Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Fingolimod

Trial Indication(s)

Primary Progressive Multiple Sclerosis (PPMS)

Protocol Number

CFTY720D2306 and CFTY720D2306E1

Protocol Title

A double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing the efficacy and safety of 0.5mg Fingolimod administered orally once daily versus placebo in patients with primary progressive multiple sclerosis and an open-label, single-arm extension study to the double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg FTY720 administered orally once daily versus placebo in patients with primary progressive multiple sclerosis

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase 3

Study Start/End Dates

Core Study Start Date: July 2008 (Actual)
Core Study Completion Date: December 2014 (Actual)

Extension Study Start Date: January 2013 (Actual)
Extension Study Completion Date: June 2015 (Actual) Early Terminated

Reason for Termination (If applicable)

The extension study was terminated early after the results of the core study became available showing that the study did not meet its primary endpoint which was defined as confirmed disability progression in this population.

Study Design/Methodology

This was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study on patients with PPMS, which included 3 periods: Pre-randomization (up to 45 days), a Double-blind treatment period (continued until the last patient completed 36 months of treatment or up to a maximum treatment duration of 5 years), and a 12-week Follow-up period for patients who completed this study but did not enter the subsequent extension study (FTY720D2306E1). Patients were randomized in a 1:1 ratio to receive either active treatment or placebo. Patients initially randomized to receive fingolimod 1.25 mg/day or matching placebo (cohort 1) were switched in a blinded manner to fingolimod 0.5 mg/day or continued on placebo (Amendment 5). Patients randomized after this amendment received either fingolimod 0.5 mg/day or matching placebo (cohort 2).

The extension study allowed Patients who were randomized in the core study to receive fingolimod 0.5 mg in the extension study. Patients who were randomized in the core study to receive placebo were switched to fingolimod 0.5 mg at Visit 1 in the extension study. Thus, all patients in the extension study received treatment with fi ngolimod 0.5 mg during the study open-label. Patients in the core study who either prematurely discontinued the study drug treatment permanently or discontinued participation in the core study were not eligible to participate in the extension study.

Centers

164 centers in 18 countries: United States(34), Turkey(5), Sweden(3), Poland(4), Netherlands(6), Italy(14), Hungary(6), United Kingdom(9), France(8), Finland(3), Spain(12), Denmark(3), Germany(18), Czech Republic(9), Switzerland(5), Canada(13), Belgium(6), Australia(6)

Objectives:

The primary objective was to evaluate the effect of fingolimod 0.5 mg relative to placebo on delaying the time to sustained disability progression. Sustained disability progression is defined based on 3 types of events for each patient:

- 3-month sustained increase of at least 20% from baseline in the time taken to complete the Timed 25-foot walk test (25'TWT), or
- 3-month sustained increase from baseline in the Expanded Disability Status Scale (EDSS) score (1 point in patients with baseline EDSS score 3.5 to 5.0; 0.5 point in patients with baseline EDSS score of 5.5 or 6.0), or
- 3-month sustained increase of at least 20% from baseline in the time taken to complete the 9-hole peg test (9-HPT)

Key secondary objectives included:

- To evaluate the effect of fingolimod 0.5 mg relative to placebo on delaying the time to 3 month sustained disability progression as measured by the EDSS
- To evaluate the effect of fingolimod 0.5 mg relative to placebo on the percent change from baseline in brain volume

Other secondary objectives included

- To evaluate the effect of fingolimod 0.5 mg relative to placebo on the time to 3-month sustained disability progression as measured by the time taken to complete the 25'TWT
- To evaluate the effect of fingolimod 0.5 mg relative to placebo on the time to 3-month sustained disability progression as measured by the time taken to complete the 9-HPT
- To evaluate the safety and tolerability of fingolimod 0.5 mg compared to placebo in patients with PPMS
- To evaluate the effect of fingolimod 0.5 mg relative to placebo on conventional magnetic resonance imaging (MRI) parameters (inflammatory disease activity, disease burden, brain atrophy)
- To evaluate the effect of fingolimod 0.5 mg relative to placebo on patient reported outcomes
- To assess the pharmacokinetics (PK) of fingolimod and fingolimod-P in patients with PPMS and evaluate the pharmacokinetic/pharmacodynamic (PK/PD) relationship for main efficacy and safety outcomes

Test Product (s), Dose(s), and Mode(s) of Administration

Fingolimod 0.5 mg oral capsules (after amendment 5)
Fingolimod 1.25 mg oral capsules (prior to amendment 5)
Placebo (matched) oral capsules

Statistical Methods

The primary and all secondary efficacy analyses were performed on the basis of the Full Analysis Set (FAS), which consists of all patients who were randomized and received at least one dose of study treatment, in patients randomized to either fingolimod 0.5mg (Cohort 2) or placebo (Cohort 1 and 2). Patients were grouped and analyzed according to the intent-to-treat principle.

No formal efficacy interim analysis was planned or performed. In order to address comments received from the health authorities, reviews of blinded efficacy data were performed to explore the primary endpoint.

The primary efficacy endpoint was to evaluate the effect of fingolimod 0.5mg versus placebo on delaying the time to confirmed disability progression (CDP). CDP was defined as the first occurrence of a progression according to at least one of the following 3 criteria: increase from baseline in the EDSS score by 1 point in patients with baseline EDSS score ≤5.0 or 0.5 point in patients with baseline EDSS score ≥5.5; increase of at least 20% from baseline in the 25'TWT; increase of at least 20% from baseline in time taken to complete the 9-HPT. Progression in at least one of the three components had to be sustained and confirmed at least 3 months later at a scheduled visit.

The primary analysis model was a Cox proportional hazards model with treatment, region, age, baseline EDSS, baseline 25'TWT, and baseline 9-HPT as covariates. The estimated hazard ratio with 95% confidence interval (CI) and p-value for testing whether the hazard ratio of fingolimod to placebo was less than 1 were presented. In addition, Kaplan-Meier curves by treatment were used to present the time-dependent cumulative frequency and percentage of patients reaching 3-month confirmed progression. Additional analyses (including analyses by Cohort) were performed as supportive or sensitivity analyses.

To control for the overall Type-I error rate, a multiplicity adjustment via a step down hierarchical testing procedure was applied to the primary and key secondary endpoints hypothesis testing. The 95% Cis were not adjusted for multiplicity.

The first key secondary endpoint (i.e., the time to 3-month confirmed disability progression based on EDSS) was analyzed in a similar way as it was for the primary efficacy endpoint.

The second key secondary endpoint (i.e., percent change from baseline in brain volume) was analyzed by a random coefficient model as main analysis. Additional analyses including repeated measure model were performed as supportive analyses.

Other efficacy endpoints, including EDSS, MSFC, MRI parameters and quality of life, were also analyzed.

All safety analyses were conducted on data from the safety set (SAF) which consists of all patients in the FAS who received at least one dose of study treatment. In all safety analyses patients were grouped and analyzed according to the treatment actually received.

Regular semiannual safety interim analysis for the drug safety management board was performed by the independent statistician and independent statistical programmer. The data was reviewed by the independent drug safety management board.

Safety assessments in the core study included: adverse events, laboratory tests, vital signs, pulmonary function tests, ophthalmic examinations, dermatological examinations, chest x-ray, ECG and echocardiography data. Safety assessments in the extension study included AEs, laboratory tests, vital signs, ECGs, ophthalmic examinations, and dermatologic examination.

Adverse events were summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event by primary system organ class and preferred term. Severe AEs, serious AEs, cases of death, drug related AEs and the AEs leading to premature discontinuation of study drug were presented in a similar format as adverse events. Other safety data was summarized as appropriate.

Patients who provided one or more evaluable blood concentration result were included in the pharmacokinetic analysis set. Fingolimod and fingolimod-phosphate blood concentrations were listed by treatment, patient, and visit and summarized with descriptive statistics by treatment and visit. For the 1.25 mg treatment, the actual administered dose was

taken into account for the Month 12 visit when some patients received 1.25 mg and some received 0.5 mg (Amendment 5). The metabolite/parent molar ratio was derived from the concentrations adjusted for molecular weight.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

General

1. sign written informed consent prior to participating in the study
2. 25 through 65 years of age inclusive
3. females of childbearing potential must:

_ have a negative pregnancy test at Baseline (prior to randomization) and
_ use simultaneously two forms of effective contraception during the treatment and 3-months after discontinuation of study medication

Primary Progressive Multiple sclerosis.

1. diagnosis of primary progressive multiple sclerosis (according to the 2005 Revised McDonald criteria):

2. time since first reported symptoms between 2 and 10 years
3. evidence of clinical disability progression in the 2 years prior to Screening
4. disability status at Screening

_ EDSS score of 3.5-6.0 inclusive
_ pyramidal functional system score of 2 or more
_ 25'TWT less than 30 seconds

Extension study Inclusion criteria

- Patients initially randomized to fingolimod 1.25 mg or placebo as part of the first study cohort, were to have completed at least 3 years on study drug treatment at the time of extension study initiation.
- Patients initially randomized to fingolimod 0.5 mg or placebo as part of the second study cohort, were to have continued on study drug treatment until such time as the last ongoing patient enrolled in the study had reached 3 years in study

Exclusion Criteria:

PPMS specific:

_ History of relapses/attacks

_ Progressive neurological disorder other than PPMS
_ Pure cerebellar syndrome or pure visual progressive syndrome or pure
_ cognitive progressive syndrome
_Presence of spinal cord compression at screening MRI
_ Relevant history of vitamin B12 deficit
_ Evidence of syphilis or borreliosis at Screening

Cardiovascular conditions:
_ Myocardial infarction within the past 6 months or current unstable ischemic heart disease
_ History of angina pectoris due to coronary spasm or history of Raynaud's phenomenon
_ Severe cardiac failure or cardiac arrest
_ History of symptomatic bradycardia
_ Resting pulse <55 bpm pre-dose
_ History of sick sinus syndrome or sino-atrial heart block
_ History or presence of second and third degree AV block or an increase QT interval (QTc>440 ms)
_ Arrythmia requiring treatment with class III antiarrythmic drugs
_ History of positive tilt test from workout of vasovagal syncope
_ Hypertension, not controlled with medication

Pulmonary:
-Severe respiratory disease or pulmonary fibrosis
- TB
- Abnormal X-ray, suggestive of active pulmonary disease
- Abnormal PFT: <70% of predicted for FEV1 and FVC; <60% for DLCO
- Patients receiving chronic (daily) therapies for asthma

Hepatic:
- Known history of alcohol abuse, chronic liver or biliary disease
- Total or conjugated Brb >ULN, unless in context of Gilbert's syndrome
- AP >1.5xULN; ALT/AST >2xULN; GGT>3xULN

Other:
_ History of chronic disease of the immune system other than MS
_ Malignancy (other than successfully treated SCC or BCC)
_ Diabetes Mellitus

_ Macular Edema present at screening
_ HIV, Hepatitis C or B, other active infection
_ History of total lymphoid irradiation or bone marrow transplantation
_ Serum creatinine >1.7 mg/dl
_ WBC <3500 cells/mm3
_ Lymphocyte count <800 cells/mm3
_ History of substance abuse or any other factor that may interfere with subject ability to cooperate and comply with the study procedures
_ Unable to undergo MRI scans
_ Participation in any therapeutical clinical research study in the 6 months prior to randomization
_ Pregnant or lactating women
_ Drugs requiring wash-out period:
3 months:
- Systemic corticosteroids or ACTH
- INF-beta

6 months:
- Immunosuppressive medication
- Immunoglobulins
- Monoclonal antibodies

_ Drugs that exclude participation in the study:
_ Cladribine
_ Cyclophosphamide
_ Mitoxantrone (except: patients who received a cumulative dose of no more than 60mg/m2 more than 5 years ago could enter the study)

Extension study Exclusion criteria –
Patients were not eligible for enrollment in the extension study if they had any of the following key exclusion criteria at the extension study Baseline visit: active chronic immune system disease other than MS (or stable disease treated with immune therapy); known immunodeficiency syndrome; active infection; uncontrolled diabetes mellitus; macularedema; treatment with Class Ia or III antiarrhythmic drugs; any of the specified cardiac, pulmonary, or hepatic conditions; or any medically unstable condition

Participant Flow Table

Core study

	FTY720 1.25 mg to 0.5 mg	FTY720 0.5 to 0.5mg	Placebo to - FTY 0.5 mg
Started	147	336	487
Safety Set (SAF)	0	336	487
Full analysis Set (FAS)	0	336	487
Pharmacokinetic Analysis Set	102	249	0
Completed	79	220	317
Not Completed	68	116	170
Lack of Efficacy	11	23	64
Physician Decision	1	0	2
Death	2	1	2
Lost to Follow-up	1	3	3
Administrative	2	2	6
Abnormal Test Procedure Result	4	3	5
Protocol Violation	4	5	8
Abnormal Lab values	6	19	5
Adverse Event	25	28	29
Withdrawal by Subject	12	32	46

Extension phase

	FTY720 1.25 mg to 0.5 mg	FTY720 0.5 to 0.5mg	Placebo to - FTY 0.5 mg
Started	74	196	301
Completed	0	0	0
Not Completed	74	196	301
Admin problems: Terminated # patients	69	189	277
Abnormal test procedure	0	0	1
Abnormal lab values	0	0	1
Lost to Follow-up	0	1	4
Withdrawal by Subject	4	5	3
Adverse Event	1	1	15

Baseline Characteristics

	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Total
Number of Participants [units: participants]	147	336	487	970
Age Continuous (units: years) Mean ± Standard Deviation	47.8±8.47	48.5±8.59	48.5±8.31	48.5±8.42
Gender, Male/Female (units: Participants)				
Female	71	163	235	469
Male	76	173	252	501
Age, Customized (units: Particpants)				
<=30	3	6	4	13
31 to 40	22	60	90	172
41 to 50	68	127	194	389
>50	54	143	199	396

Summary of Efficacy

Primary Outcome Result(s)

Kaplan-Meier estimate of the risk of 3-month confirmed disability progression based on composite endpoint

	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	336	487
Kaplan-Meier estimate of the risk of 3-month confirmed disability progression based on composite endpoint (units: Percentage of Participants) Number (95% Confidence Interval)	77.2 (71.87 to 82.51)	80.3 (73.31 to 87.25)

Secondary Outcome Result(s)

Kaplan-Meier estimate of the risk of 3- month confirmed disability progression based on Expanded Disability Status Scale (EDSS)

	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	336	487
Kaplan-Meier estimate of the risk of 3- month confirmed disability progression based on Expanded Disability Status Scale (EDSS)	54.3 (47.16 to 61.45)	58.7 (53.30 to 64.18)

(units: Percentage of Participants)
Number (95% Confidence Interval)

Percent change from baseline in brain volume at Month 36

	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	293	421
Percent change from baseline in brain volume at Month 36 (units: Percent Change) Least Squares Mean (95% Confidence Interval)	-1.49 (-1.64 to -1.35)	-1.53 (-1.65 to -1.41)

Kaplan Meier Estimate -Percentage of participants with 3- month confirmed disability progression based on 9-HPT.

	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	147	133
Kaplan Meier Estimate - Percentage of participants with 3-month confirmed disability progression based on 9-HPT. (units: Percentge of Participants)	25.0	24.9

Kaplan Meier Estimate -Percentage of participants with 3- month confirmed disability progression based on 25' TWT.

	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	147	133
Kaplan Meier Estimate - Percentage of participants with 3-month confirmed disability progression based on 25' TWT. (units: Percentage of Participants)	54.8	56.7

Number of new/enlarging T2 lesions per year measured from baseline to Month 36

	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	298	421
Number of new/enlarging T2 lesions per year measured from baseline to Month 36 (units: T2 Lesions per year) Least Squares Mean (95% Confidence Interval)	0.13 (0.10 to 0.18)	0.50 (0.40 to 0.61)

Number of Gd-enhancing lesions at month 36

	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	223	320
Number of Gd-enhancing lesions at month 36 (units: Gd-enhanced lesions per patient per scan) Least Squares Mean (95% Confidence Interval)	0.05 (0.02 to 0.09)	0.21 (0.15 to 0.30)

Percent change in total T2 lesion volume from baseline to Month 36

	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	224	326
Percent change in total T2 lesion volume from baseline to Month 36 (units: Percent Change) Mean ± Standard Deviation	-9.2 ± 30.55	8.9 ± 44.13

Change from baseline in the patient reported indices in multiple sclerosis (PRIMUS-QoL score)

	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	147	336	487

Change from baseline in the patient reported indices in multiple sclerosis (PRIMUS-QoL score) (units: Score on a scale) Mean ± Standard Deviation			
Baseline (n=100,246,352)	7.5349 ± 4.77306	7.7197 ± 5.29220	7.1693 ± 4.89106
Month 36 (n=66,150,230)	0.2424 ± 4.18444	0.5921 ± 4.77704	0.9597 ± 4.38578

Change from baseline in PRIMUS-Activities

	FTY720 1.25 mg	**FTY720 0.5 mg**	**Placebo**
Number of Participants Analyzed [units: participants]	147	336	487
Change from baseline in PRIMUS-Activities (units: Score on a scale) Mean ± Standard Deviation			
Baseline (n=104,247,357)	9.3729 ± 5.74726	10.1707 ± 5.96238	10.0543 ± 6.25051
Month 36 (n=68,153,237)	3.5504 ± 7.05241	2.6324 ± 6.22256	2.8830 ± 6.76499

Change from baseline in Unidimensional Fatigue Impact (U-FIS) score

	FTY720 1.25 mg	**FTY720 0.5 mg**	**Placebo**
Number of Participants Analyzed [units: participants]	147	336	487
Change from baseline in Unidimensional Fatigue Impact (U-FIS) score (units: Score on a scale)			

Mean ± Standard Deviation			
Baseline (n=103,248,357)	24.1937 ± 12.66758	25.7206 ± 13.63297	23.8297 ± 13.02168
Month 36 (n=70,154,241)	1.3197 ± 12.44042	2.8451 ± 14.04769	3.1394 ± 12.20929

Change from baseline in European Quality of Life – 5 dimensions (EQ-5D score)

	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	147	336	487
Change from baseline in European Quality of Life – 5 dimensions (EQ-5D score) (units: Score on a scale) Mean ± Standard Deviation			
Baseline (n=144,328,474)	0.6418 ± 0.19060	0.6154 ± 0.21562	0.6431 ± 0.18472
Month 36 (n=99,213,320)	-0.0332 ± 0.19420	-0.0475 ± 0.26099	-0.0539 ± 0.22383

Change from baseline in Multiple Sclerosis Walking Scale (MSWS-12 score)

	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	147	336	487
Change from baseline in Multiple Sclerosis Walking Scale (MSWS-12			

score) (units: Score on a scale) Mean ± Standard Deviation			
Baseline (n=115,278,397)	59.3892 ± 21.84532	60.4606 ± 23.35639	58.2921 ± 23.47897
Month 36 (n=75,182,261)	6.4444 ± 23.81568	5.5616 ± 24.59030	9.5899 ± 23.98316

Blood concentrations of fingolimod and fingolimod-phosphate

	FTY720 1.25 mg	**FTY720 1.25mg to 0.5 mg**	**FTY720 0.5 mg**
Number of Participants Analyzed [units: participants]	102	102	249
Blood concentrations of fingolimod and fingolimod-phosphate (units: ng/ml) Mean ± Standard Deviation			
Month 3 Fingolimod (n=64, 179)	6.04 ± 3.11	NA ± NA[1]	2.58 ± 1.34
Month 12 Fingolimod (n=23, 161)	6.24 ± 2.21	2.87 ± 1.70	2.55 ± 1.37
Month 18 Fingolimod (n=71,155)	NA ± NA[2]	2.44 ± 1.15	2.59 ± 1.44
Month 24 Fingolimod (n=67, 160)	NA ± NA[2]	2.41 ± 1.30	2.64 ± 1.50
Month 30 Fingolimod (n=62, 158)	NA ± NA[2]	2.52 ± 1.28	2.60 ± 1.33
Month 36 Fingolimod (n=55, 118)	NA ± NA[2]	2.44 ± 1.08	2.63 ± 1.38

End of treatment Fingolimod (n=32, 115)	NA ± NA[2]	2.02 ± 1.10	2.57 ± 1.51
Month 3 Fingolimod-Phosphate (n=64, 179)	3.20 ± 1.73	NA ± NA[1]	1.40 ± 0.747
Month 12 Fingolimod-Phosphate (n=23, 161)	3.21 ± 1.16	1.54 ± 0.871	1.43 ± 0.805
Month 18 Fingolimod-Phosphate (n=71,155)	NA ± NA[2]	1.34 ± 0.630	1.41 ± 0.758
Month 24 Fingolimod-Phosphate (n=67, 160)	NA ± NA[2]	1.35 ± 0.765	1.44 ± 0.790
Month 30 Fingolimod-Phosphate (n=62, 158)	NA ± NA[2]	1.32 ± 0.676	1.48 ± 0.759
Month 36 Fingolimod-Phosphate (n=55, 118)	NA ± NA[2]	1.32 ± 0.591	1.51 ± 0.765
End of treatment Fingolimod-Phosphate (n=32, 115	NA ± NA[2]	1.19 ± 0.618	1.50 ± 0.900

[1] No evaluable blood concentration available
[2] Patients switched to 0.5mg. No evaluable blood concentration available

Change in MSFC z-score and subscale scores from Baseline to Month 36

	FTY720 0.5 mg	Placebo
Number of Participants Analyzed [units: participants]	193	279
Change in MSFC z-score and subscale scores from Baseline to Month 36 (units: Z-scores) Mean ± Standard Deviation	-0.189 ± 0.6980	-0.212 ± 0.8468

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

Source Vocabulary for Table Default	MedDRA 15.1
Assessment Type for Table Default	Systematic Assessment

	Core: FTY720 1.25 mg N = 147	Core: FTY720 0.5 mg N = 336	Core: Placebo N = 487	Extension: FTY1.25-0.5 N = 74	Extension: FTY0.5-0.5 N = 196	Extension: Placebo-FTY0.5 N = 301
Total participants affected	38 (25.85%)	84 (25.00%)	117 (24.02%)	7 (9.46%)	10 (5.10%)	37 (12.29%)
Blood and lymphatic system disorders						
Anaemia macrocytic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Lymphadenopathy[1]	1 (0.68%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	1 (0.51%)	0 (0.00%)

Cardiac disorders						
Angina pectoris[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Arrhythmia[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Atrial fibrillation[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Atrioventricular block[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Atrioventricular block complete[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Atrioventricular block first degree[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Atrioventricular block second degree[1]	1 (0.68%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bradycardia[1]	2 (1.36%)	2 (0.60%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Coronary artery disease[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Myocardial infarction[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myocardial ischaemia[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pericarditis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sinus bradycardia[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tachycardia paroxysmal[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Endocrine disorders						
Hypothyroidism[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye disorders						
Amblyopia strabismic[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Angle closure glaucoma[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cataract cortical[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Chorioretinopathy[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cystoid macular oedema[1]	0 (0.00%)	1 (0.30%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diplopia[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Intraocular haematoma[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Macular oedema[1]	1 (0.68%)	4 (1.19%)	4 (0.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myopia[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Optic atrophy[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Retinal detachment[1]	0 (0.00%)	1 (0.30%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Retinal tear[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders						
Abdominal pain[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain lower[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Anal polyp[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Colitis ulcerative[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Constipation[1]	0 (0.00%)	2 (0.60%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Faecaloma[1]	0 (0.00%)	1 (0.30%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastric ulcer[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Inguinal hernia[1]	1 (0.68%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Intestinal obstruction[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nausea[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Obstruction gastric[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pancreatitis[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pancreatitis acute[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Upper gastrointestinal haemorrhage[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

General disorders and administration site conditions						
Asthenia[1]	1 (0.68%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Chest discomfort[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Device dislocation[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Device occlusion[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Drug ineffective[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fatigue[1]	0 (0.00%)	1 (0.30%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Gait disturbance[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
General physical health deterioration[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-cardiac chest pain[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyrexia[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Hepatobiliary disorders						
Cholecystitis[1]	1 (0.68%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cholecystitis acute[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cholelithiasis[1]	0 (0.00%)	1 (0.30%)	3 (0.62%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cholelithiasis obstructive[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations						
Appendicitis[1]	1 (0.68%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bacterial infection[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Blister infected[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bronchitis viral[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bronchopneumonia[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Bursitis infective[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.35%)	0 (0.00%)	0 (0.00%)
Cellulitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.35%)	0 (0.00%)	0 (0.00%)
Cystitis[1]	1 (0.68%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	1 (0.51%)	0 (0.00%)
Dengue fever[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diverticulitis[1]	0 (0.00%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Enterocolitis bacterial[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Epididymitis[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Gastroenteritis[1]	0 (0.00%)	2 (0.60%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
H1N1 influenza[1]	0 (0.00%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes zoster[1]	1 (0.68%)	2 (0.60%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes zoster infection neurological[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes zoster meningomyelitis[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Incision site infection[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infection[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infectious pleural effusion[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Influenza[1]	0 (0.00%)	3 (0.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Meningitis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myelitis[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ophthalmic herpes simplex[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Peritonitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Pneumonia[1]	2 (1.36%)	4 (1.19%)	2 (0.41%)	1 (1.35%)	0 (0.00%)	1 (0.33%)
Pulmonary sepsis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyelonephritis[1]	0 (0.00%)	0 (0.00%)	3 (0.62%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyelonephritis acute[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Respiratory tract infection[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Septic shock[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Serratia sepsis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Subcutaneous abscess[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.35%)	0 (0.00%)	0 (0.00%)
Systemic mycosis[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tonsillitis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tracheobronchitis[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Upper respiratory tract infection[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary tract infection[1]	2 (1.36%)	8 (2.38%)	12 (2.46%)	1 (1.35%)	0 (0.00%)	4 (1.33%)
Urinary tract infection bacterial[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urosepsis[1]	1 (0.68%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	1 (0.51%)	0 (0.00%)
Viral infection[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Viral upper respiratory tract infection[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications						
Accidental overdose[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Alcohol poisoning[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ankle fracture[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.51%)	0 (0.00%)
Clavicle fracture[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Concussion[1]	1 (0.68%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Facial bones fracture[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	1 (0.51%)	0 (0.00%)
Fall[1]	3 (2.04%)	1 (0.30%)	3 (0.62%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Femoral neck fracture[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	1 (0.33%)

Femur fracture[1]	1 (0.68%)	1 (0.30%)	3 (0.62%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Fibula fracture[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Foot fracture[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fracture displacement[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Hand fracture[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Head injury[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hip fracture[1]	0 (0.00%)	1 (0.30%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Humerus fracture[1]	1 (0.68%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Joint dislocation[1]	1 (0.68%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Laceration[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Limb traumatic amputation[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lumbar vertebral fracture[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Meniscus injury[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Overdose[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Pneumothorax traumatic[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Post procedural complication[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Post procedural haematoma[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Post procedural haemorrhage[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Radius fracture[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rib fracture[1]	1 (0.68%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Road traffic accident[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skull fracture[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Subdural haematoma[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Thermal burn[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tibia fracture[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Traumatic renal injury[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Upper limb fracture[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Wound[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Wound dehiscence[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Wrist fracture[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations						
Alanine aminotransferase increased[1]	0 (0.00%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aspartate aminotransferase increased[1]	0 (0.00%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood pressure increased[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Foetal heart rate abnormal[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
International normalised ratio decreased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Lymphocyte count decreased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.35%)	0 (0.00%)	0 (0.00%)
Troponin increased[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Weight decreased[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders						
Dehydration[1]	0 (0.00%)	1 (0.30%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypokalaemia[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Polydipsia[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders						
Arthralgia[1]	0 (0.00%)	1 (0.30%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Back pain[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.66%)
Bone swelling[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bursitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.35%)	0 (0.00%)	0 (0.00%)
Intervertebral disc disorder[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Joint swelling[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mobility decreased[1]	0 (0.00%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscular weakness[1]	0 (0.00%)	0 (0.00%)	2 (0.41%)	1 (1.35%)	0 (0.00%)	2 (0.66%)
Osteoarthritis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Osteopenia[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain in extremity[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rhabdomyolysis[1]	0 (0.00%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sjogren's syndrome[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spinal column stenosis[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tendon disorder[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Basal cell carcinoma[1]	1 (0.68%)	11 (3.27%)	9 (1.85%)	1 (1.35%)	2 (1.02%)	1 (0.33%)
Breast cancer[1]	2 (1.36%)	1 (0.30%)	0 (0.00%)	1 (1.35%)	0 (0.00%)	0 (0.00%)
Dysplastic naevus[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fibrous histiocytoma[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Invasive ductal breast carcinoma[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Invasive lobular breast carcinoma[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lung neoplasm malignant[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphocytic leukaemia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Malignant melanoma[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Malignant melanoma in situ[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Medullary thyroid cancer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Melanocytic naevus[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metastases to bone[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metastases to central nervous system[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metastases to kidney[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metastases to liver[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-Hodgkin's lymphoma[1]	1 (0.68%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Osteoma[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ovarian cancer metastatic[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Prostate cancer[1]	0 (0.00%)	1 (0.30%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Small cell lung cancer metastatic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Squamous cell carcinoma of skin[1]	0 (0.00%)	6 (1.79%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Uterine leiomyoma[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Nervous system disorders						
Aphasia[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Arachnoiditis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Brain oedema[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Central nervous system lesion[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cerebrovascular accident[1]	0 (0.00%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cerebrovascular disorder[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.35%)	0 (0.00%)	1 (0.33%)
Generalised tonic-clonic seizure[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Monoparesis[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Multiple sclerosis[1]	2 (1.36%)	3 (0.89%)	5 (1.03%)	0 (0.00%)	0 (0.00%)	2 (0.66%)
Multiple sclerosis relapse[1]	0 (0.00%)	1 (0.30%)	5 (1.03%)	0 (0.00%)	0 (0.00%)	2 (0.66%)
Muscle spasticity[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myelitis transverse[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neuralgia[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nystagmus[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Optic neuritis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Paraparesis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Peroneal nerve palsy[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Presyncope[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Primary progressive multiple sclerosis[1]	1 (0.68%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Progressive multiple sclerosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.51%)	0 (0.00%)

Quadriparesis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sciatica[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Seizure[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	1 (0.51%)	0 (0.00%)
Status epilepticus[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Syncope[1]	0 (0.00%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Transient ischaemic attack[1]	0 (0.00%)	1 (0.30%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Trigeminal neuralgia[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Uhthoff's phenomenon[1]	2 (1.36%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
VIIth nerve paralysis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders						
Adjustment disorder[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aggression[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Depression[1]	0 (0.00%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	1 (0.51%)	0 (0.00%)
Depressive symptom[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mania[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mood swings[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Panic attack[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychotic disorder[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Suicidal ideation[1]	0 (0.00%)	1 (0.30%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders						
Acute kidney injury[1]	0 (0.00%)	1 (0.30%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bladder neck sclerosis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haematuria[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nephrogenic diabetes insipidus[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Nephrolithiasis[1]	1 (0.68%)	2 (0.60%)	1 (0.21%)	0 (0.00%)	1 (0.51%)	0 (0.00%)
Neurogenic bladder[1]	1 (0.68%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Polyuria[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal failure[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urethral obstruction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.51%)	0 (0.00%)
Urinary incontinence[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary retention[1]	0 (0.00%)	2 (0.60%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders						
Adenomyosis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Adnexal torsion[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Benign prostatic hyperplasia[1]	0 (0.00%)	1 (0.30%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Breast mass[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Endometriosis[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Prostatitis[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Prostatomegaly[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders						
Asthma[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bronchopneumopathy[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dyspnoea[1]	0 (0.00%)	2 (0.60%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haemothorax[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasal obstruction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Pneumonia aspiration[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Pneumothorax[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary embolism[1]	1 (0.68%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	1 (0.33%)

Respiratory arrest[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Sleep apnoea syndrome[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders						
Actinic keratosis[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Alopecia[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Decubitus ulcer[1]	1 (0.68%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Jessner's lymphocytic infiltration[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lentigo[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Social circumstances						
Activities of daily living impaired[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Poor personal hygiene[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular disorders						
Aneurysm[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Arterial spasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Deep vein thrombosis[1]	1 (0.68%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Femoral artery occlusion[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypotension[1]	1 (0.68%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Orthostatic hypotension[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Peripheral venous disease[1]	0 (0.00%)	4 (1.19%)	2 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Raynaud's phenomenon[1]	0 (0.00%)	1 (0.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Venous thrombosis[1]	0 (0.00%)	0 (0.00%)	1 (0.21%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

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Other Adverse Events by System Organ Class

Source Vocabulary for Table Default	MedDRA 15.1
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Core: FTY720 1.25 mg N = 147	Core: FTY720 0.5 mg N = 336	Core: Placebo N = 487	Extension: FTY1.25-0.5 N = 74	Extension: FTY0.5-0.5 N = 196	Extension: Placebo-FTY0.5 N = 301
Total participants affected	132 (89.80%)	278 (82.74%)	406 (83.37%)	43 (58.11%)	70 (35.71%)	138 (45.85%)
Blood and lymphatic system disorders						
Lymphopenia[1]	13 (8.84%)	19 (5.65%)	0 (0.00%)	4 (5.41%)	7 (3.57%)	11 (3.65%)
Gastrointestinal disorders						
Abdominal pain upper[1]	3 (2.04%)	17 (5.06%)	12 (2.46%)	0 (0.00%)	1 (0.51%)	2 (0.66%)
Constipation[1]	10 (6.80%)	27 (8.04%)	35 (7.19%)	0 (0.00%)	2 (1.02%)	6 (1.99%)
Diarrhoea[1]	13 (8.84%)	15 (4.46%)	18 (3.70%)	1 (1.35%)	3 (1.53%)	1 (0.33%)
Nausea[1]	14 (9.52%)	21 (6.25%)	19 (3.90%)	2 (2.70%)	1 (0.51%)	4 (1.33%)
General disorders and administration site conditions						

Fatigue[1]	16 (10.88%)	24 (7.14%)	43 (8.83%)	0 (0.00%)	1 (0.51%)	9 (2.99%)
Gait disturbance[1]	10 (6.80%)	15 (4.46%)	24 (4.93%)	0 (0.00%)	1 (0.51%)	0 (0.00%)
Pyrexia[1]	8 (5.44%)	18 (5.36%)	20 (4.11%)	3 (4.05%)	0 (0.00%)	4 (1.33%)
Infections and infestations						
Bronchitis[1]	10 (6.80%)	16 (4.76%)	21 (4.31%)	3 (4.05%)	2 (1.02%)	1 (0.33%)
Cystitis[1]	10 (6.80%)	9 (2.68%)	17 (3.49%)	0 (0.00%)	0 (0.00%)	2 (0.66%)
Gastroenteritis[1]	10 (6.80%)	12 (3.57%)	22 (4.52%)	0 (0.00%)	3 (1.53%)	3 (1.00%)
Influenza[1]	14 (9.52%)	26 (7.74%)	43 (8.83%)	3 (4.05%)	4 (2.04%)	9 (2.99%)
Nasopharyngitis[1]	40 (27.21%)	78 (23.21%)	135 (27.72%)	9 (12.16%)	10 (5.10%)	23 (7.64%)
Upper respiratory tract infection[1]	21 (14.29%)	37 (11.01%)	57 (11.70%)	6 (8.11%)	6 (3.06%)	14 (4.65%)
Urinary tract infection[1]	21 (14.29%)	47 (13.99%)	75 (15.40%)	4 (5.41%)	11 (5.61%)	25 (8.31%)
Injury, poisoning and procedural complications						
Fall[1]	31 (21.09%)	47 (13.99%)	91 (18.69%)	6 (8.11%)	5 (2.55%)	13 (4.32%)
Investigations						
Alanine aminotransferase increased[1]	17 (11.56%)	39 (11.61%)	7 (1.44%)	0 (0.00%)	1 (0.51%)	6 (1.99%)
Blood cholesterol increased[1]	8 (5.44%)	15 (4.46%)	16 (3.29%)	0 (0.00%)	1 (0.51%)	3 (1.00%)
Gamma-glutamyltransferase increased[1]	19 (12.93%)	31 (9.23%)	3 (0.62%)	0 (0.00%)	3 (1.53%)	5 (1.66%)
Metabolism and nutrition disorders						
Hypercholesterolaemia[1]	10 (6.80%)	13 (3.87%)	19 (3.90%)	4 (5.41%)	4 (2.04%)	5 (1.66%)

Musculoskeletal and connective tissue disorders						
Arthralgia[1]	13 (8.84%)	30 (8.93%)	48 (9.86%)	3 (4.05%)	3 (1.53%)	8 (2.66%)
Back pain[1]	16 (10.88%)	36 (10.71%)	75 (15.40%)	5 (6.76%)	5 (2.55%)	10 (3.32%)
Pain in extremity[1]	9 (6.12%)	21 (6.25%)	35 (7.19%)	3 (4.05%)	3 (1.53%)	3 (1.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Melanocytic naevus[1]	21 (14.29%)	16 (4.76%)	31 (6.37%)	4 (5.41%)	3 (1.53%)	9 (2.99%)
Seborrhoeic keratosis[1]	10 (6.80%)	12 (3.57%)	14 (2.87%)	1 (1.35%)	3 (1.53%)	4 (1.33%)
Nervous system disorders						
Dizziness[1]	10 (6.80%)	19 (5.65%)	29 (5.95%)	2 (2.70%)	0 (0.00%)	2 (0.66%)
Headache[1]	28 (19.05%)	56 (16.67%)	77 (15.81%)	3 (4.05%)	3 (1.53%)	13 (4.32%)
Psychiatric disorders						
Depression[1]	11 (7.48%)	15 (4.46%)	37 (7.60%)	2 (2.70%)	2 (1.02%)	4 (1.33%)
Insomnia[1]	8 (5.44%)	12 (3.57%)	29 (5.95%)	1 (1.35%)	4 (2.04%)	7 (2.33%)
Respiratory, thoracic and mediastinal disorders						
Cough[1]	8 (5.44%)	28 (8.33%)	34 (6.98%)	2 (2.70%)	1 (0.51%)	4 (1.33%)
Dyspnoea[1]	8 (5.44%)	14 (4.17%)	16 (3.29%)	0 (0.00%)	0 (0.00%)	1 (0.33%)
Skin and subcutaneous tissue disorders						
Eczema[1]	8 (5.44%)	15 (4.46%)	19 (3.90%)	2 (2.70%)	1 (0.51%)	6 (1.99%)
Vascular disorders						
Hypertension[1]	23 (15.65%)	43 (12.80%)	28 (5.75%)	2 (2.70%)	5 (2.55%)	18 (5.98%)

1 MedDRA 18.0

Other Relevant Findings

NA

Conclusion:

The primary and key secondary objectives for this study were not met (core study). Fingolimod 0.5 mg demonstrated no statistically significant difference compared with placebo in the time to 3-month confirmed disability progression based on the composite endpoint or based on the individual components. The effect of fingolimod on lesion activity (Gd-enhancing and new/enlarging T2 lesions) was consistent with that seen in RMS studies, although relatively fewer PPMS patients had lesion activity (Gd-enhancing or new/newly enlarging T2 lesions). Results of these analyses for time to 6-month confirmed disability progression or 3-month confirmed disability sustained until end-of-study were consistent with those for time to 3-month confirmed disability progression for the composite endpoint. Fingolimod was generally well-tolerated, with the majority of fingolimod-treated patients completing the study on treatment; discontinuation from study was comparable in the fingolimod 0.5 mg, and placebo (all) groups. The overall incidence of AEs by proportion of patients was generally consistent with the known safety profile of fingolimod showing varying degrees of the same imbalances seen in prior studies in RMS patients (e.g. lymphopenia, hypertension, bradycardia, herpes zoster). Consistent with previous clinical experience, a transient decrease in heart rate and an effect on atrioventricular conduction upon treatment initiation was observed in this study. The majority of cardiac events (including bradycardia and first degree AV block) occurred during the first dose administration, were asymptomatic, did not require treatment, and patients recovered within 24 hours.

The open-label extension study was terminated after the results of the core study became available showing that the study did not meet its primary endpoint which was defined as confirmed disability progression in this population. In the extension study the overall incidence of AEs was consistent with the known safety profile of fingolimod in prior relapsing remitting MS studies and in line with the safety profile seen in the PPMS core trial. Consistent with previous clinical

experience, a transient decrease in heart rate and an effect on AV conduction upon treatment initiation were observed in this study for those patients who switched from placebo in the core study to fingolimod 0.5 mg in the extension study. In conclusion, the data of this open-label extension study were in line with fingolimod safety profile as seen in the core trial.

Date of Clinical Trial Report

Core Study Report: 07-Jul-2015

Extension Study Report: 09-Mar- 2016