150|Stable	22			
Month 153|Stable	16			
Month 156|Stable	9			
Month 159|Stable	2			
Month 162|Stable	1			
End of study|Stable	2419			
Month 3 follow-up|Stable	907			
Month 6 follow-up|Stable	111			
Month 3|Deterioration	269			
Month 6|Deterioration	340			
Month 9|Deterioration	304			
Month 12|Deterioration	322			
Month 15|Deterioration	285			
Month 18|Deterioration	271			
Month 21|Deterioration	287			
Month 24|Deterioration	294			
Month 27|Deterioration	270			
Month 30|Deterioration	287			
Month 33|Deterioration	292			
Month 36|Deterioration	288			
Month 39|Deterioration	276			
Month 42|Deterioration	287			
Month 45|Deterioration	263			
Month 48|Deterioration	264			
Month 51|Deterioration	247			
Month 54|Deterioration	251			
Month 57|Deterioration	245			
Month 60|Deterioration	234			
Month 63|Deterioration	191			
Month 66|Deterioration	216			
Month 69|Deterioration	193			
Month 72|Deterioration	206			
Month 75|Deterioration	201			
Month 78|Deterioration	226			
Month 81|Deterioration	217			
Month 84|Deterioration	207			
Month 87|Deterioration	227			
Month 90|Deterioration	204			
Month 93|Deterioration	187			
Month 96|Deterioration	186			
Month 99|Deterioration	159			
Month 102|Deterioration	154			
Month 105|Deterioration	131			
Month 108|Deterioration	138			

Month 111|Deterioration	101			
Month 114|Deterioration	79			
Month 117|Deterioration	52			
Month 120|Deterioration	42			
Month 123|Deterioration	21			
Month 126|Deterioration	26			
Month 129|Deterioration	12			
Month 132|Deterioration	21			
Month 135|Deterioration	12			
Month 138|Deterioration	18			
Month 141|Deterioration	12			
Month 144|Deterioration	19			
Month 147|Deterioration	15			
Month 150|Deterioration	15			
Month 153|Deterioration	8			
Month 156|Deterioration	5			
Month 159|Deterioration	6			
Month 162|Deterioration	1			
End of study|Deterioration	785			
Month 3 follow-up|Deterioration	381			
Month 6 follow-up|Deterioration	88			

Statistical analyses

No statistical analyses for this end point

Secondary: Part I: Change from first dose of Fingolimod in Expanded Disability Status Scale (EDSS)

End point title	Part I: Change from first dose of Fingolimod in Expanded Disability Status Scale (EDSS)

End point description:

The EDSS is a scale for assessing neurological impairment in MS (Kurtzke 1983) including (1) a series of scores in each of eight functional systems, and (2) the EDSS steps (ranging from 0 (normal) to 10 (death due to MS). The functional systems are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel and Bladder, Cerebral and Other functions. Based on the assessment of each FS, the participant's overall score is determined between 0 to 10. A negative change from baseline indicates improvement. Only descriptive analysis performed.

End point type	Secondary

End point timeframe:

Month 0 (Core Baseline) to End of Follow-up Visit (an average of 162 months)

End point values	Fingolimod 0.5 mg/day			
Subject group type	Reporting group			
Number of subjects analysed	4046			
Units: EDSS Overall score				
arithmetic mean (standard deviation)				
Baseline (BL)	2.39 (± 1.452)			

Change from BL at Month 3	-0.06 (± 0.638)			
Change from BL at Month 6	-0.07 (± 0.716)			
Change from BL at Month 9	-0.09 (± 0.750)			
Change from BL at Month 12	-0.07 (± 0.815)			
Change from BL at Month 15	-0.08 (± 0.814)			
Change from BL at Month 18	-0.05 (± 0.890)			
Change from BL at Month 21	-0.08 (± 0.876)			
Change from BL at Month 24	-0.01 (± 0.916)			
Change from BL at Month 27	-0.03 (± 0.932)			
Change from BL at Month 30	-0.00 (± 0.935)			
Change from BL at Month 33	-0.02 (± 0.951)			
Change from BL at Month 36	0.01 (± 0.997)			
Change from BL at Month 39	0.02 (± 0.963)			
Change from BL at Month 42	0.04 (± 1.015)			
Change from BL at Month 45	0.06 (± 1.006)			
Change from BL at Month 48	0.06 (± 1.063)			
Change from BL at Month 51	0.06 (± 1.071)			
Change from BL at Month 54	0.04 (± 1.120)			
Change from BL at Month 57	0.09 (± 1.077)			
Change from BL at Month 60	0.17 (± 1.144)			
Change from BL at Month 63	0.08 (± 1.123)			
Change from BL at Month 66	0.15 (± 1.220)			
Change from BL at Month 69	0.14 (± 1.116)			
Change from BL at Month 72	0.22 (± 1.205)			
Change from BL at Month 75	0.13 (± 1.159)			
Change from BL at Month 78	0.28 (± 1.259)			
Change from BL at Month 81	0.18 (± 1.158)			
Change from BL at Month 84	0.25 (± 1.236)			
Change from BL at Month 87	0.24 (± 1.206)			
Change from BL at Month 90	0.29 (± 1.282)			
Change from BL at Month 93	0.18 (± 1.219)			
Change from BL at Month 96	0.31 (± 1.355)			
Change from BL at Month 99	0.18 (± 1.220)			
Change from BL at Month 102	0.30 (± 1.332)			
Change from BL at Month 105	0.21 (± 1.320)			
Change from BL at Month 108	0.28 (± 1.270)			
Change from BL at Month 111	0.24 (± 1.343)			
Change from BL at Month 114	0.30 (± 1.258)			
Change from BL at Month 117	0.35 (± 1.389)			
Change from BL at Month 120	0.40 (± 1.271)			
Change from BL at Month 123	0.60 (± 1.302)			
Change from BL at Month 126	0.38 (± 1.441)			
Change from BL at Month 129	0.40 (± 1.448)			
Change from BL at Month 132	0.40 (± 1.450)			

Change from BL at Month 135	0.51 (± 1.519)			
Change from BL at Month 138	0.42 (± 1.527)			
Change from BL at Month 141	0.54 (± 1.509)			
Change from BL at Month 144	0.60 (± 1.553)			
Change from BL at Month 147	0.67 (± 1.640)			
Change from BL at Month 150	0.44 (± 1.483)			
Change from BL at Month 153	0.23 (± 1.534)			
Change from BL at Month 156	0.26 (± 1.427)			
Change from BL at Month 159	1.17 (± 1.369)			
Change from BL at Month 162	0.75 (± 1.061)			
Change from BL at End of study	0.14 (± 1.108)			
Change from BL at Month 3 follow-up	0.29 (± 1.248)			
Change from BL at Month 6 follow-up	0.56 (± 1.487)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment in Study Part I until end of study treatment in Study Part II plus 6 weeks post treatment, up to a maximum duration of 8 years.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Any Fingolimod Dose

Reporting group description:

Any Fingolimod Dose

Serious adverse events	Any Fingolimod Dose		
Total subjects affected by serious adverse events			
subjects affected / exposed	515 / 4083 (12.61%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
B-cell lymphoma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	30 / 4083 (0.73%)		
occurrences causally related to treatment / all	22 / 31		
deaths causally related to treatment / all	0 / 0		
Benign hydatidiform mole			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Benign neoplasm of thyroid gland			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Benign ovarian tumour			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bone giant cell tumour			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bowen's disease			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Brain neoplasm benign			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	11 / 4083 (0.27%)		
occurrences causally related to treatment / all	8 / 11		
deaths causally related to treatment / all	0 / 0		
Cervix carcinoma			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon cancer metastatic			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Desmoid tumour			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Extranodal marginal zone B-cell lymphoma (MALT type)			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fibroadenoma of breast			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal neoplasm			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive lobular breast carcinoma			

subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Leiomyoma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Melanocytic naevus			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Meningioma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to lymph nodes			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to spine			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasm			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian adenoma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cancer metastatic			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papilloma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Phyllodes tumour			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			

subjects affected / exposed	3 / 4083 (0.07%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Rectal cancer				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cancer				
subjects affected / exposed	3 / 4083 (0.07%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seminoma				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Small cell lung cancer				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Squamous cell carcinoma				
subjects affected / exposed	9 / 4083 (0.22%)			
occurrences causally related to treatment / all	7 / 11			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of lung				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				

subjects affected / exposed	3 / 4083 (0.07%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Thyroid adenoma				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine cancer				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine leiomyoma				
subjects affected / exposed	10 / 4083 (0.24%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aneurysm				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic aneurysm				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	4 / 4083 (0.10%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				

subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoperfusion				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral artery thrombosis				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral venous disease				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Phlebitis				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Shock haemorrhagic				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vasculitis				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Venous stenosis				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Abortion induced				

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abortion spontaneous			
subjects affected / exposed	10 / 4083 (0.24%)		
occurrences causally related to treatment / all	4 / 11		
deaths causally related to treatment / all	0 / 0		
Ectopic pregnancy			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperemesis gravidarum			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
Death neonatal			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fat tissue increased			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Fatigue				
subjects affected / exposed	5 / 4083 (0.12%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hernia				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypothermia				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Influenza like illness				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Non-cardiac chest pain				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral swelling				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				

subjects affected / exposed	5 / 4083 (0.12%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Vascular stent stenosis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immunodeficiency			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Adnexa uteri cyst			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast calcifications			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical dysplasia			
subjects affected / exposed	7 / 4083 (0.17%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		

Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometriosis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gynaecomastia			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metrorrhagia			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	4 / 4083 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine cyst			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine haemorrhage			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Uterine polyp			

subjects affected / exposed	4 / 4083 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aspiration			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemothorax			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasal polyps			

subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	5 / 4083 (0.12%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Acute stress disorder				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Adjustment disorder with depressed mood				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Aggression				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bipolar I disorder				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Completed suicide				

subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 3		
Confusional state			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	9 / 4083 (0.22%)		
occurrences causally related to treatment / all	1 / 9		
deaths causally related to treatment / all	0 / 0		
Drug dependence			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eating disorder			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mania			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Mental disorder			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Panic attack			

subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Persecutory delusion			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Personality change			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Personality change due to a general medical condition			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychogenic seizure			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Somatic symptom disorder			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stress			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			

subjects affected / exposed	5 / 4083 (0.12%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	3 / 4083 (0.07%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device dislocation				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Biliary colic				
subjects affected / exposed	5 / 4083 (0.12%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Biliary cyst				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary dyskinesia				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis acute				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	4 / 4083 (0.10%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cholecystitis chronic				

subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	10 / 4083 (0.24%)		
occurrences causally related to treatment / all	2 / 10		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatitis acute			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Liver disorder			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphocyte count decreased			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

Alcohol poisoning			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	6 / 4083 (0.15%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Arthropod bite			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest injury			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibula fracture			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Joint injury			

subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Kidney contusion				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Meniscus injury				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple injuries				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle injury				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Near drowning				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Patella fracture				

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pubis fracture			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	5 / 4083 (0.12%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Skull fracture			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic rupture			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	4 / 4083 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Traumatic haematoma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic spinal cord compression			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Ulnar nerve injury			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal laceration			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			

subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Bicuspid aortic valve			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital cytomegalovirus infection			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital knee dislocation			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	6 / 4083 (0.15%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block first degree			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Bradycardia			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiovascular insufficiency			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cyanosis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	4 / 4083 (0.10%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	1 / 1		
Pericarditis			

subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular extrasystoles				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Altered state of consciousness				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Brain hypoxia				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid artery occlusion				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cauda equina syndrome				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Central nervous system lesion				

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebellar infarction			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral venous thrombosis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coma			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Demyelination			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			

subjects affected / exposed	8 / 4083 (0.20%)		
occurrences causally related to treatment / all	1 / 9		
deaths causally related to treatment / all	0 / 0		
Facial spasm			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fine motor skill dysfunction			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Focal dyscognitive seizures			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	4 / 4083 (0.10%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Hemianopia homonymous			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperaesthesia			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial aneurysm			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 1		
Lacunar infarction			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis relapse			

subjects affected / exposed	34 / 4083 (0.83%)			
occurrences causally related to treatment / all	1 / 37			
deaths causally related to treatment / all	0 / 0			
Muscle spasticity				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myelitis transverse				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Neuralgia				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Optic neuritis				
subjects affected / exposed	3 / 4083 (0.07%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Sciatica				

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Secondary progressive multiple sclerosis			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Syncope			
subjects affected / exposed	4 / 4083 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Tension headache			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombotic stroke			

subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Transient ischaemic attack				
subjects affected / exposed	3 / 4083 (0.07%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Trigeminal neuralgia				
subjects affected / exposed	3 / 4083 (0.07%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Uhthoff's phenomenon				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulnar nerve palsy				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wernicke's encephalopathy				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	3 / 4083 (0.07%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Immune thrombocytopenic purpura				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Iron deficiency anaemia				

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphopenia			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 4083 (0.10%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Photophobia			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Retinal haemorrhage			

subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal vein thrombosis				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal adhesions				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal hernia				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	4 / 4083 (0.10%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Abdominal pain lower				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Anal fissure				
subjects affected / exposed	4 / 4083 (0.10%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Barrett's oesophagus				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer perforation			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Flatulence			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Food poisoning			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric disorder			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Irritable bowel syndrome			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Large intestine polyp			

subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Proctalgia				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proctitis				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal polyp				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 4083 (0.07%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Alopecia				

subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dermatitis				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis contact				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erythema				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erythema annulare				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin erosion				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Calculus urinary				

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Renal haemorrhage			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary incontinence			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperprolactinaemia			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroid mass			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Amyotrophy			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	7 / 4083 (0.17%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chondromalacia			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chondropathy			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Compartment syndrome			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foot deformity			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			

subjects affected / exposed	8 / 4083 (0.20%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Jaw disorder			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint instability			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint swelling			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lateral patellar compression syndrome			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mobility decreased			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	3 / 4083 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	6 / 4083 (0.15%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			

subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhabdomyolysis				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rotator cuff syndrome				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal column stenosis				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Synovial cyst				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Torticollis				
subjects affected / exposed	1 / 4083 (0.02%)			
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 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal sepsis				

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	10 / 4083 (0.24%)		
occurrences causally related to treatment / all	1 / 10		
deaths causally related to treatment / all	0 / 0		
Appendicitis perforated			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bartholin's abscess			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	6 / 4083 (0.15%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dermatitis infected			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epididymitis			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Furuncle			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Groin abscess			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Helicobacter infection			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis A			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis C			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatitis E			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes simplex encephalitis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	9 / 4083 (0.22%)		
occurrences causally related to treatment / all	8 / 9		
deaths causally related to treatment / all	0 / 0		
Herpes zoster infection neurological			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Histoplasmosis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infected dermal cyst			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infection			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Injection site abscess			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphangitis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mastoiditis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis cryptococcal			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Meningoencephalitis herpetic			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Orchitis			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pelvic inflammatory disease			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonsillar abscess			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pilonidal cyst			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	14 / 4083 (0.34%)		
occurrences causally related to treatment / all	4 / 14		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary tuberculosis			

subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelitis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal abscess			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Salpingitis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Salpingo-oophoritis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			

subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Spermatic cord funiculitis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 4083 (0.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	14 / 4083 (0.34%)		
occurrences causally related to treatment / all	7 / 16		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 4083 (0.02%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Viraemia			

subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral diarrhoea				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Vulval abscess				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	2 / 4083 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperamylasaemia				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obesity				
subjects affected / exposed	1 / 4083 (0.02%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Any Fingolimod Dose		
Total subjects affected by non-serious adverse events subjects affected / exposed	2125 / 4083 (52.05%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	243 / 4083 (5.95%) 254		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	348 / 4083 (8.52%) 538		
Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all)	219 / 4083 (5.36%) 266		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	232 / 4083 (5.68%) 259		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	205 / 4083 (5.02%) 233		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	208 / 4083 (5.09%) 246 279 / 4083 (6.83%) 346		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Influenza	214 / 4083 (5.24%) 285		

subjects affected / exposed	275 / 4083 (6.74%)		
occurrences (all)	384		
Nasopharyngitis			
subjects affected / exposed	706 / 4083 (17.29%)		
occurrences (all)	1318		
Upper respiratory tract infection			
subjects affected / exposed	346 / 4083 (8.47%)		
occurrences (all)	646		
Urinary tract infection			
subjects affected / exposed	335 / 4083 (8.20%)		
occurrences (all)	604		
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	212 / 4083 (5.19%)		
occurrences (all)	245		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2010	The changes made throughout the protocol are specific to Poland and the UK and update the study endpoint to reflect until fingolimod is registered and through approximately one-year post approval or maximally through 31-Dec-2012.
02 March 2011	The changes made throughout the protocol are specific to Norway and update the study endpoint to reflect the timepoint approximately 12 months following the completion of the previous fingolimod trial or maximally through 01-Aug-2012.
18 May 2011	The changes made throughout the protocol update the study end for the Phase II/III patients to fingolimod registration, commercially availability and reimbursement OR through 30-June-2016, whichever is later.
06 October 2011	This Amendment aims to further define the extended follow-up for patients who previously completed the phase II or III fingolimod clinical development studies in an interventional trial setting through 30-Jun-2016. It extends the enrollment to patients who have completed CFTY720D2309/E1 as well as the re-enrollment of CFTY720D2399 patients who have previously completed this study based on the original CFTY720D2399 study endpoint of local approval and reimbursement. Furthermore, this amendment will define additional assessments to evaluate the long-term efficacy of fingolimod in phase II and III trial patients. Lastly, this amendment aims to bring the study schedule of assessments as well as the safety monitoring guidelines in alignment with the fingolimod prescribing information of major countries where the medication has been registered.
06 February 2012	The major changes include the following: • Exclusion criteria related to the cardiovascular conditions are updated. • Appendix 4 Guidance for monitoring of patients taking their first dose of the study drug is updated. • Only for Germany: Patients requiring first dose monitoring will receive continuous 6-hour ECG monitoring after the first dose or upon re-initiation of fingolimod treatment after an interruption of greater than 14 consecutive days.
24 July 2012	The major changes include the following: • Exclusion criteria related to the cardiovascular conditions are updated. • Exclusion of patients taking medications that lower heart rate has been added. • Germany country-specific recommendations removed; additional procedures and assessments required by local prescribing information should be followed accordingly. • Appendix 4 Guidance for monitoring of patients taking their first dose of the study drug is updated to reflect final guidance.
18 August 2013	The major changes include the following: • Clarified VZV antibody guidance has been added. • The protocol title has been modified.
29 August 2014	The major changes include the following: • MRI frequency changed from annually to one at EOS • Clinical laboratory collection changed from a biennial to annual collection, with urine pregnancy tests for females being substituted at the visits during which other clinical laboratory testing has been removed. • Addition of CD4/CD8/CD19 testing as part of the chemistry panel at EOS visit • Reduction in frequency of PRO collection, for those patients who had PRO collection in their prior study

09 September 2015	The major changes include the following: Updates to the Background, Physical/neurological exam, Skin assessments, and Guidance on safety monitoring based on investigator brochure (Edition 18) updates. Updates to Study design, Rationale of study design, Population, Study completion and post-study treatment, and the Schedule of assessments related to Study Completion visit scheduling and/or reintroduction of hematology sampling at the 6-monthly visits.
14 March 2016	The major changes include the following: Updates to Study objectives, Study design, Rationale of study design, Rationale of dose/regimen, duration of treatment, Population, Study completion and post-study treatment, Discontinuation of study treatment, Laboratory evaluations, Data analysis, Guidance on Safety Monitoring, and the Schedule of assessments. Addition of Section 6.6.7, Other Biomarkers, Liver event and Laboratory trigger Definitions and Follow-up Requirements, and the Schedule of assessments for Part II.
01 April 2016	The purpose of this amendment is to add information inadvertently deleted from Amendment 10 during the publishing process. This study is ongoing with approximately 4,150 enrolled patients. The amendment changes will provide further clarification on the conduct of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported