Sponsor

Novartis

Generic Drug Name

Fingolimod

Trial Indication(s)

Multiple sclerosis

Protocol Number

CFTY720D2403

Protocol Title

Long-term, prospective, multinational, parallel-cohort study monitoring safety in patients with multiple sclerosis newly started on fingolimod once daily or treated with another approved disease-modifying therapy

Clinical Trial Phase

Phase IV

Phase of Drug Development

Approval

Study Start/End Dates

01 Aug 2011 to 10 Jul 2020

Reason for Termination

The study was terminated in consultation with US FDA due to slower enrollment rate and higher than expected discontinuation rate, with assurance that along with US PASSAGE individual study report, pooled PASSAGE study results would also be submitted.

Study Design/Methodology

This was a multi-national, multi-center, long-term, prospective, parallel-cohort PASS study to monitor and further describe the long-term safety of fingolimod. To address the comments and requests from FDA and EMA, analogous studies (CFTY720D2406 and CFTY720D2409) were created. This study (CFTY720D2403) primarily addresses FDA requests, while studies CFTY720D2406 and CFTY720D2409 primarily address EMA requests, since those are being conducted and planned in mainly in Europe countries.
As studies CFTY720D2406 and CFTY720D2409 will collect similar data, data from all three studies CFTY720D2403, CFTY720D2409 and CFTY720D2406 will be pooled in order to gain more power to detect differences in the incidence of selected safety outcomes between the fingolimod cohort and other DMT cohort.

At the study entry, MS patients eligible for participation in this study received either fingolimod (fingolimod cohort) or another approved DMT eg, IFN, glatiramer acetate, teriflunomide (parallel-cohort). Treatment decision was independent of the study participation. Patients had up to 4 mandatory visits as part of this study (Baseline, Month 3, visit in case of change in MS therapy, and End of study) in order to perform the few mandatory evaluations requested by the HA (dermatological and ophthalmic assessments). All evaluations were performed by the treating physicians according to the local prescribing information and in accordance with the standard of care.

During the course of the study, patients were allowed to switch to other approved DMT (i.e, from or to fingolimod or other DMT) while remaining in the study. Patients switching to cytotoxic agents (eg, mitoxantrone), natalizumab, an unapproved DMT, or a DMT that has been approved for marketing during the conduct of the study but not explicitly permitted for inclusion in the study by the US FDA had to discontinue from the study. The discontinued patients were expected to have their end of study visit approximately 6 months after the MS treatment switch.

Patients enrolled in this study had the option to complete PRO questionnaires, as part of an optional PRO sub-study under conditions of routine medical practice. The purpose of collecting these PRO data is to evaluate outcomes that are important to patients which include disability, health-related quality of life, productivity, and treatment satisfaction and preference. The PRO sub-study helped describe the

effect of treatment on long-term outcomes under conditions of routine medical practice which is important to understand the real-world value of fingolimod treatment.

Centers

The study was conducted in 257 sites in 6 countries (Argentina, Australia, Canada, Chile, Mexico, and United States of America).

Objectives:

Primary objective(s)

- To further explore the overall safety profile of fingolimod over the long term, as measured by adverse events and vital signs in patients with relapsing MS under conditions of routine medical practice.

Secondary objective(s)

- To investigate the incidence of selected safety outcomes including, but not limited to, cardiac and vascular events (e.g. stroke, myocardial infarction, angina pectoris and peripheral vascular disease, second and third degree AV block, hypertension), symptomatic bradyarrhythmias on treatment initiation or on re-starting after an interruption in fingolimod therapy, eye events (e.g. macular edema), liver events, infections, pulmonary events, malignancies (e.g. lymphoma), seizures, atypical MS relapses, other atypical severe neurological events and sudden/unexplained death in the target population.
- To put the fingolimod results on selected safety outcomes into context by using an internal parallel cohort whenever applicable or external benchmarking databases for less frequent events.
- To observe long-term MS disease course in fingolimod treated patients, as measured by relapses and EDSS changes.

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

- Fingolimod 0.5 mg tablet /day
- Other Approved Multiple Sclerosis disease-modifying therapy (DMT)

Statistical Methods

To make meaningful comparisons between fingolimod and the other DMT cohort, and to assess long-term safety of fingolimod, the data were analyzed using 2 different approaches:

- Group G Safety set: Includes patients enrolled in the study and assigned to fingolimod or the other DMT cohort; data were summarized by the initial cohort. In this group, data from all patients were evaluated as long as they were treated by their cohort treatment (i.e. fingolimod for fingolimod cohort patients and other DMT for other DMT cohort patients). Of note, patients who switched within the other DMT cohort (e.g. for failure or intolerance) were still displayed as "other DMT" unless they switched to fingolimod. Unless otherwise specified, effectiveness analyses in Group G only use data collected on the first DMT corresponding to cohort assignment (i.e. data from 1 single drug).
- Group F Safety set: Includes patients who were exposed to fingolimod at any time during the study; data were summarized by the fingolimod group. This group looks at the long-term safety profile of patients receiving fingolimod, considering all the data for any patient who received at least 1 dose of fingolimod irrespective of the cohort (excluding data after switch to another DMT). This approach ensures that the safety data for fingolimod treatment are presented for the entire duration of the study.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- MS patients who as part of their routine clinical care and according to the locally approved label are either:

- Starting fingolimod at the time of study entry.
- Starting, or have started within 6 months prior to study entry, another approved MS DMT.

- Patients or legal representative of the patient must provide written informed consent.

  At the study entry, patients taking fingolimod constituted the fingolimod cohort while patients on the other DMTs constituted the parallel-cohort. The FDA was consulted before including any DMT newly approved during the course of the study and patients on such DMTs are only included in the study after explicit agreement to allow the use of the new DMT is received from the FDA.

Exclusion criteria

- Patients previously or currently treated with cytotoxic agents (eg, mitoxantrone, cladribine, alemtuzumab) or natalizumab.
- Patients treated with any investigational drug unless it is as part of a Novartis Sponsored MS study lasting less than 1 month.

Participant Flow Table

Table 10-1 Patient disposition, Group G, Enrolled set

Disposition Reason	FTY720 N=2243 n (%)	Other DMTs N=1223 n (%)
Completed study	1 (<0.1)	0
Prematurely discontinued from study	2212 (98.6)	1160 (94.8)
Administrative problems	438 (19.5)	268 (21.9)
Death	8 (0.4)	12 (1.0)
Lost to follow-up	229 (10.2)	133 (10.9)
New therapy for study indication/start of forbidden medication	192 (8.6)	123 (10.1)
Study terminated by Sponsor	986 (44.0)	395 (32.3)
Subject withdrew consent	359 (16.0)	229 (18.7)
Missing study completion page	30 (1.3)	63 (5.2)

The primary reason for premature discontinuation from the study completion page is presented.
Percentage (%) is calculated using the Enrolled set as the denominator.
The reasons for discontinuation are presented in alphabetical order.
Completed: completed around 5 years after last patient was enrolled.
Study terminated by Sponsor after consultation with US-FDA.

One patient (<0.1%) in the fingolimod cohort, reported as completed the study, was a data entry error at a closed site.

Enrolled set: All patients who were enrolled into a study and were categorized to a cohort at the start of the study, excluding patients with a protocol deviation severity code of 8 (8=exclude from all analyses).

Table 10-2 Patient disposition, Group F, Safety set

Disposition Reason	FTY720 N=2189 n (%)
Completed study	1 (<0.1)
Prematurely discontinued from study	2162 (98.8)
Administrative problems	399 (18.2)
Death	8 (0.4)
Lost to follow-up	220 (10.1)
New therapy for study indication/start of forbidden medication	188 (8.6)
Study terminated by Sponsor	1027 (46.9)
Subject withdrew consent	320 (14.6)
Missing study completion page	26 (1.2)

The primary reason for premature discontinuation from the study completion page is presented.
Percentage (%) is calculated using the Safety set as the denominator.
The reasons for discontinuation are presented in alphabetical order.
Completed: completed around 5 years after last patient was enrolled.
Study terminated by Sponsor after consultation with US-FDA.

Although the table shows that the study was completed by one patient (< 0.1%), this was due to data entry error at closed sites.
Safety set: All enrolled patients who received at least one fingolimod dose in the study.

Baseline Characteristics

Table 10-5 Demographics, Group G, Enrolled set

Demographic variable Category/statistic	FTY720 N=2243	Other DMTs N=1223
Age (year)		
n (%)	2243 (100)	1223 (100)
Mean	42.2	44.9
SD	11.54	12.03
Minimum	18	16
Median	42.0	45.0
Maximum	82	78
Age group (years) n (%)		
< 18	0	4 (0.3)
18 – 40	1043 (46.5)	433 (35.4)
41 – 64	1141 (50.9)	714 (58.4)
≥ 65	59 (2.6)	72 (5.9)
Sex n (%)		
Male	514 (22.9)	318 (26.0)
Female	1729 (77.1)	905 (74.0)
Race n (%)		
Asian	9 (0.4)	9 (0.7)
Black	285 (12.7)	185 (15.1)
Caucasian	1777 (79.2)	944 (77.2)
Native American	5 (0.2)	7 (0.6)
Pacific Islander	3 (0.1)	1 (0.1)
Other	149 (6.6)	76 (6.2)
Missing	15 (0.7)	1 (0.1)
Weight (kg)		
n (%)	1818 (81.1)	1026 (83.9)
Mean	80.46	82.85
SD	20.693	22.071
Minimum	40.8	44.0
Median	77.10	80.30

Demographic variable Category/statistic	FTY720 N=2243	Other DMTs N=1223
Maximum	161.9	211.8
Height (cm)		
n (%)	1809 (80.7)	1001 (81.8)
Mean	166.99	167.16
SD	9.262	9.514
Minimum	128.0	126.0
Median	165.70	166.00
Maximum	200.7	198.1
BMI (kg/m**2)		
n (%)	1770 (78.9)	996 (81.4)
Mean	28.83	29.69
SD	7.098	7.447
Minimum	14.3	16.8
Median	27.51	28.61
Maximum	63.2	68.9
Geographic region n (%)		
North America	1981 (88.3)	1162 (95.0)
South America	121 (5.4)	41 (3.4)
Asia Pacific	141 (6.3)	20 (1.6)
Country n (%)		
USA	1867 (83.2)	1061 (86.8)
Australia	141 (6.3)	20 (1.6)
Canada	114 (5.1)	101 (8.3)
Argentina	67 (3.0)	30 (2.5)
Mexico	31 (1.4)	4 (0.3)
Chile	23 (1.0)	7 (0.6)

n = Number of patients meeting the criterion (for categorical variables) or the number of patients with a measurement (for continuous variables).
Age is calculated based on the date of first dose of initial cohort treatment. For patients who never received a dose of initial cohort treatment, Visit 1 date is used.
Baseline data reported are those prior to the first dose of initial cohort treatment in the study. For patients who never received a dose of initial cohort treatment, data up to and including Visit 1 is used.
The percentages for categorical variables are calculated using the Enrolled set as the denominator.

Table 10-6 Demographics, Group F, Safety set

Demographic variable Category/statistic	FTY720 N=2189
Age (year)	
n (%)	2189 (100)
Mean	42.2
SD	11.54
Minimum	18
Median	42.0
Maximum	82
Age group (years) n (%)	
<18	0
18 – 40	1025 (46.8)
41 – 64	1105 (50.5)
≥ 65	59 (2.7)
Sex n (%)	
Male	501 (22.9)
Female	1688 (77.1)
Race n (%)	
Asian	9 (0.4)
Black	266 (12.2)
Caucasian	1740 (79.5)
Native American	7 (0.3)
Pacific Islander	3 (0.1)
Other	149 (6.8)
Missing	15 (0.7)
Weight (kg)	
n (%)	1801 (82.3)
Mean	80.47
SD	20.837
Minimum	40.8
Median	77.10
Maximum	161.9
Height (cm)	
n (%)	1789 (81.7)
Mean	167.01
SD	9.238
Minimum	128.0
Median	166.00
Maximum	200.7
BMI (kg/m**2)	
n (%)	1752 (80.0)
Mean	28.84
SD	7.137
Minimum	14.3
Median	27.50
Maximum	63.2

Demographic variable Category/statistic	FTY720 N=2189
Geographic region n (%)	
North America	1917 (87.6)
South America	128 (5.8)
Asia Pacific	144 (6.6)
Country n (%)	
USA	1799 (82.2)
Australia	144 (6.6)
Canada	118 (5.4)
Argentina	71 (3.2)
Mexico	33 (1.5)
Chile	24 (1.1)

n = Number of patients meeting the criterion (for categorical variables) or the number of patients with a measurement (for continuous variables).
Age is calculated based on the date of first FTY720 dose in the study.
Weight is based on last measurement prior to first FTY720 dose in the study.
The percentages for categorical variables are calculated using the Safety set as the denominator.

Primary Outcome Result(s)

Overall safety profile of fingolimod over the long term, as measured by adverse events and vital signs:

Table 10-18 **IR of AEs per 100 PTY by primary SOC, PT, and initial cohort treatment with cut-off 0.5 per 100 PTY by any cohort, Group G, Safety set**

Primary system organ class	FTY720 N=2112		Other DMTs N=1138		Incidence rate ratio
Preferred term	n (%)	IR (95% CI)	n (%)	IR (95% CI)	IRR (95% CI)
-Any primary system organ class					
-Total	1747 (82.7)	163.3 (155.77; 171.18)	918 (80.7)	160.7 (150.50; 171.47)	1.02 (0.94; 1.10)
BLOOD AND LYMPHATIC SY STEM DISORDERS					
-Total	196 (9.3)	4.4 (3.77; 5.01)	79 (6.9)	2.7 (2.13; 3.35)	1.62 (1.24; 2.13)
LYMPHOPENIA	130 (6.2)	2.8 (2.35; 3.33)	33 (2.9)	1.1 (0.75; 1.53)	2.59 (1.75; 3.91)

Primary system organ class Preferred term	FTY720 N=2112 n (%)	IR (95% CI)	Other DMTs N=1138 n (%)	IR (95% CI)	Incidence rate ratio IRR (95% CI)
LEUKOPENIA	34 (1.6)	0.7 (0.49; 0.98)	9 (0.8)	0.3 (0.13; 0.55)	2.45 (1.15; 5.80)
CARDIAC DISORDERS					
-Total	225 (10.7)	5.1 (4.46; 5.81)	54 (4.7)	1.8 (1.35; 2.34)	2.85 (2.11; 3.91)
BRADYCARDIA	52 (2.5)	1.1 (0.81; 1.43)	3 (0.3)	0.1 (0.02; 0.28)	11.38 (3.69; 56.98)
PALPITATIONS	48 (2.3)	1.0 (0.74; 1.32)	20 (1.8)	0.6 (0.40; 1.00)	1.54 (0.90; 2.74)
SINUS BRADYCARDIA	48 (2.3)	1.0 (0.74; 1.33)	1 (0.1)	<.1 (<.01; 0.18)	31.48 (5.39; 1268.8)
EAR AND LABYRINTH DISORDERS					
-Total	145 (6.9)	3.2 (2.66; 3.71)	96 (8.4)	3.3 (2.65; 3.99)	0.96 (0.74; 1.26)
VERTIGO	87 (4.1)	1.8 (1.48; 2.27)	49 (4.3)	1.6 (1.20; 2.14)	1.14 (0.79; 1.65)
TINNITUS	20 (0.9)	0.4 (0.25; 0.63)	18 (1.6)	0.6 (0.34; 0.92)	0.71 (0.35; 1.42)
ENDOCRINE DISORDERS					
-Total	22 (1.0)	0.5 (0.28; 0.69)	18 (1.6)	0.6 (0.34; 0.92)	0.78 (0.40; 1.55)
EYE DISORDERS					
-Total	386 (18.3)	9.5 (8.55; 10.47)	193 (17.0)	7.2 (6.18; 8.24)	1.32 (1.11; 1.58)
VISION BLURRED	118 (5.6)	2.5 (2.10; 3.04)	69 (6.1)	2.3 (1.80; 2.93)	1.10 (0.81; 1.50)
EYE PAIN	59 (2.8)	1.2 (0.94; 1.59)	21 (1.8)	0.7 (0.42; 1.04)	1.82 (1.09; 3.15)
DRY EYE	28 (1.3)	0.6 (0.39; 0.84)	12 (1.1)	0.4 (0.20; 0.67)	1.51 (0.74; 3.25)
VISUAL IMPAIRMENT	28 (1.3)	0.6 (0.38; 0.84)	23 (2.0)	0.7 (0.47; 1.11)	0.78 (0.43; 1.42)
DIPLOPIA	26 (1.2)	0.5 (0.35; 0.78)	23 (2.0)	0.7 (0.47; 1.12)	0.72 (0.39; 1.32)
GASTROINTESTINAL DISORDERS					
-Total	449 (21.3)	11.3 (10.24; 12.34)	353 (31.0)	15.8 (14.18; 17.52)	0.71 (0.62; 0.82)
NAUSEA	141 (6.7)	3.1 (2.57; 3.61)	101 (8.9)	3.5 (2.84; 4.23)	0.88 (0.67; 1.14)
DIARRHOEA	89 (4.2)	1.9 (1.51; 2.32)	93 (8.2)	3.2 (2.57; 3.90)	0.59 (0.44; 0.80)
CONSTIPATION	73 (3.5)	1.5 (1.20; 1.93)	53 (4.7)	1.8 (1.32; 2.31)	0.87 (0.60; 1.26)
VOMITING	49 (2.3)	1.0 (0.76; 1.35)	51 (4.5)	1.7 (1.26; 2.22)	0.60 (0.40; 0.91)
ABDOMINAL PAIN	40 (1.9)	0.8 (0.59; 1.13)	36 (3.2)	1.2 (0.83; 1.63)	0.71 (0.44; 1.14)
GASTROOESOPHAGEAL REFLUX DISEASE	37 (1.8)	0.8 (0.54; 1.06)	26 (2.3)	0.8 (0.55; 1.24)	0.91 (0.54; 1.56)
DYSPHAGIA	27 (1.3)	0.6 (0.37; 0.81)	26 (2.3)	0.8 (0.55; 1.23)	0.66 (0.37; 1.18)
ABDOMINAL PAIN UPPER	21 (1.0)	0.4 (0.27; 0.66)	22 (1.9)	0.7 (0.44; 1.07)	0.61 (0.32; 1.16)
ABDOMINAL DISCOMFORT	17 (0.8)	0.3 (0.20; 0.56)	29 (2.5)	0.9 (0.63; 1.36)	0.37 (0.19; 0.69)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
-Total	588 (27.8)	15.8 (14.58; 17.17)	440 (38.7)	21.6 (19.60; 23.68)	0.73 (0.65; 0.83)
FATIGUE	366 (17.3)	8.8 (7.96; 9.80)	223 (19.6)	8.5 (7.43; 9.71)	1.04 (0.88; 1.23)
GAIT DISTURBANCE	89 (4.2)	1.9 (1.51; 2.31)	80 (7.0)	2.7 (2.14; 3.36)	0.69 (0.51; 0.95)
ASTHENIA	49 (2.3)	1.0 (0.76; 1.35)	39 (3.4)	1.3 (0.90; 1.74)	0.81 (0.52; 1.26)
PAIN	35 (1.7)	0.7 (0.50; 1.00)	35 (3.1)	1.1 (0.79; 1.58)	0.63 (0.38; 1.04)
NON-CARDIAC CHEST PAIN	30 (1.4)	0.6 (0.42; 0.88)	20 (1.8)	0.6 (0.40; 1.00)	0.96 (0.53; 1.78)
OEDEMA PERIPHERAL	27 (1.3)	0.6 (0.37; 0.81)	21 (1.8)	0.7 (0.42; 1.04)	0.82 (0.44; 1.52)
CHEST DISCOMFORT	26 (1.2)	0.5 (0.35; 0.79)	23 (2.0)	0.7 (0.47; 1.12)	0.72 (0.39; 1.32)
TEMPERATURE INTOLERANCE	25 (1.2)	0.5 (0.33; 0.76)	10 (0.9)	0.3 (0.15; 0.59)	1.61 (0.74; 3.75)
PERIPHERAL SWELLING	23 (1.1)	0.5 (0.30; 0.71)	23 (2.0)	0.7 (0.47; 1.12)	0.63 (0.34; 1.18)
PYREXIA	21 (1.0)	0.4 (0.27; 0.66)	28 (2.5)	0.9 (0.61; 1.32)	0.47 (0.26; 0.87)
CHILLS	15 (0.7)	0.3 (0.17; 0.51)	20 (1.8)	0.6 (0.40; 1.00)	0.47 (0.23; 0.97)
INFLUENZA LIKE ILLNESS	13 (0.6)	0.3 (0.14; 0.46)	38 (3.3)	1.2 (0.88; 1.71)	0.21 (0.10; 0.41)
INJECTION SITE ERYTHEMA	0	0 (0; 0.08)	23 (2.0)	0.7 (0.47; 1.12)	
INJECTION SITE PAIN	0	0 (0; 0.08)	26 (2.3)	0.8 (0.55; 1.24)	
INJECTION SITE PRURITUS	0	0 (0; 0.08)	17 (1.5)	0.5 (0.32; 0.88)	
INJECTION SITE REACTION	0	0 (0; 0.08)	36 (3.2)	1.2 (0.83; 1.64)	
HEPATOBILIARY DISORDERS					
-Total	40 (1.9)	0.8 (0.59; 1.12)	19 (1.7)	0.6 (0.37; 0.96)	1.34 (0.76; 2.46)
IMMUNE SYSTEM DISORDERS					
-Total	33 (1.6)	0.7 (0.47; 0.96)	28 (2.5)	0.9 (0.61; 1.32)	0.75 (0.44; 1.29)
INFECTIONS AND INFESTATIONS					
-Total	649 (30.7)	18.4 (17.03; 19.90)	362 (31.8)	16.3 (14.66; 18.07)	1.13 (0.99; 1.29)
URINARY TRACT INFECTION	139 (6.6)	3.0 (2.53; 3.55)	78 (6.9)	2.6 (2.07; 3.27)	1.15 (0.86; 1.54)
UPPER RESPIRATORY TRACT INFECTION	119 (5.6)	2.6 (2.13; 3.07)	78 (6.9)	2.7 (2.10; 3.31)	0.97 (0.72; 1.31)
SINUSITIS	83 (3.9)	1.8 (1.40; 2.18)	50 (4.4)	1.7 (1.23; 2.19)	1.06 (0.74; 1.53)
NASOPHARYNGITIS	79 (3.7)	1.7 (1.33; 2.09)	32 (2.8)	1.1 (0.72; 1.48)	1.60 (1.05; 2.49)
BRONCHITIS	53 (2.5)	1.1 (0.83; 1.45)	36 (3.2)	1.2 (0.82; 1.63)	0.94 (0.61; 1.48)
HERPES ZOSTER	52 (2.5)	1.1 (0.81; 1.43)	23 (2.0)	0.7 (0.47; 1.12)	1.46 (0.88; 2.50)

Primary system organ class Preferred term	FTY720 N=2112 n (%)	IR (95% CI)	Other DMTs N=1138 n (%)	IR (95% CI)	Incidence rate ratio IRR (95% CI)
INFLUENZA	44 (2.1)	0.9 (0.66; 1.23)	23 (2.0)	0.7 (0.47; 1.12)	1.23 (0.73; 2.13)
PNEUMONIA	35 (1.7)	0.7 (0.50; 1.00)	15 (1.3)	0.5 (0.27; 0.80)	1.50 (0.80; 2.95)
CELLULITIS	13 (0.6)	0.3 (0.14; 0.46)	18 (1.6)	0.6 (0.34; 0.92)	0.46 (0.21; 0.99)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS					
-Total	263 (12.5)	6.0 (5.32; 6.80)	223 (19.6)	8.8 (7.64; 9.98)	0.69 (0.57; 0.83)
FALL	115 (5.4)	2.5 (2.03; 2.95)	97 (8.5)	3.3 (2.71; 4.08)	0.73 (0.56; 0.97)
CONTUSION	25 (1.2)	0.5 (0.33; 0.76)	21 (1.8)	0.7 (0.42; 1.04)	0.76 (0.41; 1.42)
INVESTIGATIONS					
-Total	457 (21.6)	11.5 (10.45; 12.58)	198 (17.4)	7.4 (6.44; 8.55)	1.54 (1.30; 1.83)
LYMPHOCYTE COUNT DECREASED	138 (6.5)	3.0 (2.52; 3.54)	32 (2.8)	1.0 (0.71; 1.47)	2.89 (1.95; 4.38)
ALANINE AMINOTRANSFERASE INCREASED	56 (2.7)	1.2 (0.88; 1.51)	15 (1.3)	0.5 (0.27; 0.80)	2.42 (1.35; 4.60)
WEIGHT INCREASED	44 (2.1)	0.9 (0.66; 1.22)	36 (3.2)	1.2 (0.83; 1.64)	0.77 (0.48; 1.23)
WHITE BLOOD CELL COUNT DECREASED	43 (2.0)	0.9 (0.65; 1.20)	10 (0.9)	0.3 (0.15; 0.59)	2.78 (1.38; 6.21)
HEPATIC ENZYME INCREASED	37 (1.8)	0.8 (0.54; 1.06)	9 (0.8)	0.3 (0.13; 0.55)	2.66 (1.26; 6.27)
WEIGHT DECREASED	36 (1.7)	0.7 (0.52; 1.03)	33 (2.9)	1.1 (0.74; 1.52)	0.69 (0.42; 1.14)
ASPARTATE AMINOTRANSFERASE INCREASED	29 (1.4)	0.6 (0.40; 0.86)	9 (0.8)	0.3 (0.13; 0.55)	2.07 (0.95; 4.97)
BLOOD PRESSURE INCREASED	28 (1.3)	0.6 (0.38; 0.84)	10 (0.9)	0.3 (0.15; 0.59)	1.81 (0.85; 4.18)
LIVER FUNCTION TEST INCREASED	26 (1.2)	0.5 (0.35; 0.78)	11 (1.0)	0.4 (0.18; 0.63)	1.52 (0.72; 3.40)
METABOLISM AND NUTRITION DISORDERS					
-Total	160 (7.6)	3.5 (2.98; 4.09)	124 (10.9)	4.4 (3.64; 5.22)	0.80 (0.63; 1.02)
VITAMIN D DEFICIENCY	52 (2.5)	1.1 (0.81; 1.42)	50 (4.4)	1.7 (1.24; 2.20)	0.65 (0.43; 0.98)
DECREASED APPETITE	26 (1.2)	0.5 (0.35; 0.78)	15 (1.3)	0.5 (0.27; 0.79)	1.11 (0.57; 2.26)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS					
-Total	663 (31.4)	18.8 (17.35; 20.23)	445 (39.1)	22.5 (20.41; 24.64)	0.84 (0.74; 0.94)
PAIN IN EXTREMITY	168 (8.0)	3.7 (3.14; 4.28)	139 (12.2)	5.0 (4.17; 5.86)	0.74 (0.59; 0.93)
MUSCULAR WEAKNESS	148 (7.0)	3.2 (2.71; 3.76)	119 (10.5)	4.1 (3.41; 4.92)	0.78 (0.61; 1.00)
MUSCLE SPASMS	142 (6.7)	3.1 (2.59; 3.62)	103 (9.1)	3.6 (2.90; 4.31)	0.86 (0.67; 1.13)
ARTHRALGIA	136 (6.4)	2.9 (2.46; 3.47)	83 (7.3)	2.9 (2.27; 3.54)	1.03 (0.78; 1.37)
BACK PAIN	133 (6.3)	2.9 (2.40; 3.40)	101 (8.9)	3.5 (2.85; 4.25)	0.82 (0.63; 1.08)
NECK PAIN	54 (2.6)	1.1 (0.84; 1.46)	37 (3.3)	1.2 (0.86; 1.68)	0.92 (0.59; 1.44)
MUSCULOSKELETAL PAIN	39 (1.8)	0.8 (0.57; 1.10)	38 (3.3)	1.2 (0.88; 1.72)	0.65 (0.40; 1.04)
MUSCULOSKELETAL STIFFNESS	38 (1.8)	0.8 (0.56; 1.08)	26 (2.3)	0.8 (0.55; 1.24)	0.93 (0.55; 1.60)
MUSCULOSKELETAL CHEST PAIN	25 (1.2)	0.5 (0.33; 0.76)	13 (1.1)	0.4 (0.22; 0.71)	1.24 (0.61; 2.64)
MYALGIA	21 (1.0)	0.4 (0.27; 0.66)	17 (1.5)	0.5 (0.32; 0.88)	0.79 (0.39; 1.59)
SPINAL OSTEOARTHRITIS	11 (0.5)	0.2 (0.11; 0.40)	16 (1.4)	0.5 (0.29; 0.84)	0.44 (0.18; 1.01)
OSTEOARTHRITIS	10 (0.5)	0.2 (0.10; 0.38)	16 (1.4)	0.5 (0.29; 0.84)	0.40 (0.16; 0.93)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)					
-Total	318 (15.1)	7.3 (6.55; 8.19)	243 (21.4)	10.0 (8.75; 11.29)	0.74 (0.62; 0.87)
MELANOCYTIC NAEVUS	175 (8.3)	3.8 (3.25; 4.40)	144 (12.7)	5.3 (4.50; 6.29)	0.71 (0.57; 0.89)
SEBORRHOEIC KERATOSIS	108 (5.1)	2.3 (1.87; 2.75)	72 (6.3)	2.5 (1.92; 3.09)	0.93 (0.68; 1.27)
HAEMANGIOMA OF SKIN	48 (2.3)	1.0 (0.73; 1.32)	46 (4.0)	1.5 (1.13; 2.05)	0.65 (0.42; 0.99)
BASAL CELL CARCINOMA	26 (1.2)	0.5 (0.35; 0.79)	11 (1.0)	0.4 (0.18; 0.63)	1.52 (0.73; 3.41)
SKIN PAPILLOMA	20 (0.9)	0.4 (0.25; 0.64)	16 (1.4)	0.5 (0.30; 0.84)	0.80 (0.39; 1.65)
FIBROUS HISTIOCYTOMA	19 (0.9)	0.4 (0.24; 0.61)	27 (2.4)	0.9 (0.58; 1.28)	0.44 (0.23; 0.83)
HAEMANGIOMA	16 (0.8)	0.3 (0.19; 0.53)	19 (1.7)	0.6 (0.37; 0.96)	0.53 (0.26; 1.10)
NERVOUS SYSTEM DISORDERS					
-Total	955 (45.2)	32.9 (30.85; 35.06)	553 (48.6)	30.9 (28.36; 33.56)	1.07 (0.96; 1.19)
HEADACHE	292 (13.8)	6.7 (6.00; 7.57)	122 (10.7)	4.2 (3.52; 5.06)	1.59 (1.29; 1.98)
HYPOAESTHESIA	168 (8.0)	3.7 (3.13; 4.26)	143 (12.6)	5.1 (4.27; 5.97)	0.72 (0.57; 0.91)
PARAESTHESIA	156 (7.4)	3.4 (2.90; 3.99)	130 (11.4)	4.6 (3.85; 5.47)	0.74 (0.58; 0.94)
DIZZINESS	98 (4.6)	2.1 (1.68; 2.53)	43 (3.8)	1.4 (1.02; 1.91)	1.47 (1.01; 2.15)
MIGRAINE	98 (4.6)	2.1 (1.69; 2.54)	40 (3.5)	1.3 (0.94; 1.79)	1.59 (1.09; 2.36)
DIZZINESS POSTURAL	67 (3.2)	1.4 (1.09; 1.79)	27 (2.4)	0.9 (0.58; 1.28)	1.60 (1.01; 2.60)
TREMOR	56 (2.7)	1.2 (0.88; 1.52)	38 (3.3)	1.2 (0.88; 1.70)	0.94 (0.61; 1.46)

Primary system organ class Preferred term	FTY720 N=2112 n (%)	IR (95% CI)	Other DMTs N=1138 n (%)	IR (95% CI)	Incidence rate ratio IRR (95% CI)
BALANCE DISORDER	54 (2.6)	1.1 (0.85; 1.47)	52 (4.6)	1.7 (1.28; 2.24)	0.66 (0.44; 0.98)
MEMORY IMPAIRMENT	54 (2.6)	1.1 (0.85; 1.47)	32 (2.8)	1.0 (0.72; 1.48)	1.08 (0.69; 1.73)
COGNITIVE DISORDER	48 (2.3)	1.0 (0.74; 1.32)	48 (4.2)	1.6 (1.17; 2.09)	0.63 (0.41; 0.96)
MUSCLE SPASTICITY	43 (2.0)	0.9 (0.65; 1.20)	38 (3.3)	1.2 (0.88; 1.71)	0.72 (0.45; 1.14)
NEURALGIA	35 (1.7)	0.7 (0.50; 1.01)	16 (1.4)	0.5 (0.29; 0.84)	1.40 (0.76; 2.72)
OPTIC NEURITIS	34 (1.6)	0.7 (0.49; 0.98)	28 (2.5)	0.9 (0.60; 1.31)	0.77 (0.46; 1.32)
DISTURBANCE IN ATTENTION	33 (1.6)	0.7 (0.47; 0.96)	15 (1.3)	0.5 (0.27; 0.80)	1.41 (0.75; 2.80)
MULTIPLE SCLEROSIS RELAPSE	32 (1.5)	0.7 (0.45; 0.93)	11 (1.0)	0.4 (0.18; 0.63)	1.87 (0.92; 4.12)
BURNING SENSATION	30 (1.4)	0.6 (0.42; 0.89)	24 (2.1)	0.8 (0.50; 1.16)	0.80 (0.45; 1.43)
AMNESIA	27 (1.3)	0.6 (0.37; 0.81)	35 (3.1)	1.1 (0.80; 1.59)	0.49 (0.28; 0.83)
RESTLESS LEGS SYNDROME	24 (1.1)	0.5 (0.32; 0.74)	18 (1.6)	0.6 (0.35; 0.92)	0.85 (0.44; 1.66)
CARPAL TUNNEL SYNDROME	19 (0.9)	0.4 (0.24; 0.61)	24 (2.1)	0.8 (0.50; 1.16)	0.50 (0.26; 0.96)
DYSARTHRIA	17 (0.8)	0.3 (0.20; 0.56)	18 (1.6)	0.6 (0.34; 0.91)	0.60 (0.29; 1.24)
PERONEAL NERVE PALSY	10 (0.5)	0.2 (0.10; 0.38)	16 (1.4)	0.5 (0.29; 0.84)	0.40 (0.16; 0.93)
NEUROPATHY PERIPHERAL	8 (0.4)	0.2 (0.07; 0.32)	17 (1.5)	0.5 (0.32; 0.87)	0.30 (0.11; 0.73)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS					
-Total	30 (1.4)	0.6 (0.42; 0.88)	18 (1.6)	0.6 (0.34; 0.92)	1.06 (0.57; 2.02)
PREGNANCY	24 (1.1)	0.5 (0.32; 0.73)	18 (1.6)	0.6 (0.34; 0.92)	0.85 (0.44; 1.66)
PSYCHIATRIC DISORDERS					
-Total	410 (19.4)	10.1 (9.12; 11.09)	248 (21.8)	9.6 (8.42; 10.84)	1.05 (0.90; 1.24)
DEPRESSION	154 (7.3)	3.4 (2.84; 3.93)	101 (8.9)	3.4 (2.80; 4.18)	0.98 (0.75; 1.27)
ANXIETY	122 (5.8)	2.6 (2.18; 3.14)	65 (5.7)	2.2 (1.67; 2.75)	1.22 (0.89; 1.67)
INSOMNIA	91 (4.3)	1.9 (1.56; 2.38)	59 (5.2)	2.0 (1.50; 2.53)	0.99 (0.70; 1.39)
RENAL AND URINARY DISORDERS					
-Total	217 (10.3)	4.9 (4.23; 5.54)	195 (17.1)	7.4 (6.36; 8.46)	0.66 (0.54; 0.80)
MICTURITION URGENCY	73 (3.5)	1.5 (1.21; 1.94)	57 (5.0)	1.9 (1.44; 2.47)	0.81 (0.56; 1.16)
URINARY INCONTINENCE	41 (1.9)	0.9 (0.61; 1.15)	43 (3.8)	1.4 (1.02; 1.91)	0.60 (0.38; 0.94)
POLLAKIURIA	34 (1.6)	0.7 (0.49; 0.99)	42 (3.7)	1.4 (1.00; 1.88)	0.51 (0.31; 0.82)
NEPHROLITHIASIS	20 (0.9)	0.4 (0.25; 0.64)	20 (1.8)	0.6 (0.39; 1.00)	0.64 (0.33; 1.25)
NEUROGENIC BLADDER	14 (0.7)	0.3 (0.16; 0.48)	16 (1.4)	0.5 (0.29; 0.84)	0.56 (0.25; 1.22)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS					
-Total	93 (4.4)	2.0 (1.59; 2.42)	58 (5.1)	1.9 (1.48; 2.52)	1.01 (0.72; 1.43)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
-Total	244 (11.6)	5.5 (4.83; 6.24)	143 (12.6)	5.1 (4.29; 6.00)	1.08 (0.88; 1.34)
DYSPNOEA	70 (3.3)	1.5 (1.14; 1.85)	30 (2.6)	1.0 (0.66; 1.40)	1.50 (0.96; 2.38)
COUGH	64 (3.0)	1.3 (1.04; 1.72)	31 (2.7)	1.0 (0.69; 1.43)	1.33 (0.85; 2.12)
OROPHARYNGEAL PAIN	33 (1.6)	0.7 (0.47; 0.96)	19 (1.7)	0.6 (0.37; 0.96)	1.11 (0.61; 2.06)
SLEEP APNOEA SYNDROME	13 (0.6)	0.3 (0.14; 0.46)	24 (2.1)	0.8 (0.50; 1.16)	0.34 (0.16; 0.70)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
-Total	424 (20.1)	10.5 (9.52; 11.55)	371 (32.6)	17.4 (15.68; 19.27)	0.60 (0.52; 0.70)
RASH	50 (2.4)	1.0 (0.77; 1.37)	40 (3.5)	1.3 (0.94; 1.79)	0.79 (0.51; 1.23)
SOLAR LENTIGO	49 (2.3)	1.0 (0.75; 1.34)	44 (3.9)	1.5 (1.06; 1.97)	0.69 (0.45; 1.07)
ALOPECIA	41 (1.9)	0.9 (0.61; 1.16)	60 (5.3)	2.0 (1.54; 2.59)	0.43 (0.28; 0.64)
ACNE	34 (1.6)	0.7 (0.49; 0.99)	17 (1.5)	0.6 (0.32; 0.88)	1.28 (0.69; 2.44)
PRURITUS	30 (1.4)	0.6 (0.42; 0.89)	41 (3.6)	1.4 (0.97; 1.84)	0.46 (0.28; 0.75)
ACTINIC KERATOSIS	29 (1.4)	0.6 (0.40; 0.86)	32 (2.8)	1.0 (0.71; 1.47)	0.57 (0.33; 0.98)
LENTIGO	29 (1.4)	0.6 (0.40; 0.86)	49 (4.3)	1.6 (1.22; 2.17)	0.36 (0.22; 0.59)
DRY SKIN	17 (0.8)	0.3 (0.20; 0.56)	16 (1.4)	0.5 (0.30; 0.84)	0.68 (0.32; 1.43)
VASCULAR DISORDERS					
-Total	156 (7.4)	3.4 (2.89; 3.98)	186 (16.3)	7.1 (6.11; 8.19)	0.48 (0.39; 0.60)
HYPERTENSION	91 (4.3)	1.9 (1.55; 2.37)	34 (3.0)	1.1 (0.77; 1.55)	1.73 (1.16; 2.65)
HOT FLUSH	16 (0.8)	0.3 (0.19; 0.53)	23 (2.0)	0.7 (0.47; 1.12)	0.44 (0.22; 0.87)
FLUSHING	10 (0.5)	0.2 (0.10; 0.38)	115 (10.1)	4.1 (3.38; 4.91)	0.05 (0.02; 0.10)

n refers to patients
Data as per Group G general safety rules are used.
Primary system organ classes and preferred terms with an occurrence of at least 0.5 per 100 patient years in any cohort are displayed.
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by frequency from highest to lowest in the FTY720 column.
A patient with multiple occurrences of an AE for a preferred term or primary system organ class is counted only once in each specific category.
Incidence rate: The number of patients who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
Incidence rate ratio: The incidence rate of the FTY720 cohort divided by the incidence rate of the Other DMT cohort for a particular AE term/category. It is only calculated if both incidence rates are >0.
MedDRA Version 22.1 has been used for the reporting of adverse events.

Table 10-44 Summary of patients with clinically notable vital signs, Group G, Safety set

		FTY720 N=2112		Other DMT N=1138	
Vital signs	**Notable criteria**	**m**	**n (%)**	**m**	**n (%)**
Sitting pulse (bpm)	> 120 or increase ≥ 15	1835	374 (20.4)	976	256 (26.2)
	< 50 or decrease ≥ 15		348 (19.0)		164 (16.8)
Sitting systolic blood pressure (mmHg)	≥ 160 or increase ≥ 20	1890	590 (31.2)	980	242 (24.7)
	≤ 90 or decrease ≥ 20		285 (15.1)		204 (20.8)
Sitting diastolic blood pressure (mmHg)	≥ 100 or increase ≥ 15	1890	526 (27.8)	980	212 (21.6)
	≤ 50 or decrease ≥ 15		297 (15.7)		184 (18.8)
Body Weight (kg)	Increase ≥ 7%	1495	306 (20.5)	794	196 (24.7)
	Decrease ≥ 7%		255 (17.1)		163 (20.5)

Data as per Group G general safety rules are summarized, but note that first dose monitoring values are excluded.
An increase or decrease refers to a change from the value assessed prior to first dose of initial cohort treatment in the study.
A patient can be counted in more than one criterion.
m is the number of patients who have at least one vital sign assessment after first dose date of initial cohort treatment in study. For weight, m is the number of patients who have a non-missing change from the value assessed prior to first dose of initial cohort treatment in study. Percentages are calculated using m as a denominator.
n is the number of patients out of m patients with at least one non-missing assessment value after first dose date of initial cohort treatment in study satisfying clinically notable criterion.

Secondary Outcome Result(s)

Incidence rate of AEs on selected safety outcomes

Table 10-30 Incidence rate of AEs on selected safety outcomes per 100 PTY, by initial cohort treatment, Group G, Safety set

Level 1	FTY720 N=2112 n (%)	FTY720 N=2112 IR (95% CI)	Other DMT N=1138 n (%)	Other DMT N=1138 IR (95% CI)	Incidence Rate Ratio IRR (95% CI)
Bradyarrhythmias and bradycardia (NMQ) (narrow)	143 (6.8)	3.1 (2.64; 3.69)	7 (0.6)	0.2 (0.09; 0.46)	13.94 (6.59; 35.30)
• Atrioventricular block (CMQ)	34 (1.6)	0.7 (0.49; 0.98)	0	0.0 (0.00; 0.12)	
• QT interval prolongation (specific) (CMQ)	6 (0.3)	0.1 (0.05; 0.27)	1 (0.1)	<.1 (<.01; 0.18)	3.85 (0.47; 177.05)
• Torsade de pointes/QT prolongation (SMQ) (broad)	34 (1.6)	0.7 (0.49; 0.98)	13 (1.1)	0.4 (0.22; 0.71)	1.68 (0.86; 3.47)
Convulsions (SMQ) (broad)	30 (1.4)	0.6 (0.42; 0.88)	8 (0.7)	0.3 (0.11; 0.50)	2.42 (1.08; 6.10)
Infections and infestations (SOC)	659 (31.2)	18.8 (17.41; 20.31)	364 (32.0)	16.5 (14.82; 18.25)	1.14 (1.00; 1.30)
• Varicella-Zoster virus infections (NMQ) (broad)	60 (2.8)	1.3 (0.96; 1.62)	27 (2.4)	0.9 (0.58; 1.28)	1.44 (0.90; 2.35)
• Varicella-Zoster virus infections (NMQ) (narrow)	55 (2.6)	1.2 (0.87; 1.50)	24 (2.1)	0.8 (0.50; 1.16)	1.48 (0.90; 2.50)
Opportunistic infections (CMQ)	4 (0.2)	0.1 (0.02; 0.21)	4 (0.4)	0.1 (0.03; 0.33)	0.64 (0.12; 3.44)
• Opportunistic Candida infections [FTY720,FINGOLIMOD,GILENYA] (CMQ)	0	0.0 (0.00; 0.08)	1 (0.1)	<.1 (<.01; 0.18)	
• Tuberculosis (CMQ)	1 (<.1)	<.1 (<.01; 0.11)	4 (0.4)	0.1 (0.03; 0.33)	0.16 (<.01; 1.62)
• Infections (HVI other than VZV-Broad)	24 (1.1)	0.5 (0.32; 0.74)	15 (1.3)	0.5 (0.27; 0.80)	1.02 (0.52; 2.10)
• Infections (HVI other than VZV-Narrow)	20 (0.9)	0.4 (0.25; 0.64)	8 (0.7)	0.3 (0.11; 0.51)	1.60 (0.68; 4.21)
Macular oedema (NMQ) (narrow)	19 (0.9)	0.4 (0.23; 0.61)	1 (0.1)	<.1 (<.01; 0.18)	12.21 (1.94; 507.40)
Hypertension (SMQ) (narrow)	124 (5.9)	2.7 (2.22; 3.18)	46 (4.0)	1.5 (1.11; 2.02)	1.76 (1.24; 2.52)
Liver transaminase elevation	158 (7.5)	3.4 (2.91; 4.01)	46 (4.0)	1.5 (1.11; 2.02)	2.26 (1.62; 3.22)
Malignant or unspecified tumours (SMQ)	75 (3.6)	1.6 (1.23; 1.97)	39 (3.4)	1.3 (0.91; 1.75)	1.23 (0.82; 1.86)
• Nervous system neoplasms malignant and unspecified NEC (HLGT)	2 (0.1)	<.1 (<.01; 0.15)	2 (0.2)	0.1 (0.01; 0.23)	0.64 (0.05; 8.84)
• Breast and nipple neoplasms malignant (HLT)	8 (0.4)	0.2 (0.07; 0.32)	2 (0.2)	0.1 (0.01; 0.23)	2.57 (0.51; 24.81)
• Other malignant neoplasms (Cervical cancer) (CMQ)	1 (<.1)	<.1 (<.01; 0.11)	2 (0.2)	0.1 (0.01; 0.23)	0.32 (0.01; 6.15)
• Thyroid neoplasms malignant (HLT)	0	0.0 (0.00; 0.08)	1 (0.1)	<.1 (<.01; 0.18)	
• Skin neoplasms, malignant and unspecified (SMQ) (narrow)	50 (2.4)	1.0 (0.77; 1.37)	22 (1.9)	0.7 (0.45; 1.08)	1.46 (0.87; 2.53)
• Skin cancer (BCC) (CMQ)	26 (1.2)	0.5 (0.35; 0.79)	11 (1.0)	0.4 (0.18; 0.63)	1.52 (0.73; 3.41)
• Skin cancer (Melanoma) (CMQ)	9 (0.4)	0.2 (0.08; 0.35)	3 (0.3)	0.1 (0.02; 0.28)	1.93 (0.48; 11.06)
• Skin cancer (SCC) (CMQ)	7 (0.3)	0.1 (0.06; 0.29)	3 (0.3)	0.1 (0.02; 0.28)	1.49 (0.34; 8.96)
All thromboembolic events (NMQ)	109 (5.2)	2.3 (1.90; 2.78)	81 (7.1)	2.7 (2.16; 3.39)	0.85 (0.63; 1.14)
• All strokes (NMQ)	81 (3.8)	1.7 (1.35; 2.11)	61 (5.4)	2.0 (1.55; 2.59)	0.84 (0.60; 1.19)
• Haemorrhagic central nervous system vascular conditions (SMQ)	1 (<0.1)	<0.1 (<0.01; 0.11)	3 (0.3)	0.1 (0.02; 0.28)	0.21 (<.01; 2.66)
• Ischaemic central nervous system vascular conditions (SMQ)	2 (0.1)	<0.1 (<0.01; 0.15)	3 (0.3)	0.1 (0.02; 0.28)	0.43 (0.04; 3.73)
Embolic and thrombotic events (SMQ)	56 (2.7)	1.2 (0.88; 1.52)	33 (2.9)	1.1 (0.74; 1.51)	1.09 (0.69; 1.72)
• Pulmonary embolism (PT)	7 (0.3)	0.1 (0.06; 0.29)	2 (0.2)	0.1 (0.01; 0.23)	2.24 (0.43; 22.10)
Pregnancy (PSUR) (NMQ)	40 (1.9)	0.8 (0.59; 1.13)	28 (2.5)	0.9 (0.61; 1.32)	0.91 (0.55; 1.53)

Data as per Group G general safety rules are used.
Selected safety outcomes as documented in the Gilenya risk mitigation plan are summarized.
Level 1 risks are presented alphabetically.
A patient with multiple occurrences of an AE is counted only once in each specific category.
Incidence rate: The number of patients who reported at least one event in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
Incidence rate ratio: The incidence rate of the FTY720 cohort divided by the incidence rate of the Other DMT cohort for a particular AE term/category. It is only calculated if both incidence rates are >0.
MedDRA Version 22.1 has been used for the reporting of adverse events.

Table 10-31 Incidence rate of AEs on selected safety outcomes per 100 PTY, Group F, Safety set

Level 1	FTY720 N=2189 n (%)	IR (95% CI)
Bradyarrhythmias and bradycardia (NMQ) (narrow)	146 (6.7)	3.1 (2.60; 3.62)
• Atrioventricular block (CMQ)	34 (1.6)	0.7 (0.47; 0.95)
• QT interval prolongation (specific) (CMQ)	6 (0.3)	0.1 (0.04; 0.26)
• Torsade de pointes/QT prolongation (SMQ) (broad)	36 (1.6)	0.7 (0.50; 0.99)
Convulsions (SMQ) (broad)	35 (1.6)	0.7 (0.48; 0.97)
Infections and infestations (SOC)	690 (31.5)	18.8 (17.47; 20.31)
• Infections (HVI other than VZV-Broad)	26 (1.2)	0.5 (0.34; 0.76)
• Infections (HVI other than VZV-Narrow)	21 (1.0)	0.4 (0.26; 0.64)

Level 1	N=2189 n (%)	IR (95% CI)
• Varicella-Zoster virus infections (NMQ) (broad)	64 (2.9)	1.3 (1.00; 1.65)
• Varicella-Zoster virus infections (NMQ) (narrow)	58 (2.6)	1.2 (0.89; 1.51)
• Tuberculosis (CMQ)	1 (<0.1)	<0.1 (<0.01; 0.11)
• Opportunistic infections (CMQ)	4 (0.2)	0.1 (0.02; 0.20)
Macular oedema (NMQ) (narrow)	21 (1.0)	0.4 (0.26; 0.63)
Hypertension (SMQ) (narrow)	129 (5.9)	2.7 (2.23; 3.17)
Liver transaminase elevation	166 (7.6)	3.5 (2.96; 4.04)
Malignant or unspecified tumours (SMQ)	83 (3.8)	1.7 (1.33; 2.07)
• Nervous system neoplasms malignant and unspecified NEC (HLGT)	2 (0.1)	<0.1 (<0.01; 0.14)
• Non-Hodgkin's lymphoma (CMQ)	1 (<0.1)	<0.1 (<0.01; 0.11)
• Malignant lymphomas (SMQ) (narrow)	1 (<0.1)	<0.1 (<0.01; 0.11)
• Other malignant neoplasms (Cervical cancer) (CMQ)	1 (<0.1)	<0.1 (<0.01; 0.11)
• Skin cancer (BCC) (CMQ)	29 (1.3)	0.6 (0.39; 0.83)
• Skin cancer (Melanoma) (CMQ)	10 (0.5)	0.2 (0.09; 0.36)
• Skin cancer (SCC) (CMQ)	7 (0.3)	0.1 (0.06; 0.28)
• Skin neoplasms, malignant and unspecified (SMQ) (narrow)	55 (2.5)	1.1 (0.83; 1.43)
• Breast and nipple neoplasms malignant (HLT)	8 (0.4)	0.2 (0.07; 0.31)
All thromboembolic events (NMQ)	113 (5.2)	2.3 (1.90; 2.77)
• All strokes (NMQ)	85 (3.9)	1.7 (1.37; 2.12)
• Embolic and thrombotic events (SMQ)	56 (2.6)	1.1 (0.85; 1.46)
• Haemorrhagic central nervous system vascular conditions (SMQ)	1 (<0.1)	<0.1 (<0.01; 0.11)
• Pulmonary embolism (PT)	7 (0.3)	0.1 (0.06; 0.28)
• Ischaemic central nervous system vascular conditions (SMQ)	2 (0.1)	<0.1 (<0.01; 0.14)
Pregnancy (PSUR) (NMQ)	44 (2.0)	0.9 (0.64; 1.18)

Data as per Group F general safety rules are used.
Selected safety outcomes as documented in the Gilenya risk mitigation plan are summarized.
Level 1 risks are presented alphabetically.
A patient with multiple occurrences of an AE is counted only once in each specific category.
Incidence rate: The number of patients who reported at least one event in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
MedDRA Version 22.1 has been used for the reporting of adverse events.

Table 10-41 Incidence rate of deaths per 100 patient-years, by primary system organ class, preferred term and initial cohort treatment, Group G, Safety set

Primary system organ class / Preferred term	FTY720 N=2112		Other DMT N=1138		Incidence Rate Ratio
	n (%)	IR (95% CI)	n (%)	IR (95% CI)	IRR (95% CI)
-Any primary system organ class					
-Total	7 (0.3)	0.1 (0.06; 0.29)	12 (1.1)	0.4 (0.20; 0.67)	0.37 (0.12; 1.03)
CARDIAC DISORDERS					
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)	2 (0.2)	0.1 (0.01; 0.23)	0.32 (0.01; 6.16)
CARDIO-RESPIRATORY ARREST	1 (<0.1)	<0.1 (<0.01; 0.11)	0	0.0 (0.00; 0.12)	

Primary system organ class Preferred term	FTY720 N=2112 n (%)	 IR (95% CI)	Other DMT N=1138 n (%)	 IR (95% CI)	Incidence Rate Ratio IRR (95% CI)
MYOCARDIAL INFARCTION	0	0.0 (0.00; 0.08)	2 (0.2)	0.1 (0.01; 0.23)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
-Total	4 (0.2)	0.1 (0.02; 0.21)	2 (0.2)	0.1 (0.01; 0.23)	1.28 (0.18; 14.18)
DEATH	2 (0.1)	<0.1 (<0.01; 0.15)	2 (0.2)	0.1 (0.01; 0.23)	0.64 (0.05; 8.85)
PAIN	1 (<0.1)	<0.1 (<0.01; 0.11)	0	0.0 (0.00; 0.12)	
PYREXIA	1 (<0.1)	<0.1 (<0.01; 0.11)	0	0.0 (0.00; 0.12)	
INFECTIONS AND INFESTATIONS					
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)	2 (0.2)	0.1 (0.01; 0.23)	0.32 (0.01; 6.16)
HIV INFECTION	1 (<0.1)	<0.1 (<0.01; 0.11)	0	0.0 (0.00; 0.12)	
SEPTIC SHOCK	0	0.0 (0.00; 0.08)	1 (0.1)	<0.1 (<0.01; 0.18)	
UROSEPSIS	0	0.0 (0.00; 0.08)	1 (0.1)	<0.1 (<0.01; 0.18)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS					
-Total	0	0.0 (0.00; 0.08)	1 (0.1)	<0.1 (<0.01; 0.18)	
ALCOHOL POISONING	0	0.0 (0.00; 0.08)	1 (0.1)	<0.1 (<0.01; 0.18)	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)					
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)	3 (0.3)	0.1 (0.02; 0.28)	0.21 (<.01; 2.66)
BLADDER TRANSITIONAL CELL CARCINOMA STAGE IV	1 (<0.1)	<0.1 (<0.01; 0.11)	0	0.0 (0.00; 0.12)	
ADENOCARCINOMA PANCREAS	0	0.0 (0.00; 0.08)	1 (0.1)	<0.1 (<0.01; 0.18)	
LUNG NEOPLASM MALIGNANT	0	0.0 (0.00; 0.08)	1 (0.1)	<0.1 (<0.01; 0.18)	
SARCOMA METASTATIC	0	0.0 (0.00; 0.08)	1 (0.1)	<0.1 (<0.01; 0.18)	
NERVOUS SYSTEM DISORDERS					
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)	1 (0.1)	<0.1 (<0.01; 0.18)	0.64 (0.01; 50.33)
MULTIPLE SCLEROSIS	1 (<0.1)	<0.1 (<0.01; 0.11)	1 (0.1)	<0.1 (<0.01; 0.18)	0.64 (0.01; 50.33)
PSYCHIATRIC DISORDERS					
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)	1 (0.1)	<0.1 (<0.01; 0.18)	0.64 (0.01; 50.33)
CONFUSIONAL STATE	1 (<0.1)	<0.1 (<0.01; 0.11)	0	0.0 (0.00; 0.12)	
COMPLETED SUICIDE	0	0.0 (0.00; 0.08)	1 (0.1)	<.1 (<0.01; 0.18)	
VASCULAR DISORDERS					
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)	0	0.0 (0.00; 0.12)	
EXSANGUINATION	1 (<0.1)	<0.1 (<0.01; 0.11)	0	0.0 (0.00; 0.12)	

Data as per Group G general safety rules are used.
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by frequency from highest to lowest in the FTY720 column.
A patient with multiple occurrences of a death term for a primary system organ class is counted only once in each specific category.
Incidence rate: The number of patients who died in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
Incidence rate ratio: The incidence rate of the FTY720 cohort divided by the incidence rate of the Other DMT cohort for a particular death term/category. It is only calculated if both incidence rates are >0.
MedDRA Version 22.1 has been used for the reporting of adverse events.

Table 10-43 Incidence rate of deaths per 100 patient-years, by primary SOC and PT, Group F, Safety set

Primary system organ class Preferred term	FTY720 N=2189 n (%)	IR (95% CI)
-Any primary system organ class		
-Total	7 (0.3)	0.1 (0.06; 0.28)

Primary system organ class Preferred term	FTY720 N=2189 n (%)	IR (95% CI)
CARDIAC DISORDERS		
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)
CARDIO-RESPIRATORY ARREST	1 (<0.1)	<0.1 (<0.01; 0.11)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
-Total	4 (0.2)	0.1 (0.02; 0.20)
DEATH	2 (0.1)	<0.1 (<0.01; 0.14)
PAIN	1 (<0.1)	<0.1 (<0.01; 0.11)
PYREXIA	1 (<0.1)	<0.1 (<0.01; 0.11)
INFECTIONS AND INFESTATIONS		
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)
HIV INFECTION	1 (<0.1)	<0.1 (<0.01; 0.11)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)
BLADDER TRANSITIONAL CELL CARCINOMA STAGE IV	1 (<0.1)	<0.1 (<0.01; 0.11)
NERVOUS SYSTEM DISORDERS		
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)
MULTIPLE SCLEROSIS	1 (<0.1)	<0.1 (<0.01; 0.11)
PSYCHIATRIC DISORDERS		
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)
CONFUSIONAL STATE	1 (<0.1)	<0.1 (<0.01; 0.11)
VASCULAR DISORDERS		
-Total	1 (<0.1)	<0.1 (<0.01; 0.11)
EXSANGUINATION	1 (<0.1)	<0.1 (<0.01; 0.11)

Data as per Group F general safety rules are used.
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by frequency from highest to lowest.
A patient with multiple occurrences of a death term for a primary system organ class is counted only once in each specific category.
Incidence rate: The number of patients who died in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
MedDRA Version 22.1 has been used for the reporting of adverse events.

Fingolimod results on selected safety topics into context by using an internal parallel-cohort whenever applicable or external benchmarking databases for less frequent events:

Table 10-32 Time to first onset of AESIs, by time interval, primary SOC, PT and initial cohort treatment, with cutoff of 1.0 percent per cohort and time interval, Group G, Safety set

Primary system organ class Preferred term	Months 0-<3 FTY720 N'=2112 n (%)	 Other DMT N'=1138 n (%)	Months 3-<6 FTY720 N'=1986 n (%)	 Other DMT N'=1087 n (%)	Months 6-<9 FTY720 N'=1799 n (%)	 Other DMT N'=1000 n (%)	Months 9-<12 FTY720 N'=1624 n (%)	 Other DMT N'=925 n (%)
CARDIAC DISORDERS								
-Total	162 (72.0)	5 (9.3)	19 (8.4)	6 (11.1)	6 (2.7)	7 (13.0)	9 (4.0)	6 (11.1)
BRADYCARDIA	46 (88.5)	0	2 (3.8)	1 (33.3)	0	0	1 (1.9)	1 (33.3)
PALPITATIONS	24 (50.0)	0	7 (14.6)	3 (15.0)	2 (4.2)	6 (30.0)	5 (10.4)	1 (5.0)
SINUS BRADYCARDIA	48 (100.0)	0	0	0	0	0	0	1 (100.0)
ATRIOVENTRICULAR BLOCK FIRST DEGREE	22 (91.7)	0	0	0	0	0	0	0
INFECTIONS AND INFESTATIONS								
-Total	222 (34.2)	98 (27.1)	106 (16.3)	44 (12.2)	68 (10.5)	40 (11.0)	49 (7.6)	43 (11.9)
URINARY TRACT INFECTION	28 (20.1)	15 (19.2)	22 (15.8)	7 (9.0)	20 (14.4)	10 (12.8)	15 (10.8)	6 (7.7)
UPPER RESPIRATORY TRACT INFECTION	35 (29.4)	9 (11.5)	18 (15.1)	10 (12.8)	10 (8.4)	5 (6.4)	9 (7.6)	8 (10.3)
SINUSITIS	22 (26.5)	11 (22.0)	11 (13.3)	5 (10.0)	13 (15.7)	6 (12.0)	9 (10.8)	6 (12.0)
NASOPHARYNGITIS	26 (32.9)	7 (21.9)	7 (8.9)	2 (6.3)	12 (15.2)	4 (12.5)	7 (8.9)	5 (15.6)
BRONCHITIS	16 (30.2)	8 (22.2)	8 (15.1)	2 (5.6)	2 (3.8)	1 (2.8)	6 (11.3)	4 (11.1)
HERPES ZOSTER	6 (11.5)	2 (8.7)	9 (17.3)	3 (13.0)	2 (3.8)	2 (8.7)	5 (9.6)	1 (4.3)
INFLUENZA	8 (18.2)	5 (21.7)	5 (11.4)	1 (4.3)	3 (6.8)	2 (8.7)	0	2 (8.7)
PNEUMONIA	2 (5.7)	2 (13.3)	5 (14.3)	1 (6.7)	4 (11.4)	1 (6.7)	1 (2.9)	2 (13.3)
GASTROENTERITIS VIRAL	3 (14.3)	2 (15.4)	2 (9.5)	3 (23.1)	2 (9.5)	1 (7.7)	4 (19.0)	0
CELLULITIS	1 (7.7)	2 (11.1)	4 (30.8)	1 (5.6)	3 (23.1)	2 (11.1)	1 (7.7)	1 (5.6)
FOLLICULITIS	6 (46.2)	5 (38.5)	1 (7.7)	2 (15.4)	1 (7.7)	1 (7.7)	1 (7.7)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)								
-Total	154 (48.4)	154 (63.4)	36 (11.3)	31 (12.8)	8 (2.5)	7 (2.9)	10 (3.1)	2 (0.8)
MELANOCYTIC NAEVUS	109 (62.3)	98 (68.1)	19 (10.9)	20 (13.9)	6 (3.4)	2 (1.4)	2 (1.1)	1 (0.7)
SEBORRHOEIC KERATOSIS	59 (54.6)	50 (69.4)	10 (9.3)	8 (11.1)	2 (1.9)	1 (1.4)	4 (3.7)	1 (1.4)
HAEMANGIOMA OF SKIN	29 (60.4)	36 (78.3)	3 (6.3)	3 (6.5)	2 (4.2)	0	1 (2.1)	0

Primary system organ class Preferred term	Months 0-<3 FTY720 N'=2112 n (%)	 Other DMT N'=1138 n (%)	Months 3-<6 FTY720 N'=1986 n (%)	 Other DMT N'=1087 n (%)	Months 6-<9 FTY720 N'=1799 n (%)	 Other DMT N'=1000 n (%)	Months 9-<12 FTY720 N'=1624 n (%)	 Other DMT N'=925 n (%)
BASAL CELL CARCINOMA	4 (15.4)	3 (27.3)	2 (7.7)	1 (9.1)	2 (7.7)	0	3 (11.5)	0
SKIN PAPILLOMA	5 (25.0)	6 (37.5)	2 (10.0)	2 (12.5)	0	0	1 (5.0)	0
ACROCHORDON	8 (42.1)	9 (60.0)	3 (15.8)	2 (13.3)	0	1 (6.7)	2 (10.5)	1 (6.7)
FIBROUS HISTIOCYTOMA	9 (47.4)	22 (81.5)	1 (5.3)	1 (3.7)	0	1 (3.7)	1 (5.3)	0
DYSPLASTIC NAEVUS	6 (37.5)	5 (41.7)	0	2 (16.7)	0	0	0	0
HAEMANGIOMA	11 (68.8)	13 (68.4)	2 (12.5)	2 (10.5)	0	0	0	1 (5.3)

Primary system organ class Preferred term	Months 12-<24 FTY720 N'=1484 n (%)	 Other DMT N'=873 n (%)	Months 24-<36 FTY720 N'=1018 n (%)	 Other DMT N'=668 n (%)	Months 36-<48 FTY720 N'=673 n (%)	 Other DMT N'=530 n (%)	≥ Month 48 FTY720 N'=438 n (%)	 Other DMT N'=383 n (%)
CARDIAC DISORDERS								
-Total	13 (5.8)	13 (24.1)	7 (3.1)	10 (18.5)	5 (2.2)	4 (7.4)	4 (1.8)	3 (5.6)
BRADYCARDIA	2 (3.8)	1 (33.3)	0	0	1 (1.9)	0	0	0
PALPITATIONS	4 (8.3)	6 (30.0)	3 (6.3)	2 (10.0)	1 (2.1)	1 (5.0)	2 (4.2)	1 (5.0)
SINUS BRADYCARDIA	0	0	0	0	0	0	0	0
ATRIOVENTRICULAR BLOCK FIRST DEGREE	0	0	0	0	1 (4.2)	0	1 (4.2)	0
INFECTIONS AND INFESTATIONS								
-Total	123 (19.0)	80 (22.1)	45 (6.9)	25 (6.9)	22 (3.4)	22 (6.1)	14 (2.2)	10 (2.8)
URINARY TRACT INFECTION	39 (28.1)	19 (24.4)	9 (6.5)	9 (11.5)	1 (0.7)	7 (9.0)	5 (3.6)	5 (6.4)
UPPER RESPIRATORY TRACT INFECTION	21 (17.6)	25 (32.1)	12 (10.1)	12 (15.4)	7 (5.9)	5 (6.4)	7 (5.9)	4 (5.1)
SINUSITIS	17 (20.5)	13 (26.0)	8 (9.6)	7 (14.0)	2 (2.4)	1 (2.0)	1 (1.2)	1 (2.0)
NASOPHARYNGITIS	16 (20.3)	8 (25.0)	4 (5.1)	3 (9.4)	5 (6.3)	2 (6.3)	2 (2.5)	1 (3.1)
BRONCHITIS	14 (26.4)	6 (16.7)	2 (3.8)	8 (22.2)	4 (7.5)	3 (8.3)	1 (1.9)	4 (11.1)
HERPES ZOSTER	16 (30.8)	9 (39.1)	6 (11.5)	2 (8.7)	4 (7.7)	2 (8.7)	4 (7.7)	2 (8.7)
INFLUENZA	15 (34.1)	7 (30.4)	8 (18.2)	2 (8.7)	4 (9.1)	3 (13.0)	1 (2.3)	1 (4.3)
PNEUMONIA	13 (37.1)	3 (20.0)	4 (11.4)	2 (13.3)	4 (11.4)	3 (20.0)	2 (5.7)	1 (6.7)

Primary system organ class Preferred term	Months 12-<24 FTY720 N'=1484 n (%)	Months 12-<24 Other DMT N'=873 n (%)	Months 24-<36 FTY720 N'=1018 n (%)	Months 24-<36 Other DMT N'=668 n (%)	Months 36-<48 FTY720 N'=673 n (%)	Months 36-<48 Other DMT N'=530 n (%)	≥ Month 48 FTY720 N'=438 n (%)	≥ Month 48 Other DMT N'=383 n (%)
GASTROENTERITIS VIRAL	5 (23.8)	4 (30.8)	2 (9.5)	1 (7.7)	1 (4.8)	1 (7.7)	2 (9.5)	1 (7.7)
CELLULITIS	1 (7.7)	3 (16.7)	1 (7.7)	4 (22.2)	2 (15.4)	3 (16.7)	0	2 (11.1)
FOLLICULITIS	1 (7.7)	1 (7.7)	2 (15.4)	2 (15.4)	0	1 (7.7)	1 (7.7)	1 (7.7)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)								
-Total	40 (12.6)	13 (5.3)	25 (7.9)	19 (7.8)	22 (6.9)	9 (3.7)	23 (7.2)	8 (3.3)
MELANOCYTIC NAEVUS	12 (6.9)	8 (5.6)	8 (4.6)	6 (4.2)	7 (4.0)	5 (3.5)	12 (6.9)	4 (2.8)
SEBORRHOEIC KERATOSIS	9 (8.3)	2 (2.8)	7 (6.5)	4 (5.6)	6 (5.6)	3 (4.2)	11 (10.2)	3 (4.2)
HAEMANGIOMA OF SKIN	5 (10.4)	2 (4.3)	1 (2.1)	3 (6.5)	3 (6.3)	1 (2.2)	4 (8.3)	1 (2.2)
BASAL CELL CARCINOMA	5 (19.2)	1 (9.1)	3 (11.5)	4 (36.4)	5 (19.2)	1 (9.1)	2 (7.7)	1 (9.1)
SKIN PAPILLOMA	5 (25.0)	3 (18.8)	1 (5.0)	3 (18.8)	2 (10.0)	2 (12.5)	4 (20.0)	0
ACROCHORDON	2 (10.5)	0	2 (10.5)	1 (6.7)	2 (10.5)	1 (6.7)	0	0
FIBROUS HISTIOCYTOMA	5 (26.3)	0	1 (5.3)	1 (3.7)	1 (5.3)	1 (3.7)	1 (5.3)	1 (3.7)
DYSPLASTIC NAEVUS	3 (18.8)	0	3 (18.8)	2 (16.7)	2 (12.5)	1 (8.3)	2 (12.5)	2 (16.7)
HAEMANGIOMA	2 (12.5)	1 (5.3)	1 (6.3)	1 (5.3)	0	1 (5.3)	0	0

Data as per Group G general safety rules are used.
N'=Number of patients at risk for at least 1 day in the time interval being reported. n=Number of patients who experienced at least one AE in this category. AEs are reported for a particular interval if the first AE start date falls into that interval.
Percentages are based on the total number of patients experiencing a specific event in the corresponding cohort.
AEs of special interest are defined as events from the SOCs Cardiac disorders, Infections & infestations and Neoplasms, benign, malignant and unspecified (incl cysts and polyps).
Primary system organ classes and preferred terms with an occurrence of at least 1.0 percent of overall incidence in any cohort are displayed.
The overall incidence is calculated by using the number of patients in the Safety Set of the corresponding cohort as denominator and the number of patients experiencing the specific event as numerator.
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by overall frequency from highest to lowest in the FTY720 column.
MedDRA Version 22.1 has been used for the reporting of adverse events.
Source: Table 14.3.1-1.16

Long-term MS disease course in fingolimod treated patients, as measured by relapses and Expanded Disability Status Scale (EDSS)

Table 10-94 Annualized relapse rates by first DMT corresponding to cohort assignment, Group G, Effectiveness set

Category of first DMT	No. of patients with relapse	Total number of relapses for all patients	Total time period on first DMT for all patients(days)	Group-level ARR			Patient-level ARR (mean/SD/ (95% CI))
				Raw	Estimate	(95% CI)	
FTY720 (N=1639)	352	498	1582443	0.115	0.132	(0.117,0.149)	0.16/0.413/ (0.14,0.18)
Interferon (N=123)	34	48	102511	0.171	0.221	(0.145,0.336)	0.29/0.605/ (0.19,0.40)
Glatiramer Acetate (N=182)	43	59	162566	0.133	0.176	(0.122,0.255)	0.26/0.589/ (0.18,0.35)
Dimethyl fumarate (N=324)	68	101	323066	0.114	0.128	(0.098,0.169)	0.16/0.420/ (0.12,0.21)
Teriflunomide (N=137)	31	41	137884	0.109	0.128	(0.083,0.195)	0.17/0.431 /(0.10,0.24)
Natalizumab (N=0)	0	0	0	n.e.	n.e.	n.e.	n.e.
Other MS therapies (N=1)	0	0	375	0	0	0	0/n.e./n.e.

Data as per Group G general effectiveness rules are summarized.
Time on first DMT is the time in study from first dose date of first DMT to last dose date of first DMT prior to any switch in DMT and prior to any interruption in the first DMT of more than 45 days. If last dose date of first DMT is not available it is imputed using the end of study participation date or the last visit date if the former is not available.
The annualized relapse rate (ARR) is defined as the number of relapses with onset occurring during a specific period of time, adjusted to a one-year period.
Raw group-level ARR = total number of relapses with onset occurring during time on first DMT for all patients in the group / the total number of days on first DMT for all patients in the group x 365.25.
Group-level ARR estimate and 95% CI from negative binomial model including category of first DMT as explanatory variable.
Patient-level ARR = the number of relapses with onset occurring during time on first DMT / days on first DMT x 365.25. Patient-level ARR 95% CI calculated using normal approximation.
When there are no relapse start dates entered, the number of relapses since the patient's last visit is assumed to be 0.
n.e. = not estimable

Table 10-96 Summary of EDSS score by time interval, Group G, Effectiveness set

	FTY720 N=1639								
	Base			Post			Change		
Time interval	n (%)	Mean	SD	n (%)	Mean	SD	n (%)	Mean	SD
Baseline	597 (36.4)	2.42	1.859						
Month 3	282 (17.2)	2.51	1.958	282 (17.2)	2.40	2.025	282 (17.2)	-0.12	0.879
Month 6	287 (17.5)	2.44	1.891	287 (17.5)	2.39	1.966	287 (17.5)	-0.06	1.024
Month 12	313 (19.1)	2.41	1.877	313 (19.1)	2.31	1.952	313 (19.1)	-0.09	1.035
Month 24	250 (15.3)	2.38	1.828	250 (15.3)	2.30	1.985	250 (15.3)	-0.08	1.232
Year 3 (M36)	148 (9.0)	2.17	1.827	148 (9.0)	2.14	1.979	148 (9.0)	-0.03	1.189
Year 4 (M48)	88 (5.4)	2.13	1.567	88 (5.4)	2.14	1.800	88 (5.4)	0.01	1.433
Year 5 (M60)	63 (3.8)	1.94	1.554	63 (3.8)	1.98	1.605	63 (3.8)	0.04	1.305

	Interferon N=123								
	Base			Post			Change		
Time interval	n (%)	Mean	SD	n (%)	Mean	SD	n (%)	Mean	SD
Baseline	53 (43.1)	2.57	2.062						
Month 3	24 (19.5)	2.02	1.925	24 (19.5)	1.75	1.865	24 (19.5)	-0.27	1.429
Month 6	28 (22.8)	1.98	1.653	28 (22.8)	1.77	1.601	28 (22.8)	-0.21	1.436
Month 12	28 (22.8)	1.98	1.518	28 (22.8)	1.91	1.534	28 (22.8)	-0.07	1.152
Month 24	16 (13.0)	1.78	1.437	16 (13.0)	1.66	1.758	16 (13.0)	-0.13	2.004
Year 3 (M36)	9 (7.3)	1.78	1.906	9 (7.3)	1.83	2.121	9 (7.3)	0.06	2.855
Year 4 (M48)	6 (4.9)	1.33	1.169	6 (4.9)	2.08	2.108	6 (4.9)	0.75	1.405
Year 5 (M60)	2 (1.6)	0.50	0.707	2 (1.6)	0.50	0.707	2 (1.6)	0.00	1.414

	Glatiramer acetate N=182								
	Base			Post			Change		
Time interval	n (%)	Mean	SD	n (%)	Mean	SD	n (%)	Mean	SD
Baseline	51 (28.0)	2.05	1.484						
Month 3	31 (17.0)	2.21	1.526	31 (17.0)	2.19	1.662	31 (17.0)	-0.02	1.255
Month 6	26 (14.3)	1.92	1.354	26 (14.3)	2.02	1.688	26 (14.3)	0.10	1.428
Month 12	27 (14.8)	1.96	1.487	27 (14.8)	1.89	1.443	27 (14.8)	-0.07	0.885
Month 24	18 (9.9)	2.00	1.581	18 (9.9)	2.03	1.921	18 (9.9)	0.03	1.289
Year 3 (M36)	10 (5.5)	1.85	1.313	10 (5.5)	1.80	1.703	10 (5.5)	-0.05	0.762
Year 4 (M48)	4 (2.2)	1.88	0.854	4 (2.2)	0.88	1.031	4 (2.2)	-1.00	1.414
Year 5 (M60)	2 (1.1)	1.50	0.707	2 (1.1)	1.00	1.414	2 (1.1)	-0.50	0.707

	Dimethyl fumarate N=324								
	Base			Post			Change		
Time interval	n (%)	Mean	SD	n (%)	Mean	SD	n (%)	Mean	SD
Baseline	115 (35.5)	2.84	1.995						
Month 3	53 (16.4)	3.03	1.910	53 (16.4)	2.97	1.960	53 (16.4)	-0.06	0.543
Month 6	55 (17.0)	2.96	1.830	55 (17.0)	2.86	1.996	55 (17.0)	-0.10	0.690
Month 12	55 (17.0)	2.97	2.062	55 (17.0)	2.98	2.244	55 (17.0)	0.01	1.219
Month 24	47 (14.5)	2.67	1.918	47 (14.5)	3.02	2.182	47 (14.5)	0.35	1.588
Year 3 (M36)	39 (12.0)	2.85	2.027	39 (12.0)	3.08	2.172	39 (12.0)	0.23	1.302
Year 4 (M48)	23 (7.1)	2.76	1.959	23 (7.1)	2.74	2.349	23 (7.1)	-0.02	1.722
Year 5 (M60)	13 (4.0)	2.04	1.493	13 (4.0)	1.92	1.631	13 (4.0)	-0.12	1.244

	Teriflunomide N=137								
	Base			Post			Change		
Time interval	n (%)	Mean	SD	n (%)	Mean	SD	n (%)	Mean	SD
Baseline	40 (29.2)	2.93	1.890						
Month 3	21 (15.3)	3.26	2.137	21 (15.3)	3.24	2.206	21 (15.3)	-0.02	0.512
Month 6	21 (15.3)	3.52	1.997	21 (15.3)	3.60	2.095	21 (15.3)	0.07	0.676
Month 12	24 (17.5)	3.31	1.999	24 (17.5)	3.31	2.354	24 (17.5)	0.00	0.872
Month 24	21 (15.3)	3.05	2.067	21 (15.3)	2.83	2.431	21 (15.3)	-0.21	1.338
Year 3 (M36)	13 (9.5)	3.00	1.958	13 (9.5)	2.88	2.338	13 (9.5)	-0.12	0.961
Year 4 (M48)	10 (7.3)	2.45	1.322	10 (7.3)	2.45	1.787	10 (7.3)	0.00	0.782
Year 5 (M60)	3 (2.2)	2.83	1.041	3 (2.2)	3.17	2.466	3 (2.2)	0.33	1.528

	Natalizumab N=0								
	Base			Post			Change		
Time interval	n (%)	Mean	SD	n (%)	Mean	SD	n (%)	Mean	SD
Baseline	0 (0.0)								
Month 3	0 (0.0)			0 (0.0)			0 (0.0)		
Month 6	0 (0.0)			0 (0.0)			0 (0.0)		
Month 12	0 (0.0)			0 (0.0)			0 (0.0)		
Month 24	0 (0.0)			0 (0.0)			0 (0.0)		
Year 3 (M36)	0 (0.0)			0 (0.0)			0 (0.0)		
Year 4 (M48)	0 (0.0)			0 (0.0)			0 (0.0)		
Year 5 (M60)	0 (0.0)			0 (0.0)			0 (0.0)		

	Other MS therapies N=1								
	Base			Post			Change		
Time interval	n (%)	Mean	SD	n (%)	Mean	SD	n (%)	Mean	SD
Baseline	0 (0.0)								
Month 3	0 (0.0)			0 (0.0)			0 (0.0)		
Month 6	0 (0.0)			0 (0.0)			0 (0.0)		
Month 12	0 (0.0)			0 (0.0)			0 (0.0)		
Month 24	0 (0.0)			0 (0.0)			0 (0.0)		

	Other MS therapies N=1								
	Base			Post			Change		
Time interval	n (%)	Mean	SD	n (%)	Mean	SD	n (%)	Mean	SD
Year 3 (M36)	0 (0.0)			0 (0.0)			0 (0.0)		
Year 4 (M48)	0 (0.0)			0 (0.0)			0 (0.0)		
Year 5 (M60)	0 (0.0)			0 (0.0)			0 (0.0)		

Data as per Group G general effectiveness rules are summarized.
Base = Baseline, Post = Post-baseline, Change = Post-baseline - baseline.
At each visit, only patients with a value at both baseline and the respective day are included.
Baseline is defined as last value prior to administration of the first dose of initial cohort treatment in the study.
If a patient had more than one assessment in a time interval, the one closest to the target time point was summarized. If two assessments were equally close the latter was chosen.

Effectiveness set: All patients who were treated with the first DMT corresponding to cohort assignment for a minimum of 180 days in the study, excluding interruptions. The determination of whether a patient completed a minimum of 180 days was based on the duration on first DMT, which was the time in study from first dose date of first DMT corresponding to cohort assignment to last dose date of first DMT corresponding to cohort assignment prior to any switch in DMT and prior to any interruption in the first DMT corresponding to cohort assignment of more than 45 days, excluding any interruptions. Patients with a protocol deviation severity of 0 (0=exclude from all efficacy analyses), 1 (1=exclude from all per protocol analyses), or 8 (8=exclude from all analyses) was excluded.

Summary of PRIMUS activity scale score by visit

Table 10-89 Summary of PRIMUS activity scale score by visit, Group G, Safety set, PRO sub-study

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change
Baseline						
n (%)	1287 (79.9)			624 (73.3)		
Mean	4.9			5.9		
SD	6.32			6.74		
Minimum	0			0		
Q1	0			0		
Median	2.0			3.0		
Q3	8.0			10.0		
Maximum	30			30		
Month 6						
n (%)	689 (42.8)	689 (42.8)	689 (42.8)	324 (38.1)	324 (38.1)	324 (38.1)
Mean	4.4	4.5	0.2	5.9	6.1	0.2
SD	5.87	5.90	3.58	6.51	6.81	3.56
Minimum	0	0	-21	0	0	-13
Q1	0	0	-1.0	0	0	-1.0
Median	2.0	2.0	0	3.0	3.0	0
Q3	7.0	7.0	1.0	10.0	10.0	1.1
Maximum	29	30	20	25	27	16
Month 12						
n (%)	569 (35.3)	569 (35.3)	569 (35.3)	303 (35.6)	303 (35.6)	303 (35.6)
Mean	3.9	4.3	0.4	4.9	5.5	0.7

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change
SD	5.53	6.00	4.29	6.10	6.52	3.57
Minimum	0	0	-19	0	0	-18
Q1	0	0	-1.0	0	0	0
Median	1.0	2.0	0	2.0	3.0	0
Q3	6.0	6.0	1.0	8.0	9.0	2.0
Maximum	29	30	30	22	27	26
Month 24						
n (%)	397 (24.6)	397 (24.6)	397 (24.6)	236 (27.7)	236 (27.7)	236 (27.7)
Mean	3.5	3.8	0.2	5.5	6.1	0.6
SD	5.43	5.52	4.16	6.43	6.84	4.43
Minimum	0	0	-19	0	0	-20
Q1	0	0	0	0	0	-1.0
Median	0	1.0	0	3.0	3.0	0
Q3	5.0	5.0	1.0	9.5	11.0	2.0
Maximum	29	24	21	27	27	16
Year 3 (M36)						
n (%)	232 (14.4)	232 (14.4)	232 (14.4)	159 (18.7)	159 (18.7)	159 (18.7)
Mean	3.6	3.7	0.2	4.8	5.6	0.8
SD	5.28	5.21	4.38	6.07	6.68	4.78
Minimum	0	0	-15	0	0	-14
Q1	0	0	-1.0	0	0	0
Median	1.0	2.0	0	2.0	3.0	0
Q3	5.0	5.0	1.0	8.0	9.0	2.0
Maximum	29	22	20	22	30	20
Year 4 (M48)						
n (%)	133 (8.3)	133 (8.3)	133 (8.3)	124 (14.6)	124 (14.6)	124 (14.6)
Mean	3.8	4.3	0.5	4.6	6.3	1.7
SD	5.62	6.27	5.39	5.94	7.50	5.46
Minimum	0	0	-16	0	0	-10
Q1	0	0	0	0	0	-0.5
Median	1.0	2.0	0	2.0	3.0	0
Q3	5.0	5.0	2.0	7.5	11.8	3.0
Maximum	28	30	25	21	30	30
Year 5 (M60)						
n (%)	72 (4.5)	72 (4.5)	72 (4.5)	64 (7.5)	64 (7.5)	64 (7.5)
Mean	3.2	4.1	0.9	3.3	4.4	1.1
SD	4.92	6.50	6.21	5.54	7.18	4.88
Minimum	0	0	-15	0	0	-18
Q1	0	0	0	0	0	0
Median	0	0.5	0	0	0.5	0
Q3	4.0	5.0	2.0	4.0	6.2	2.0
Maximum	18	30	25	22	29	20

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change

n = the number of patients with data at baseline and respective post-dose assessment. At Baseline visit n is the number of all patients with baseline data.
Baseline is defined as last value prior to administration of the first dose of initial cohort treatment in the study.
Data as per Group G general safety rules are used.
Change = post - base.
If a patient had more than one assessment in a time interval, the one closest to the target time point was summarized. If two assessments were equally close the latter was chosen.
PRIMUS = Patient Reported Outcome Indices for Multiple Sclerosis.
PRIMUS activities scale score ranges from 0 to 30 with higher summary scores indicating worse health.

Table 10-90 Summary of TSQM-9 scores by visit, Group G, Safety set, PRO sub-study

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change
Parameter: Effectiveness (%)						
Baseline						
n (%)	524 (32.5)			475 (55.8)		
Mean	61.5			64.2		
SD	20.00			19.71		
Minimum	0			0		
Q1	50.0			50.0		
Median	66.7			66.7		
Q3	72.2			77.8		
Maximum	100			100		
Month 6						
n (%)	308 (19.1)	308 (19.1)	308 (19.1)	292 (34.3)	292 (34.3)	292 (34.3)
Mean	61.9	73.1	11.2	64.4	66.9	2.5
SD	20.24	21.02	24.23	19.56	21.98	23.76
Minimum	0	0	-67	0	0	-94
Q1	50.0	61.1	0.0	50.0	55.6	-8.3
Median	66.7	72.2	11.1	66.7	66.7	0
Q3	72.2	88.9	27.8	77.8	83.3	16.7
Maximum	100	100	89	100	100	89
Parameter: Convenience (%)						
Baseline						
n (%)	622 (38.6)			478 (56.2)		
Mean	80.3			75.1		
SD	22.50			21.81		
Minimum	0			0		
Q1	66.7			61.1		
Median	86.1			77.8		
Q3	100.0			100.0		
Maximum	100			100		
Month 6						
n (%)	361 (22.4)	361 (22.4)	361 (22.4)	294 (34.5)	294 (34.5)	294 (34.5)
Mean	80.6	92.5	11.9	75.7	78.9	3.2
SD	22.49	12.14	22.92	21.74	20.60	20.41
Minimum	0	44	-44	0	0	-89
Q1	66.7	83.3	0	61.1	66.7	-5.6
Median	88.9	100.0	0	77.8	83.3	0
Q3	100.0	100.0	22.2	100.0	100.0	11.1
Maximum	100	100	100	100	100	83

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change
Parameter: Global Satisfaction (%)						
Baseline						
n (%)	599 (37.2)			471 (55.3)		
Mean	61.6			65.1		
SD	23.34			21.02		
Minimum	0			0		
Q1	50.0			50.0		
Median	64.3			64.3		
Q3	78.6			78.6		
Maximum	100			100		
Month 6						
n (%)	353 (21.9)	353 (21.9)	353 (21.9)	289 (34.0)	289 (34.0)	289 (34.0)
Mean	61.3	73.4	12.2	65.3	69.0	3.7
SD	24.97	22.37	26.71	21.18	23.22	23.82
Minimum	0	0	-71	0	0	-93
Q1	50.0	57.1	0	50.0	57.1	-7.1
Median	62.5	78.6	7.1	64.3	71.4	0
Q3	78.6	92.9	28.6	78.6	85.7	14.3
Maximum	100	100	100	100	100	86

n = the number of patients with data at baseline and respective post-dose assessment. At Baseline visit n is the number of all patients with baseline data.
Baseline is defined as last value prior to administration of the first dose of initial cohort treatment in the study.
Data as per Group G general safety rules are used.
Change = post - base.
If a patient had more than one assessment in a time interval, the one closest to the target time point was summarized. If two assessments were equally close the latter was chosen.
TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9.

Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH)

Table 10-88 Summary of WPAI-GH scores by visit, Group G, Safety set, PRO sub-study

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change
Parameter: Absenteeism (%)						
Baseline						
n (%)	760 (47.2)			317 (37.3)		
Mean	9.7			11.0		
SD	22.77			25.41		
Minimum	0			0		
Q1	0			0		
Median	0			0		

Visit Statistic	FTY720 N=1611 Base	Post	Change	Other DMT N=851 Base	Post	Change
Q3	6.3			5.1		
Maximum	100			100		
Month 6						
n (%)	362 (22.5)	362 (22.5)	362 (22.5)	148 (17.4)	148 (17.4)	148 (17.4)
Mean	8.2	6.2	-2.0	9.6	7.0	-2.6
SD	20.47	17.34	21.94	23.54	17.40	22.53
Minimum	0	0	-100	0	0	-100
Q1	0	0	0	0	0	0
Median	0	0	0	0	0	0
Q3	0	0	0	4.9	3.3	0
Maximum	100	100	100	100	100	91
Month 12						
n (%)	300 (18.6)	300 (18.6)	300 (18.6)	131 (15.4)	131 (15.4)	131 (15.4)
Mean	7.5	6.4	-1.1	8.6	6.0	-2.7
SD	20.18	17.32	21.25	21.98	14.22	22.68
Minimum	0	0	-100	0	0	-100
Q1	0.0	0.0	0.0	0.0	0.0	0.0
Median	0.0	0.0	0.0	0.0	0.0	0.0
Q3	0	0	0	2.4	0	0
Maximum	100	100	100	100	67	67
Month 24						
n (%)	208 (12.9)	208 (12.9)	208 (12.9)	102 (12.0)	102 (12.0)	102 (12.0)
Mean	7.9	3.6	-4.3	7.7	9.2	1.5
SD	21.13	13.98	23.44	18.77	21.31	26.90
Minimum	0	0	-100	0	0	-100
Q1	0	0	0	0	0	0
Median	0	0	0	0	0	0
Q3	0	0	0	6.3	9.7	0
Maximum	100	100	100	100	100	100
Year 3 (M36)						
n (%)	116 (7.2)	116 (7.2)	116 (7.2)	75 (8.8)	75 (8.8)	75 (8.8)
Mean	7.7	3.9	-3.8	5.5	5.1	-0.4
SD	21.02	16.43	26.18	14.26	14.93	14.18
Minimum	0	0	-100	0	0	-35
Q1	0.0	0.0	0.0	0.0	0.0	0.0
Median	0.0	0.0	0.0	0.0	0.0	0.0
Q3	0	0	0	5.0	0	0
Maximum	100	100	100	100	100	86
Year 4 (M48)						
n (%)	57 (3.5)	57 (3.5)	57 (3.5)	58 (6.8)	58 (6.8)	58 (6.8)
Mean	10.2	3.9	-6.3	4.7	4.5	-0.2
SD	25.27	15.42	27.66	14.72	10.70	17.59
Minimum	0	0	-100	0	0	-100
Q1	0	0	0	0	0	0

Visit Statistic	FTY720 N=1611 Base	Post	Change	Other DMT N=851 Base	Post	Change
Median	0	0	0	0	0	0
Q3	0	0	0	0	0	0
Maximum	100	100	80	100	41	41
Year 5 (M60)						
n (%)	34 (2.1)	34 (2.1)	34 (2.1)	27 (3.2)	27 (3.2)	27 (3.2)
Mean	4.5	2.2	-2.3	6.1	3.2	-2.9
SD	14.09	7.06	15.80	12.63	8.57	14.00
Minimum	0	0	-75	0	0	-33
Q1	0	0	0	0	0	-6.3
Median	0	0	0	0	0	0
Q3	0	0	0	6.3	0	0
Maximum	75	35	35	50	37	37
Parameter: Presentism (%)						
Baseline						
n (%)	798 (49.5)			347 (40.8)		
Mean	2.3			2.7		
SD	2.93			2.78		
Minimum	0			0		
Q1	0			0		
Median	1.0			2.0		
Q3	3.0			4.0		
Maximum	40			10		
Month 6						
n (%)	398 (24.7)	398 (24.7)	398 (24.7)	162 (19.0)	162 (19.0)	162 (19.0)
Mean	2.0	1.8	-0.2	2.3	2.5	0.2
SD	3.13	2.49	3.14	2.41	2.81	2.61
Minimum	0	0	-40	0	0	-8
Q1	0	0	-1.0	0	0	-1.0
Median	1.0	1.0	0	2.0	2.0	0
Q3	3.0	3.0	1.0	4.0	5.0	1.0
Maximum	40	20	19	10	10	10
Month 12						
n (%)	332 (20.6)	332 (20.6)	332 (20.6)	151 (17.7)	151 (17.7)	151 (17.7)
Mean	2.0	1.7	-0.2	2.2	2.1	0
SD	3.05	2.16	2.71	2.39	2.60	2.57
Minimum	0	0	-30	0	0	-8
Q1	0	0	-1.0	0	0	-1.0
Median	1.0	1.0	0	2.0	1.0	0
Q3	3.0	3.0	1.0	3.0	4.0	1.0
Maximum	40	10	8	10	10	10
Month 24						
n (%)	220 (13.7)	220 (13.7)	220 (13.7)	107 (12.6)	107 (12.6)	107 (12.6)
Mean	2.0	1.6	-0.4	2.3	2.3	0
SD	2.44	2.13	2.50	2.30	2.64	2.51

Visit / Statistic	FTY720 N=1611 Base	Post	Change	Other DMT N=851 Base	Post	Change
Minimum	0	0	-10	0	0	-6
Q1	0	0	-1.0	0	0	-2.0
Median	1.0	1.0	0	2.0	1.0	0
Q3	3.0	2.0	1.0	3.0	5.0	1.0
Maximum	10	10	9	10	10	8
Year 3 (M36)						
n (%)	127 (7.9)	127 (7.9)	127 (7.9)	82 (9.6)	82 (9.6)	82 (9.6)
Mean	2.0	1.4	-0.6	2.3	2.0	-0.2
SD	2.50	2.00	2.47	2.27	2.44	2.74
Minimum	0	0	-10	0	0	-8
Q1	0	0	-1.0	0	0	-2.0
Median	1.0	1.0	0	2.0	1.0	0
Q3	3.0	2.0	0	3.0	3.0	1.0
Maximum	10	10	5	10	10	8
Year 4 (M48)						
n (%)	60 (3.7)	60 (3.7)	60 (3.7)	65 (7.6)	65 (7.6)	65 (7.6)
Mean	1.8	1.6	-0.2	2.2	1.8	-0.3
SD	2.57	2.05	2.58	2.40	2.27	2.53
Minimum	0	0	-8	0	0	-8
Q1	0	0	-1.0	0	0	-2.0
Median	1.0	1.0	0	2.0	1.0	0
Q3	2.0	2.0	1.0	3.0	3.0	1.0
Maximum	10	8	6	10	10	8
Year 5 (M60)						
n (%)	38 (2.4)	38 (2.4)	38 (2.4)	32 (3.8)	32 (3.8)	32 (3.8)
Mean	1.4	1.5	0.1	2.3	1.6	-0.6
SD	1.85	2.23	2.28	2.00	2.55	2.46
Minimum	0	0	-7	0	0	-6
Q1	0	0	-1.0	0.5	0	-2.0
Median	1.0	0	0	2.0	0.5	-0.5
Q3	2.0	2.0	1.0	3.0	2.0	0
Maximum	8	9	7	7	9	7
Parameter: Work productivity loss (%)						
Baseline						
n (%)	737 (45.7)			302 (35.5)		
Mean	25.9			28.1		
SD	28.96			28.73		
Minimum	0			0		
Q1	0			0		
Median	13.3			20.0		
Q3	41.7			47.5		
Maximum	100			100		
Month 6						
n (%)	346 (21.5)	346 (21.5)	346 (21.5)	138 (16.2)	138 (16.2)	138 (16.2)

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change
Mean	22.3	20.8	-1.5	26.5	26.7	0.1
SD	26.89	25.44	26.01	26.83	27.67	23.70
Minimum	0	0	-100	0	0	-100
Q1	0	0	-10.0	0	0	-10.0
Median	10.0	10.0	0.0	20.0	20.0	0
Q3	31.8	30.0	10.0	41.9	46.0	10.0
Maximum	100	100	80	100	100	63
Month 12						
n (%)	287 (17.8)	287 (17.8)	287 (17.8)	125 (14.7)	125 (14.7)	125 (14.7)
Mean	21.2	20.9	-0.4	25.7	23.1	-2.6
SD	25.01	24.18	25.13	26.26	26.31	28.03
Minimum	0	0	-100	0	0	-90
Q1	0	0	-10.0	0	0	-20.0
Median	10.0	10.0	0	20.0	10.0	0
Q3	30.0	30.0	10.0	40.0	40.0	10.0
Maximum	100	100	84	100	100	90
Month 24						
n (%)	196 (12.2)	196 (12.2)	196 (12.2)	95 (11.2)	95 (11.2)	95 (11.2)
Mean	22.8	18.5	-4.3	26.2	25.6	-0.6
SD	26.24	23.12	27.33	24.84	27.06	24.13
Minimum	0	0	-100	0	0	-80
Q1	0.0	0.0	-18.7	0.0	0.0	-10.3
Median	10.0	10.0	0.0	20.0	13.9	0.0
Q3	30.0	30.0	10.0	40.6	50.0	13.6
Maximum	100	100	90	100	100	60
Year 3 (M36)						
n (%)	108 (6.7)	108 (6.7)	108 (6.7)	73 (8.6)	73 (8.6)	73 (8.6)
Mean	22.5	15.3	-7.2	24.3	22.9	-1.5
SD	27.48	22.32	29.37	23.64	24.73	24.51
Minimum	0	0	-100	0	0	-60
Q1	0	0	-19.4	10.0	0	-17.8
Median	10.0	10.0	0	20.0	20.0	0
Q3	39.4	20.0	2.2	36.8	33.3	10.0
Maximum	100	100	100	100	100	60
Year 4 (M48)						
n (%)	52 (3.2)	52 (3.2)	52 (3.2)	57 (6.7)	57 (6.7)	57 (6.7)
Mean	21.4	15.4	-6.0	19.9	20.1	0.1
SD	28.63	20.97	27.09	19.53	23.65	26.06
Minimum	0	0	-82	0	0	-60
Q1	0	0	-10.0	10.0	0	-20.0
Median	10.0	10.0	0	16.7	10.0	0
Q3	36.3	20.0	2.1	30.0	30.6	16.3
Maximum	100	90	60	88	80	80
Year 5 (M60)						

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change
n (%)	33 (2.0)	33 (2.0)	33 (2.0)	26 (3.1)	26 (3.1)	26 (3.1)
Mean	18.4	16.6	-1.7	23.9	16.8	-7.1
SD	21.65	23.77	25.74	21.10	25.14	26.12
Minimum	0	0	-85	0	0	-47
Q1	0	0	-10.0	10	0.0	-20.0
Median	10.0	0	0	20.0	5.0	-10.0
Q3	30.0	30.0	4.1	34.4	28.0	0
Maximum	95	94	74	75	94	74
Parameter: Activity impairment (%)						
Baseline						
n (%)	1245 (77.3)			591 (69.4)		
Mean	33.3			37.1		
SD	29.94			30.33		
Minimum	0			0		
Q1	0			10.0		
Median	30.0			30.0		
Q3	60.0			60.0		
Maximum	100			100		
Month 6						
n (%)	667 (41.4)	667 (41.4)	667 (41.4)	308 (36.2)	308 (36.2)	308 (36.2)
Mean	30.4	29.5	-0.9	36.8	36.8	0
SD	29.04	28.46	23.86	29.64	29.26	23.62
Minimum	0	0	-80	0	0	-70
Q1	0	0	-10.0	10.0	10.0	-10.0
Median	20.0	20.0	0	30.0	40.0	0
Q3	50.0	50.0	10.0	60.0	60.0	10.0
Maximum	100	100	80	100	100	100
Month 12						
n (%)	529 (32.8)	529 (32.8)	529 (32.8)	283 (33.3)	283 (33.3)	283 (33.3)
Mean	28.5	26.0	-2.5	32.8	32.8	0
SD	27.73	26.95	24.46	28.29	29.55	26.69
Minimum	0	0	-100	0	0	-90
Q1	0	0	-10.0	10.0	0	-10.0
Median	20.0	20.0	0	30.0	30.0	0
Q3	50.0	50.0	10.0	60.0	60.0	10.0
Maximum	100	100	80	90	100	100
Month 24						
n (%)	373 (23.2)	373 (23.2)	373 (23.2)	215 (25.3)	215 (25.3)	215 (25.3)
Mean	27.7	24.3	-3.5	36.3	36.5	0.1
SD	26.98	26.42	25.79	28.32	30.53	23.89
Minimum	0	0	-80	0	0	-70
Q1	0	0	-20.0	10.0	10.0	-10.0
Median	20.0	10.0	0	30.0	30.0	0
Q3	50.0	40.0	10.0	60.0	60.0	10.0

Visit Statistic	FTY720 N=1611 Base	Post	Change	Other DMT N=851 Base	Post	Change
Maximum	100	100	80	100	100	80
Year 3 (M36)						
n (%)	216 (13.4)	216 (13.4)	216 (13.4)	147 (17.3)	147 (17.3)	147 (17.3)
Mean	27.4	23.6	-3.8	33.7	34.2	0.5
SD	27.85	25.48	27.81	27.02	29.72	28.21
Minimum	0	0	-90	0	0	-80
Q1	0.0	0	-15.0	10.0	10.0	-20.0
Median	20.0	20.0	0	30.0	30.0	0
Q3	50.0	40.0	10.0	60.0	60.0	20.0
Maximum	100	100	80	100	100	90
Year 4 (M48)						
n (%)	122 (7.6)	122 (7.6)	122 (7.6)	123 (14.5)	123 (14.5)	123 (14.5)
Mean	27.4	26.4	-1.0	29.8	33.7	3.9
SD	27.51	27.06	26.83	26.21	30.36	26.94
Minimum	0	0	-70	0	0	-90
Q1	0.0	0	-10.0	10.0	0	-10.0
Median	20.0	20.0	0	20.0	30.0	0
Q3	50.0	50.0	10.0	60.0	60.0	20.0
Maximum	100	100	80	90	100	80
Year 5 (M60)						
n (%)	63 (3.9)	63 (3.9)	63 (3.9)	59 (6.9)	59 (6.9)	59 (6.9)
Mean	24.4	22.9	-1.6	28.6	23.1	-5.6
SD	26.63	27.03	30.33	26.68	29.08	28.42
Minimum	0	0	-70	0	0	-70
Q1	0	0	-10.0	0	0	-20.0
Median	10.0	10.0	0	20.0	10.0	0
Q3	40.0	40.0	10.0	50.0	40.0	0
Maximum	100	90	80	100	90	90

n = the number of patients with data at baseline and respective post-dose assessment. At Baseline visit n is the number of all patients with baseline data.
Baseline is defined as last value prior to administration of the first dose of initial cohort treatment in the study.
Data as per Group G general safety rules are used.
Change = post - base.
If a patient had more than one assessment in a time interval, the one closest to the target time point was summarized. If two assessments were equally close the latter was chosen.
WPAI-GH = Work Productivity and Activity Impairment Questionnaire: General Health.

Multiple Sclerosis Impact Scale (MSIS-29):

Table 10-87 Summary of MSIS-29 scores by visit, Group G, Safety set, PRO sub-study

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change
Parameter: Physical impact (%)						
Baseline						
n (%)	1254 (77.8)			606 (71.2)		
Mean	25.7			30.0		
SD	23.94			25.28		
Minimum	0			0		
Q1	5.0			7.5		
Median	17.5			23.8		
Q3	42.5			48.7		
Maximum	99			100		
Month 6						
n (%)	673 (41.8)	673 (41.8)	673 (41.8)	317 (37.3)	317 (37.3)	317 (37.3)
Mean	23.8	22.1	-1.7	28.8	28.3	-0.5
SD	22.87	21.68	13.64	25.23	24.83	14.89
Minimum	0	0	-81	0	0	-68
Q1	5.0	3.8	-7.5	6.3	6.3	-5.0
Median	16.3	15.0	-0.9	22.5	22.5	0
Q3	38.8	36.3	3.8	47.5	47.5	6.3
Maximum	98	100	55	96	94	55
Month 12						
n (%)	547 (34.0)	547 (34.0)	547 (34.0)	301 (35.4)	301 (35.4)	301 (35.4)
Mean	21.3	20.0	-1.3	24.9	25.9	1.0
SD	21.34	20.61	14.23	22.73	24.42	14.82
Minimum	0	0	-61	0	0	-79
Q1	3.8	2.5	-7.5	5.9	5.0	-5.0
Median	15.0	13.8	0	17.5	18.8	0
Q3	32.5	30.0	3.8	40.0	41.3	6.3
Maximum	96	93	58	91	100	54
Month 24						
n (%)	385 (23.9)	385 (23.9)	385 (23.9)	222 (26.1)	222 (26.1)	222 (26.1)
Mean	20.2	19.3	-0.9	27.0	27.8	0.8
SD	20.97	20.60	15.68	22.39	24.15	15.81
Minimum	0	0	-85	0	0	-79
Q1	3.8	2.5	-6.3	8.8	7.5	-8.8
Median	12.5	12.5	0	23.8	22.5	0
Q3	31.3	28.8	5.0	41.3	43.8	8.8

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change
Maximum	98	94	63	91	99	53
Year 3 (M36)						
n (%)	226 (14.0)	226 (14.0)	226 (14.0)	147 (17.3)	147 (17.3)	147 (17.3)
Mean	19.7	18.1	-1.6	24.2	26.0	1.9
SD	20.40	18.63	16.41	21.58	25.15	18.27
Minimum	0	0	-81	0	0	-79
Q1	3.8	2.5	-8.8	6.3	5.0	-6.3
Median	12.5	12.5	0	18.8	16.3	0
Q3	30.0	27.5	6.3	37.5	42.5	9.9
Maximum	96	85	59	84	100	69
Year 4 (M48)						
n (%)	130 (8.1)	130 (8.1)	130 (8.1)	124 (14.6)	124 (14.6)	124 (14.6)
Mean	19.3	17.8	-1.4	24.9	24.8	-0.1
SD	20.70	19.10	16.61	21.82	22.08	17.62
Minimum	0	0	-66	0	0	-54
Q1	2.5	3.8	-5.0	7.5	4.4	-6.3
Median	12.5	12.5	0	19.4	19.4	0
Q3	30.0	25.0	3.8	37.5	40.0	10.0
Maximum	76	88	60	89	90	56
Year 5 (M60)						
n (%)	63 (3.9)	63 (3.9)	63 (3.9)	59 (6.9)	59 (6.9)	59 (6.9)
Mean	17.8	18.6	0.7	20.4	22.8	2.3
SD	19.62	21.13	18.88	22.39	26.53	23.49
Minimum	0	0	-67	0	0	-78
Q1	3.8	2.5	-6.3	5.0	3.8	-6.3
Median	12.5	10.5	-1.3	12.5	12.5	0
Q3	25.0	28.8	5.0	26.3	33.8	8.8
Maximum	76	85	69	89	95	89
Parameter: Psychological impact (%)						
Baseline						
n (%)	1244 (77.2)			598 (70.3)		
Mean	34.5			34.9		
SD	25.85			25.75		
Minimum	0			0		
Q1	13.9			13.9		
Median	30.6			30.6		
Q3	52.8			50.0		
Maximum	100			100		
Month 6						
n (%)	668 (41.5)	668 (41.5)	668 (41.5)	308 (36.2)	308 (36.2)	308 (36.2)
Mean	32.0	28.7	-3.3	33.4	32.5	-0.9
SD	25.11	24.19	17.79	25.65	25.80	19.91
Minimum	0	0	-81	0	0	-76
Q1	11.8	8.3	-11.1	11.1	11.1	-8.3

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change
Median	25.0	22.2	-2.8	27.8	27.8	0
Q3	47.2	43.1	5.6	47.2	50.0	5.6
Maximum	100	100	58	100	100	72
Month 12						
n (%)	541 (33.6)	541 (33.6)	541 (33.6)	292 (34.3)	292 (34.3)	292 (34.3)
Mean	29.7	26.3	-3.4	30.7	30.4	-0.3
SD	23.53	22.93	18.78	24.13	25.91	21.14
Minimum	0	0	-72	0	0	-92
Q1	11.1	8.3	-13.9	11.1	8.3	-11.1
Median	25.0	19.4	-2.8	25.0	22.2	0
Q3	41.7	40.6	5.6	44.4	51.4	11.1
Maximum	100	94	94	100	100	69
Month 24						
n (%)	375 (23.3)	375 (23.3)	375 (23.3)	218 (25.6)	218 (25.6)	218 (25.6)
Mean	28.7	24.6	-4.0	31.8	30.8	-1.0
SD	23.83	22.53	21.08	22.57	24.52	19.44
Minimum	0	0	-72	0	0	-92
Q1	11.1	5.6	-13.9	13.9	11.1	-11.1
Median	22.2	19.4	-2.8	27.8	26.4	0
Q3	41.7	36.1	5.6	44.4	50.0	8.3
Maximum	100	100	58	97	100	78
Year 3 (M36)						
n (%)	225 (14.0)	225 (14.0)	225 (14.0)	142 (16.7)	142 (16.7)	142 (16.7)
Mean	29.6	24.0	-5.7	30.7	29.1	-1.6
SD	24.19	21.44	20.74	22.37	24.81	20.35
Minimum	0	0	-86	0	0	-83
Q1	11.1	5.6	-16.7	11.1	11.1	-11.1
Median	22.2	19.4	-5.6	26.4	20.8	-1.4
Q3	41.7	38.9	5.6	44.4	44.4	8.3
Maximum	100	89	53	97	100	58
Year 4 (M48)						
n (%)	129 (8.0)	129 (8.0)	129 (8.0)	121 (14.2)	121 (14.2)	121 (14.2)
Mean	27.1	22.8	-4.3	31.0	26.6	-4.4
SD	23.78	20.69	20.47	22.04	21.70	19.53
Minimum	0	0	-64	3	0	-53
Q1	8.3	5.6	-13.9	11.1	8.3	-13.9
Median	22.2	16.7	-2.8	27.8	19.4	-2.8
Q3	38.9	33.3	5.6	44.4	41.7	5.6
Maximum	97	92	61	97	94	61
Year 5 (M60)						
n (%)	63 (3.9)	63 (3.9)	63 (3.9)	59 (6.9)	59 (6.9)	59 (6.9)
Mean	30.4	23.4	-7.0	29.1	22.9	-6.2
SD	23.69	20.55	21.95	23.73	24.58	22.67
Minimum	0	0	-67	0	0	-67

Visit	FTY720 N=1611			Other DMT N=851		
Statistic	Base	Post	Change	Base	Post	Change
Q1	13.9	8.3	-16.7	11.1	5.6	-19.4
Median	25.0	16.7	-8.3	25.0	13.9	-5.6
Q3	41.7	38.9	0	44.4	27.8	0
Maximum	92	75	64	97	100	64

n = the number of patients with data at baseline and respective post-dose assessment. At Baseline visit n is the number of all patients with baseline data.
Baseline is defined as last value prior to administration of the first dose of initial cohort treatment in the study.
Data as per Group G general safety rules are used.
Change = post - base.
If a patient had more than one assessment in a time interval, the one closest to the target time point was summarized. If two assessments were equally close the latter was chosen.
MSIS = MS Impact Scale.

Safety Results

Table 10-18 **IR of AEs per 100 PTY by primary SOC, PT, and initial cohort treatment with cut-off 0.5 per 100 PTY by any cohort, Group G, Safety set**

Primary system organ class Preferred term	FTY720 N=2112 n (%)	 IR (95% CI)	Other DMTs N=1138 n (%)	 IR (95% CI)	Incidence rate ratio IRR (95% CI)
-Any primary system organ class					
-Total	1747 (82.7)	163.3 (155.77; 171.18)	918 (80.7)	160.7 (150.50; 171.47)	1.02 (0.94; 1.10)
BLOOD AND LYMPHATIC SY STEM DISORDERS					
-Total	196 (9.3)	4.4 (3.77; 5.01)	79 (6.9)	2.7 (2.13; 3.35)	1.62 (1.24; 2.13)
LYMPHOPENIA	130 (6.2)	2.8 (2.35; 3.33)	33 (2.9)	1.1 (0.75; 1.53)	2.59 (1.75; 3.91)

Primary system organ class Preferred term	FTY720 N=2112 n (%)	IR (95% CI)	Other DMTs N=1138 n (%)	IR (95% CI)	Incidence rate ratio IRR (95% CI)
LEUKOPENIA	34 (1.6)	0.7 (0.49; 0.98)	9 (0.8)	0.3 (0.13; 0.55)	2.45 (1.15; 5.80)
CARDIAC DISORDERS					
-Total	225 (10.7)	5.1 (4.46; 5.81)	54 (4.7)	1.8 (1.35; 2.34)	2.85 (2.11; 3.91)
BRADYCARDIA	52 (2.5)	1.1 (0.81; 1.43)	3 (0.3)	0.1 (0.02; 0.28)	11.38 (3.69; 56.98)
PALPITATIONS	48 (2.3)	1.0 (0.74; 1.32)	20 (1.8)	0.6 (0.40; 1.00)	1.54 (0.90; 2.74)
SINUS BRADYCARDIA	48 (2.3)	1.0 (0.74; 1.33)	1 (0.1)	<.1 (<.01; 0.18)	31.48 (5.39; 1268.8)
EAR AND LABYRINTH DISORDERS					
-Total	145 (6.9)	3.2 (2.66; 3.71)	96 (8.4)	3.3 (2.65; 3.99)	0.96 (0.74; 1.26)
VERTIGO	87 (4.1)	1.8 (1.48; 2.27)	49 (4.3)	1.6 (1.20; 2.14)	1.14 (0.79; 1.65)
TINNITUS	20 (0.9)	0.4 (0.25; 0.63)	18 (1.6)	0.6 (0.34; 0.92)	0.71 (0.35; 1.42)
ENDOCRINE DISORDERS					
-Total	22 (1.0)	0.5 (0.28; 0.69)	18 (1.6)	0.6 (0.34; 0.92)	0.78 (0.40; 1.55)
EYE DISORDERS					
-Total	386 (18.3)	9.5 (8.55; 10.47)	193 (17.0)	7.2 (6.18; 8.24)	1.32 (1.11; 1.58)
VISION BLURRED	118 (5.6)	2.5 (2.10; 3.04)	69 (6.1)	2.3 (1.80; 2.93)	1.10 (0.81; 1.50)
EYE PAIN	59 (2.8)	1.2 (0.94; 1.59)	21 (1.8)	0.7 (0.42; 1.04)	1.82 (1.09; 3.15)
DRY EYE	28 (1.3)	0.6 (0.39; 0.84)	12 (1.1)	0.4 (0.20; 0.67)	1.51 (0.74; 3.25)
VISUAL IMPAIRMENT	28 (1.3)	0.6 (0.38; 0.84)	23 (2.0)	0.7 (0.47; 1.11)	0.78 (0.43; 1.42)
DIPLOPIA	26 (1.2)	0.5 (0.35; 0.78)	23 (2.0)	0.7 (0.47; 1.12)	0.72 (0.39; 1.32)
GASTROINTESTINAL DISORDERS					
-Total	449 (21.3)	11.3 (10.24; 12.34)	353 (31.0)	15.8 (14.18; 17.52)	0.71 (0.62; 0.82)
NAUSEA	141 (6.7)	3.1 (2.57; 3.61)	101 (8.9)	3.5 (2.84; 4.23)	0.88 (0.67; 1.14)
DIARRHOEA	89 (4.2)	1.9 (1.51; 2.32)	93 (8.2)	3.2 (2.57; 3.90)	0.59 (0.44; 0.80)
CONSTIPATION	73 (3.5)	1.5 (1.20; 1.93)	53 (4.7)	1.8 (1.32; 2.31)	0.87 (0.60; 1.26)
VOMITING	49 (2.3)	1.0 (0.76; 1.35)	51 (4.5)	1.7 (1.26; 2.22)	0.60 (0.40; 0.91)
ABDOMINAL PAIN	40 (1.9)	0.8 (0.59; 1.13)	36 (3.2)	1.2 (0.83; 1.63)	0.71 (0.44; 1.14)
GASTROOESOPHAGEAL REFLUX DISEASE	37 (1.8)	0.8 (0.54; 1.06)	26 (2.3)	0.8 (0.55; 1.24)	0.91 (0.54; 1.56)
DYSPHAGIA	27 (1.3)	0.6 (0.37; 0.81)	26 (2.3)	0.8 (0.55; 1.23)	0.66 (0.37; 1.18)
ABDOMINAL PAIN UPPER	21 (1.0)	0.4 (0.27; 0.66)	22 (1.9)	0.7 (0.44; 1.07)	0.61 (0.32; 1.16)
ABDOMINAL DISCOMFORT	17 (0.8)	0.3 (0.20; 0.56)	29 (2.5)	0.9 (0.63; 1.36)	0.37 (0.19; 0.69)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					

Primary system organ class Preferred term	FTY720 N=2112 n (%)	IR (95% CI)	Other DMTs N=1138 n (%)	IR (95% CI)	Incidence rate ratio IRR (95% CI)
LEUKOPENIA	34 (1.6)	0.7 (0.49; 0.98)	9 (0.8)	0.3 (0.13; 0.55)	2.45 (1.15; 5.80)
CARDIAC DISORDERS					
-Total	225 (10.7)	5.1 (4.46; 5.81)	54 (4.7)	1.8 (1.35; 2.34)	2.85 (2.11; 3.91)
BRADYCARDIA	52 (2.5)	1.1 (0.81; 1.43)	3 (0.3)	0.1 (0.02; 0.28)	11.38 (3.69; 56.98)
PALPITATIONS	48 (2.3)	1.0 (0.74; 1.32)	20 (1.8)	0.6 (0.40; 1.00)	1.54 (0.90; 2.74)
SINUS BRADYCARDIA	48 (2.3)	1.0 (0.74; 1.33)	1 (0.1)	<.1 (<.01; 0.18)	31.48 (5.39; 1268.8)
EAR AND LABYRINTH DISORDERS					
-Total	145 (6.9)	3.2 (2.66; 3.71)	96 (8.4)	3.3 (2.65; 3.99)	0.96 (0.74; 1.26)
VERTIGO	87 (4.1)	1.8 (1.48; 2.27)	49 (4.3)	1.6 (1.20; 2.14)	1.14 (0.79; 1.65)
TINNITUS	20 (0.9)	0.4 (0.25; 0.63)	18 (1.6)	0.6 (0.34; 0.92)	0.71 (0.35; 1.42)
ENDOCRINE DISORDERS					
-Total	22 (1.0)	0.5 (0.28; 0.69)	18 (1.6)	0.6 (0.34; 0.92)	0.78 (0.40; 1.55)
EYE DISORDERS					
-Total	386 (18.3)	9.5 (8.55; 10.47)	193 (17.0)	7.2 (6.18; 8.24)	1.32 (1.11; 1.58)
VISION BLURRED	118 (5.6)	2.5 (2.10; 3.04)	69 (6.1)	2.3 (1.80; 2.93)	1.10 (0.81; 1.50)
EYE PAIN	59 (2.8)	1.2 (0.94; 1.59)	21 (1.8)	0.7 (0.42; 1.04)	1.82 (1.09; 3.15)
DRY EYE	28 (1.3)	0.6 (0.39; 0.84)	12 (1.1)	0.4 (0.20; 0.67)	1.51 (0.74; 3.25)
VISUAL IMPAIRMENT	28 (1.3)	0.6 (0.38; 0.84)	23 (2.0)	0.7 (0.47; 1.11)	0.78 (0.43; 1.42)
DIPLOPIA	26 (1.2)	0.5 (0.35; 0.78)	23 (2.0)	0.7 (0.47; 1.12)	0.72 (0.39; 1.32)
GASTROINTESTINAL DISORDERS					
-Total	449 (21.3)	11.3 (10.24; 12.34)	353 (31.0)	15.8 (14.18; 17.52)	0.71 (0.62; 0.82)
NAUSEA	141 (6.7)	3.1 (2.57; 3.61)	101 (8.9)	3.5 (2.84; 4.23)	0.88 (0.67; 1.14)
DIARRHOEA	89 (4.2)	1.9 (1.51; 2.32)	93 (8.2)	3.2 (2.57; 3.90)	0.59 (0.44; 0.80)
CONSTIPATION	73 (3.5)	1.5 (1.20; 1.93)	53 (4.7)	1.8 (1.32; 2.31)	0.87 (0.60; 1.26)
VOMITING	49 (2.3)	1.0 (0.76; 1.35)	51 (4.5)	1.7 (1.26; 2.22)	0.60 (0.40; 0.91)
ABDOMINAL PAIN	40 (1.9)	0.8 (0.59; 1.13)	36 (3.2)	1.2 (0.83; 1.63)	0.71 (0.44; 1.14)
GASTROOESOPHAGEAL REFLUX DISEASE	37 (1.8)	0.8 (0.54; 1.06)	26 (2.3)	0.8 (0.55; 1.24)	0.91 (0.54; 1.56)
DYSPHAGIA	27 (1.3)	0.6 (0.37; 0.81)	26 (2.3)	0.8 (0.55; 1.23)	0.66 (0.37; 1.18)
ABDOMINAL PAIN UPPER	21 (1.0)	0.4 (0.27; 0.66)	22 (1.9)	0.7 (0.44; 1.07)	0.61 (0.32; 1.16)
ABDOMINAL DISCOMFORT	17 (0.8)	0.3 (0.20; 0.56)	29 (2.5)	0.9 (0.63; 1.36)	0.37 (0.19; 0.69)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					

Primary system organ class Preferred term	FTY720 N=2112 n (%)	 IR (95% CI)	Other DMTs N=1138 n (%)	 IR (95% CI)	Incidence rate ratio IRR (95% CI)
INFLUENZA	44 (2.1)	0.9 (0.66; 1.23)	23 (2.0)	0.7 (0.47; 1.12)	1.23 (0.73; 2.13)
PNEUMONIA	35 (1.7)	0.7 (0.50; 1.00)	15 (1.3)	0.5 (0.27; 0.80)	1.50 (0.80; 2.95)
CELLULITIS	13 (0.6)	0.3 (0.14; 0.46)	18 (1.6)	0.6 (0.34; 0.92)	0.46 (0.21; 0.99)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS					
-Total	263 (12.5)	6.0 (5.32; 6.80)	223 (19.6)	8.8 (7.64; 9.98)	0.69 (0.57; 0.83)
FALL	115 (5.4)	2.5 (2.03; 2.95)	97 (8.5)	3.3 (2.71; 4.08)	0.73 (0.56; 0.97)
CONTUSION	25 (1.2)	0.5 (0.33; 0.76)	21 (1.8)	0.7 (0.42; 1.04)	0.76 (0.41; 1.42)
INVESTIGATIONS					
-Total	457 (21.6)	11.5 (10.45; 12.58)	198 (17.4)	7.4 (6.44; 8.55)	1.54 (1.30; 1.83)
LYMPHOCYTE COUNT DECREASED	138 (6.5)	3.0 (2.52; 3.54)	32 (2.8)	1.0 (0.71; 1.47)	2.89 (1.95; 4.38)
ALANINE AMINOTRANSFERASE INCREASED	56 (2.7)	1.2 (0.88; 1.51)	15 (1.3)	0.5 (0.27; 0.80)	2.42 (1.35; 4.60)
WEIGHT INCREASED	44 (2.1)	0.9 (0.66; 1.22)	36 (3.2)	1.2 (0.83; 1.64)	0.77 (0.48; 1.23)
WHITE BLOOD CELL COUNT DECREASED	43 (2.0)	0.9 (0.65; 1.20)	10 (0.9)	0.3 (0.15; 0.59)	2.78 (1.38; 6.21)
HEPATIC ENZYME INCREASED	37 (1.8)	0.8 (0.54; 1.06)	9 (0.8)	0.3 (0.13; 0.55)	2.66 (1.26; 6.27)
WEIGHT DECREASED	36 (1.7)	0.7 (0.52; 1.03)	33 (2.9)	1.1 (0.74; 1.52)	0.69 (0.42; 1.14)
ASPARTATE AMINOTRANSFERASE INCREASED	29 (1.4)	0.6 (0.40; 0.86)	9 (0.8)	0.3 (0.13; 0.55)	2.07 (0.95; 4.97)
BLOOD PRESSURE INCREASED	28 (1.3)	0.6 (0.38; 0.84)	10 (0.9)	0.3 (0.15; 0.59)	1.81 (0.85; 4.18)
LIVER FUNCTION TEST INCREASED	26 (1.2)	0.5 (0.35; 0.78)	11 (1.0)	0.4 (0.18; 0.63)	1.52 (0.72; 3.40)
METABOLISM AND NUTRITION DISORDERS					
-Total	160 (7.6)	3.5 (2.98; 4.09)	124 (10.9)	4.4 (3.64; 5.22)	0.80 (0.63; 1.02)
VITAMIN D DEFICIENCY	52 (2.5)	1.1 (0.81; 1.42)	50 (4.4)	1.7 (1.24; 2.20)	0.65 (0.43; 0.98)
DECREASED APPETITE	26 (1.2)	0.5 (0.35; 0.78)	15 (1.3)	0.5 (0.27; 0.79)	1.11 (0.57; 2.26)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS					
-Total	663 (31.4)	18.8 (17.35; 20.23)	445 (39.1)	22.5 (20.41; 24.64)	0.84 (0.74; 0.94)
PAIN IN EXTREMITY	168 (8.0)	3.7 (3.14; 4.28)	139 (12.2)	5.0 (4.17; 5.86)	0.74 (0.59; 0.93)
MUSCULAR WEAKNESS	148 (7.0)	3.2 (2.71; 3.76)	119 (10.5)	4.1 (3.41; 4.92)	0.78 (0.61; 1.00)

Primary system organ class Preferred term	FTY720 N=2112 n (%)	 IR (95% CI)	Other DMTs N=1138 n (%)	 IR (95% CI)	Incidence rate ratio IRR (95% CI)
MUSCLE SPASMS	142 (6.7)	3.1 (2.59; 3.62)	103 (9.1)	3.6 (2.90; 4.31)	0.86 (0.67; 1.13)
ARTHRALGIA	136 (6.4)	2.9 (2.46; 3.47)	83 (7.3)	2.9 (2.27; 3.54)	1.03 (0.78; 1.37)
BACK PAIN	133 (6.3)	2.9 (2.40; 3.40)	101 (8.9)	3.5 (2.85; 4.25)	0.82 (0.63; 1.08)
NECK PAIN	54 (2.6)	1.1 (0.84; 1.46)	37 (3.3)	1.2 (0.86; 1.68)	0.92 (0.59; 1.44)
MUSCULOSKELETAL PAIN	39 (1.8)	0.8 (0.57; 1.10)	38 (3.3)	1.2 (0.88; 1.72)	0.65 (0.40; 1.04)
MUSCULOSKELETAL STIFFNESS	38 (1.8)	0.8 (0.56; 1.08)	26 (2.3)	0.8 (0.55; 1.24)	0.93 (0.55; 1.60)
MUSCULOSKELETAL CHEST PAIN	25 (1.2)	0.5 (0.33; 0.76)	13 (1.1)	0.4 (0.22; 0.71)	1.24 (0.61; 2.64)
MYALGIA	21 (1.0)	0.4 (0.27; 0.66)	17 (1.5)	0.5 (0.32; 0.88)	0.79 (0.39; 1.59)
SPINAL OSTEOARTHRITIS	11 (0.5)	0.2 (0.11; 0.40)	16 (1.4)	0.5 (0.29; 0.84)	0.44 (0.18; 1.01)
OSTEOARTHRITIS	10 (0.5)	0.2 (0.10; 0.38)	16 (1.4)	0.5 (0.29; 0.84)	0.40 (0.16; 0.93)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)					
-Total	318 (15.1)	7.3 (6.55; 8.19)	243 (21.4)	10.0 (8.75; 11.29)	0.74 (0.62; 0.87)
MELANOCYTIC NAEVUS	175 (8.3)	3.8 (3.25; 4.40)	144 (12.7)	5.3 (4.50; 6.29)	0.71 (0.57; 0.89)
SEBORRHOEIC KERATOSIS	108 (5.1)	2.3 (1.87; 2.75)	72 (6.3)	2.5 (1.92; 3.09)	0.93 (0.68; 1.27)
HAEMANGIOMA OF SKIN	48 (2.3)	1.0 (0.73; 1.32)	46 (4.0)	1.5 (1.13; 2.05)	0.65 (0.42; 0.99)
BASAL CELL CARCINOMA	26 (1.2)	0.5 (0.35; 0.79)	11 (1.0)	0.4 (0.18; 0.63)	1.52 (0.73; 3.41)
SKIN PAPILLOMA	20 (0.9)	0.4 (0.25; 0.64)	16 (1.4)	0.5 (0.30; 0.84)	0.80 (0.39; 1.65)
FIBROUS HISTIOCYTOMA	19 (0.9)	0.4 (0.24; 0.61)	27 (2.4)	0.9 (0.58; 1.28)	0.44 (0.23; 0.83)
HAEMANGIOMA	16 (0.8)	0.3 (0.19; 0.53)	19 (1.7)	0.6 (0.37; 0.96)	0.53 (0.26; 1.10)
NERVOUS SYSTEM DISORDERS					
-Total	955 (45.2)	32.9 (30.85; 35.06)	553 (48.6)	30.9 (28.36; 33.56)	1.07 (0.96; 1.19)
HEADACHE	292 (13.8)	6.7 (6.00; 7.57)	122 (10.7)	4.2 (3.52; 5.06)	1.59 (1.29; 1.98)
HYPOAESTHESIA	168 (8.0)	3.7 (3.13; 4.26)	143 (12.6)	5.1 (4.27; 5.97)	0.72 (0.57; 0.91)
PARAESTHESIA	156 (7.4)	3.4 (2.90; 3.99)	130 (11.4)	4.6 (3.85; 5.47)	0.74 (0.58; 0.94)
DIZZINESS	98 (4.6)	2.1 (1.68; 2.53)	43 (3.8)	1.4 (1.02; 1.91)	1.47 (1.01; 2.15)
MIGRAINE	98 (4.6)	2.1 (1.69; 2.54)	40 (3.5)	1.3 (0.94; 1.79)	1.59 (1.09; 2.36)
DIZZINESS POSTURAL	67 (3.2)	1.4 (1.09; 1.79)	27 (2.4)	0.9 (0.58; 1.28)	1.60 (1.01; 2.60)
TREMOR	56 (2.7)	1.2 (0.88; 1.52)	38 (3.3)	1.2 (0.88; 1.70)	0.94 (0.61; 1.46)

Primary system organ class Preferred term	FTY720 N=2112 n (%)	 IR (95% CI)	Other DMTs N=1138 n (%)	 IR (95% CI)	Incidence rate ratio IRR (95% CI)
BALANCE DISORDER	54 (2.6)	1.1 (0.85; 1.47)	52 (4.6)	1.7 (1.28; 2.24)	0.66 (0.44; 0.98)
MEMORY IMPAIRMENT	54 (2.6)	1.1 (0.85; 1.47)	32 (2.8)	1.0 (0.72; 1.48)	1.08 (0.69; 1.73)
COGNITIVE DISORDER	48 (2.3)	1.0 (0.74; 1.32)	48 (4.2)	1.6 (1.17; 2.09)	0.63 (0.41; 0.96)
MUSCLE SPASTICITY	43 (2.0)	0.9 (0.65; 1.20)	38 (3.3)	1.2 (0.88; 1.71)	0.72 (0.45; 1.14)
NEURALGIA	35 (1.7)	0.7 (0.50; 1.01)	16 (1.4)	0.5 (0.29; 0.84)	1.40 (0.76; 2.72)
OPTIC NEURITIS	34 (1.6)	0.7 (0.49; 0.98)	28 (2.5)	0.9 (0.60; 1.31)	0.77 (0.46; 1.32)
DISTURBANCE IN ATTENTION	33 (1.6)	0.7 (0.47; 0.96)	15 (1.3)	0.5 (0.27; 0.80)	1.41 (0.75; 2.80)
MULTIPLE SCLEROSIS RELAPSE	32 (1.5)	0.7 (0.45; 0.93)	11 (1.0)	0.4 (0.18; 0.63)	1.87 (0.92; 4.12)
BURNING SENSATION	30 (1.4)	0.6 (0.42; 0.89)	24 (2.1)	0.8 (0.50; 1.16)	0.80 (0.45; 1.43)
AMNESIA	27 (1.3)	0.6 (0.37; 0.81)	35 (3.1)	1.1 (0.80; 1.59)	0.49 (0.28; 0.83)
RESTLESS LEGS SYNDROME	24 (1.1)	0.5 (0.32; 0.74)	18 (1.6)	0.6 (0.35; 0.92)	0.85 (0.44; 1.66)
CARPAL TUNNEL SYNDROME	19 (0.9)	0.4 (0.24; 0.61)	24 (2.1)	0.8 (0.50; 1.16)	0.50 (0.26; 0.96)
DYSARTHRIA	17 (0.8)	0.3 (0.20; 0.56)	18 (1.6)	0.6 (0.34; 0.91)	0.60 (0.29; 1.24)
PERONEAL NERVE PALSY	10 (0.5)	0.2 (0.10; 0.38)	16 (1.4)	0.5 (0.29; 0.84)	0.40 (0.16; 0.93)
NEUROPATHY PERIPHERAL	8 (0.4)	0.2 (0.07; 0.32)	17 (1.5)	0.5 (0.32; 0.87)	0.30 (0.11; 0.73)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS					
-Total	30 (1.4)	0.6 (0.42; 0.88)	18 (1.6)	0.6 (0.34; 0.92)	1.06 (0.57; 2.02)
PREGNANCY	24 (1.1)	0.5 (0.32; 0.73)	18 (1.6)	0.6 (0.34; 0.92)	0.85 (0.44; 1.66)
PSYCHIATRIC DISORDERS					
-Total	410 (19.4)	10.1 (9.12; 11.09)	248 (21.8)	9.6 (8.42; 10.84)	1.05 (0.90; 1.24)
DEPRESSION	154 (7.3)	3.4 (2.84; 3.93)	101 (8.9)	3.4 (2.80; 4.18)	0.98 (0.75; 1.27)
ANXIETY	122 (5.8)	2.6 (2.18; 3.14)	65 (5.7)	2.2 (1.67; 2.75)	1.22 (0.89; 1.67)
INSOMNIA	91 (4.3)	1.9 (1.56; 2.38)	59 (5.2)	2.0 (1.50; 2.53)	0.99 (0.70; 1.39)
RENAL AND URINARY DISORDERS					
-Total	217 (10.3)	4.9 (4.23; 5.54)	195 (17.1)	7.4 (6.36; 8.46)	0.66 (0.54; 0.80)
MICTURITION URGENCY	73 (3.5)	1.5 (1.21; 1.94)	57 (5.0)	1.9 (1.44; 2.47)	0.81 (0.56; 1.16)
URINARY INCONTINENCE	41 (1.9)	0.9 (0.61; 1.15)	43 (3.8)	1.4 (1.02; 1.91)	0.60 (0.38; 0.94)
POLLAKIURIA	34 (1.6)	0.7 (0.49; 0.99)	42 (3.7)	1.4 (1.00; 1.88)	0.51 (0.31; 0.82)
NEPHROLITHIASIS	20 (0.9)	0.4 (0.25; 0.64)	20 (1.8)	0.6 (0.39; 1.00)	0.64 (0.33; 1.25)
NEUROGENIC BLADDER	14 (0.7)	0.3 (0.16; 0.48)	16 (1.4)	0.5 (0.29; 0.84)	0.56 (0.25; 1.22)

Primary system organ class Preferred term	FTY720 N=2112 n (%)	 IR (95% CI)	Other DMTs N=1138 n (%)	 IR (95% CI)	Incidence rate ratio IRR (95% CI)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS					
-Total	93 (4.4)	2.0 (1.59; 2.42)	58 (5.1)	1.9 (1.48; 2.52)	1.01 (0.72; 1.43)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
-Total	244 (11.6)	5.5 (4.83; 6.24)	143 (12.6)	5.1 (4.29; 6.00)	1.08 (0.88; 1.34)
DYSPNOEA	70 (3.3)	1.5 (1.14; 1.85)	30 (2.6)	1.0 (0.66; 1.40)	1.50 (0.96; 2.38)
COUGH	64 (3.0)	1.3 (1.04; 1.72)	31 (2.7)	1.0 (0.69; 1.43)	1.33 (0.85; 2.12)
OROPHARYNGEAL PAIN	33 (1.6)	0.7 (0.47; 0.96)	19 (1.7)	0.6 (0.37; 0.96)	1.11 (0.61; 2.06)
SLEEP APNOEA SYNDROME	13 (0.6)	0.3 (0.14; 0.46)	24 (2.1)	0.8 (0.50; 1.16)	0.34 (0.16; 0.70)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
-Total	424 (20.1)	10.5 (9.52; 11.55)	371 (32.6)	17.4 (15.68; 19.27)	0.60 (0.52; 0.70)
RASH	50 (2.4)	1.0 (0.77; 1.37)	40 (3.5)	1.3 (0.94; 1.79)	0.79 (0.51; 1.23)
SOLAR LENTIGO	49 (2.3)	1.0 (0.75; 1.34)	44 (3.9)	1.5 (1.06; 1.97)	0.69 (0.45; 1.07)
ALOPECIA	41 (1.9)	0.9 (0.61; 1.16)	60 (5.3)	2.0 (1.54; 2.59)	0.43 (0.28; 0.64)
ACNE	34 (1.6)	0.7 (0.49; 0.99)	17 (1.5)	0.6 (0.32; 0.88)	1.28 (0.69; 2.44)
PRURITUS	30 (1.4)	0.6 (0.42; 0.89)	41 (3.6)	1.4 (0.97; 1.84)	0.46 (0.28; 0.75)
ACTINIC KERATOSIS	29 (1.4)	0.6 (0.40; 0.86)	32 (2.8)	1.0 (0.71; 1.47)	0.57 (0.33; 0.98)
LENTIGO	29 (1.4)	0.6 (0.40; 0.86)	49 (4.3)	1.6 (1.22; 2.17)	0.36 (0.22; 0.59)
DRY SKIN	17 (0.8)	0.3 (0.20; 0.56)	16 (1.4)	0.5 (0.30; 0.84)	0.68 (0.32; 1.43)
VASCULAR DISORDERS					
-Total	156 (7.4)	3.4 (2.89; 3.98)	186 (16.3)	7.1 (6.11; 8.19)	0.48 (0.39; 0.60)
HYPERTENSION	91 (4.3)	1.9 (1.55; 2.37)	34 (3.0)	1.1 (0.77; 1.55)	1.73 (1.16; 2.65)
HOT FLUSH	16 (0.8)	0.3 (0.19; 0.53)	23 (2.0)	0.7 (0.47; 1.12)	0.44 (0.22; 0.87)
FLUSHING	10 (0.5)	0.2 (0.10; 0.38)	115 (10.1)	4.1 (3.38; 4.91)	0.05 (0.02; 0.10)

n refers to patients
Data as per Group G general safety rules are used.
Primary system organ classes and preferred terms with an occurrence of at least 0.5 per 100 patient years in any cohort are displayed.
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by frequency from highest to lowest in the FTY720 column.
A patient with multiple occurrences of an AE for a preferred term or primary system organ class is counted only once in each specific category.
Incidence rate: The number of patients who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
Incidence rate ratio: The incidence rate of the FTY720 cohort divided by the incidence rate of the Other DMT cohort for a particular AE term/category. It is only calculated if both incidence rates are >0.
MedDRA Version 22.1 has been used for the reporting of adverse events.

Table 10-19 IR of AEs per 100 PTY by primary SOC, and PT, with cut-off 0.5 per 100 PTY, Group F, Safety set

Primary system organ class Preferred term	FTY720 N=2189 n (%)	IR (95% CI)
-Any primary system organ class		
-Total	1812 (82.8)	161.2 (153.89; 168.83)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
-Total	205 (9.4)	4.4 (3.80; 5.02)
LYMPHOPENIA	134 (6.1)	2.8 (2.33; 3.30)
LEUKOPENIA	34 (1.6)	0.7 (0.47; 0.95)
CARDIAC DISORDERS		
-Total	231 (10.6)	5.0 (4.41; 5.73)
BRADYCARDIA	53 (2.4)	1.1 (0.80; 1.40)
SINUS BRADYCARDIA	50 (2.3)	1.0 (0.75; 1.33)
PALPITATIONS	48 (2.2)	1.0 (0.71; 1.27)
EAR AND LABYRINTH DISORDERS		
-Total	149 (6.8)	3.1 (2.64; 3.66)
VERTIGO	90 (4.1)	1.8 (1.47; 2.25)

Primary system organ class Preferred term	FTY720 N=2189 n (%)	IR (95% CI)
EYE DISORDERS		
-Total	399 (18.2)	9.4 (8.50; 10.37)
VISION BLURRED	121 (5.5)	2.5 (2.08; 2.99)
EYE PAIN	59 (2.7)	1.2 (0.90; 1.53)
DRY EYE	29 (1.3)	0.6 (0.39; 0.83)
VISUAL IMPAIRMENT	28 (1.3)	0.6 (0.37; 0.80)
DIPLOPIA	27 (1.2)	0.5 (0.35; 0.78)
GASTROINTESTINAL DISORDERS		
-Total	464 (21.2)	11.2 (10.16; 12.21)
NAUSEA	148 (6.8)	3.1 (2.61; 3.63)
DIARRHOEA	93 (4.2)	1.9 (1.53; 2.32)
CONSTIPATION	76 (3.5)	1.5 (1.21; 1.92)
VOMITING	51 (2.3)	1.0 (0.76; 1.35)
ABDOMINAL PAIN	43 (2.0)	0.9 (0.62; 1.16)
GASTROOESOPHAGEAL REFLUX DISEASE	37 (1.7)	0.7 (0.52; 1.02)
DYSPHAGIA	27 (1.2)	0.5 (0.35; 0.78)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
-Total	620 (28.3)	16.0 (14.81; 17.36)
FATIGUE	377 (17.2)	8.7 (7.89; 9.67)
GAIT DISTURBANCE	93 (4.2)	1.9 (1.53; 2.31)
ASTHENIA	51 (2.3)	1.0 (0.76; 1.35)
PAIN	37 (1.7)	0.7 (0.52; 1.01)
NON-CARDIAC CHEST PAIN	34 (1.6)	0.7 (0.47; 0.94)
OEDEMA PERIPHERAL	30 (1.4)	0.6 (0.40; 0.85)
CHEST DISCOMFORT	28 (1.3)	0.6 (0.37; 0.80)
HEPATOBILIARY DISORDERS		
-Total	44 (2.0)	0.9 (0.64; 1.17)
IMMUNE SYSTEM DISORDERS		
-Total	37 (1.7)	0.7 (0.52; 1.02)
INFECTIONS AND INFESTATIONS		
-Total	679 (31.0)	18.4 (17.06; 19.86)
URINARY TRACT INFECTION	148 (6.8)	3.1 (2.60; 3.62)
UPPER RESPIRATORY TRACT INFECTION	124 (5.7)	2.6 (2.14; 3.07)
SINUSITIS	84 (3.8)	1.7 (1.37; 2.12)
NASOPHARYNGITIS	82 (3.7)	1.7 (1.33; 2.08)
HERPES ZOSTER	55 (2.5)	1.1 (0.83; 1.44)

Primary system organ class Preferred term	FTY720 N=2189 n (%)	IR (95% CI)
BRONCHITIS	54 (2.5)	1.1 (0.81; 1.42)
INFLUENZA	46 (2.1)	0.9 (0.67; 1.23)
PNEUMONIA	36 (1.6)	0.7 (0.50; 0.99)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
-Total	278 (12.7)	6.1 (5.42; 6.88)
FALL	119 (5.4)	2.4 (2.02; 2.92)
CONTUSION	26 (1.2)	0.5 (0.34; 0.76)
LIGAMENT SPRAIN	26 (1.2)	0.5 (0.34; 0.76)
INVESTIGATIONS		
-Total	486 (22.2)	11.8 (10.75; 12.87)
LYMPHOCYTE COUNT DECREASED	149 (6.8)	3.1 (2.64; 3.67)
ALANINE AMINOTRANSFERASE INCREASED	57 (2.6)	1.1 (0.87; 1.48)
WHITE BLOOD CELL COUNT DECREASED	47 (2.1)	0.9 (0.69; 1.25)
WEIGHT INCREASED	45 (2.1)	0.9 (0.65; 1.20)
HEPATIC ENZYME INCREASED	38 (1.7)	0.8 (0.54; 1.04)
WEIGHT DECREASED	38 (1.7)	0.8 (0.54; 1.04)
ASPARTATE AMINOTRANSFERASE INCREASED	30 (1.4)	0.6 (0.40; 0.85)
BLOOD PRESSURE INCREASED	29 (1.3)	0.6 (0.39; 0.83)
LIVER FUNCTION TEST INCREASED	29 (1.3)	0.6 (0.39; 0.83)
METABOLISM AND NUTRITION DISORDERS		
-Total	167 (7.6)	3.5 (3.01; 4.10)
VITAMIN D DEFICIENCY	52 (2.4)	1.0 (0.78; 1.37)
DECREASED APPETITE	27 (1.2)	0.5 (0.35; 0.78)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
-Total	688 (31.4)	18.7 (17.30; 20.11)
PAIN IN EXTREMITY	176 (8.0)	3.7 (3.18; 4.29)
MUSCULAR WEAKNESS	154 (7.0)	3.2 (2.72; 3.75)
MUSCLE SPASMS	146 (6.7)	3.0 (2.57; 3.57)
ARTHRALGIA	144 (6.6)	3.0 (2.52; 3.52)
BACK PAIN	138 (6.3)	2.9 (2.41; 3.39)
NECK PAIN	56 (2.6)	1.1 (0.85; 1.45)
MUSCULOSKELETAL PAIN	42 (1.9)	0.8 (0.60; 1.13)
MUSCULOSKELETAL STIFFNESS	39 (1.8)	0.8 (0.55; 1.06)
MUSCULOSKELETAL CHEST PAIN	27 (1.2)	0.5 (0.35; 0.78)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
-Total	331 (15.1)	7.4 (6.59; 8.20)

Primary system organ class Preferred term	FTY720 N=2189	
	n (%)	IR (95% CI)
MELANOCYTIC NAEVUS	179 (8.2)	3.7 (3.21; 4.33)
SEBORRHOEIC KERATOSIS	111 (5.1)	2.2 (1.85; 2.71)
HAEMANGIOMA OF SKIN	51 (2.3)	1.0 (0.76; 1.34)
BASAL CELL CARCINOMA	29 (1.3)	0.6 (0.39; 0.83)
NERVOUS SYSTEM DISORDERS		
-Total	992 (45.3)	32.8 (30.76; 34.87)
HEADACHE	304 (13.9)	6.8 (6.03; 7.57)
HYPOAESTHESIA	175 (8.0)	3.7 (3.15; 4.26)
PARAESTHESIA	162 (7.4)	3.4 (2.91; 3.98)
MIGRAINE	103 (4.7)	2.1 (1.72; 2.56)
DIZZINESS	102 (4.7)	2.1 (1.70; 2.53)
DIZZINESS POSTURAL	70 (3.2)	1.4 (1.10; 1.79)
TREMOR	58 (2.6)	1.2 (0.88; 1.50)
BALANCE DISORDER	56 (2.6)	1.1 (0.85; 1.46)
MEMORY IMPAIRMENT	54 (2.5)	1.1 (0.82; 1.42)
COGNITIVE DISORDER	49 (2.2)	1.0 (0.73; 1.30)
MUSCLE SPASTICITY	43 (2.0)	0.9 (0.62; 1.16)
NEURALGIA	36 (1.6)	0.7 (0.50; 0.99)
OPTIC NEURITIS	35 (1.6)	0.7 (0.48; 0.97)
DISTURBANCE IN ATTENTION	33 (1.5)	0.7 (0.45; 0.92)
MULTIPLE SCLEROSIS RELAPSE	33 (1.5)	0.7 (0.45; 0.92)
BURNING SENSATION	32 (1.5)	0.6 (0.44; 0.90)
AMNESIA	28 (1.3)	0.6 (0.37; 0.81)
CENTRAL NERVOUS SYSTEM LESION	27 (1.2)	0.5 (0.35; 0.78)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS		
-Total	33 (1.5)	0.7 (0.45; 0.92)
PREGNANCY	27 (1.2)	0.5 (0.35; 0.78)
PSYCHIATRIC DISORDERS		
-Total	427 (19.5)	10.1 (9.15; 11.09)
DEPRESSION	159 (7.3)	3.3 (2.83; 3.89)
ANXIETY	128 (5.8)	2.7 (2.22; 3.16)
INSOMNIA	96 (4.4)	2.0 (1.59; 2.40)
RENAL AND URINARY DISORDERS		
-Total	231 (10.6)	5.0 (4.36; 5.66)
MICTURITION URGENCY	76 (3.5)	1.5 (1.22; 1.94)
URINARY INCONTINENCE	43 (2.0)	0.9 (0.62; 1.16)

Primary system organ class Preferred term	FTY720 N=2189 n (%)	IR (95% CI)
POLLAKIURIA	35 (1.6)	0.7 (0.49; 0.97)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
-Total	97 (4.4)	2.0 (1.60; 2.41)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
-Total	257 (11.7)	5.6 (4.91; 6.29)
DYSPNOEA	76 (3.5)	1.5 (1.21; 1.92)
COUGH	66 (3.0)	1.3 (1.03; 1.70)
OROPHARYNGEAL PAIN	35 (1.6)	0.7 (0.49; 0.97)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
-Total	446 (20.4)	10.6 (9.67; 11.66)
RASH	51 (2.3)	1.0 (0.76; 1.34)
SOLAR LENTIGO	50 (2.3)	1.0 (0.74; 1.32)
ALOPECIA	43 (2.0)	0.9 (0.63; 1.16)
ACNE	36 (1.6)	0.7 (0.50; 0.99)
PRURITUS	33 (1.5)	0.7 (0.45; 0.92)
ACTINIC KERATOSIS	32 (1.5)	0.6 (0.43; 0.90)
LENTIGO	32 (1.5)	0.6 (0.44; 0.90)
VASCULAR DISORDERS		
-Total	171 (7.8)	3.6 (3.08; 4.18)
HYPERTENSION	95 (4.3)	1.9 (1.57; 2.37)

Data as per Group F general safety rules are used.
Primary system organ classes and preferred terms with an occurrence of at least 0.5 per 100 patient years are displayed.
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by frequency from highest to lowest.
A patient with multiple occurrences of an AE for a preferred term or primary system organ class is counted only once in each specific category.
Incidence rate: The number of patients who reported at least one AE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
MedDRA Version 22.1 has been used for the reporting of adverse events.

Table 10-24 IR of SAEs per 100 PTY, by primary SOC, PT and initial cohort treatment with cut-off 0.1 per 100 PTY by any cohort, Group G, Safety set

Primary system organ class	FTY720 N=2112		Other DMTs N=1138		Incidence rate ratio
Preferred term	n (%)	IR (95% CI)	n (%)	IR (95% CI)	IRR (95% CI)
-Any primary system organ class					
-Total	262 (12.4)	5.9 (5.17; 6.61)	138 (12.1)	4.8 (4.02; 5.65)	1.22 (0.99; 1.52)
BLOOD AND LYMPHATIC SYSTEM DISORDERS					
-Total	6 (0.3)	0.1 (0.05; 0.27)	3 (0.3)	0.1 (0.02; 0.28)	1.28 (0.27; 7.93)
CARDIAC DISORDERS					
-Total	31 (1.5)	0.6 (0.43; 0.91)	15 (1.3)	0.5 (0.27; 0.79)	1.33 (0.70; 2.65)
BRADYCARDIA	5 (0.2)	0.1 (0.03; 0.24)	1 (0.1)	<0.1 (<0.01; 0.18)	3.21 (0.36; 151.94)
EAR AND LABYRINTH DISORDERS					
-Total	5 (0.2)	0.1 (0.03; 0.24)	0	0.0 (0.00; 0.12)	
EYE DISORDERS					
-Total	9 (0.4)	0.2 (0.08; 0.35)	1 (0.1)	<0.1 (<0.01; 0.18)	5.77 (0.80; 252.75)
GASTROINTESTINAL DISORDERS					
-Total	26 (1.2)	0.5 (0.35; 0.78)	18 (1.6)	0.6 (0.34; 0.91)	0.92 (0.49; 1.79)
VOMITING	4 (0.2)	0.1 (0.02; 0.21)	4 (0.4)	0.1 (0.03; 0.33)	0.64 (0.12; 3.44)

Primary system organ class Preferred term	FTY720 N=2112 n (%)	 IR (95% CI)	Other DMTs N=1138 n (%)	 IR (95% CI)	Incidence rate ratio IRR (95% CI)
NAUSEA	3 (0.1)	0.1 (0.01; 0.18)	4 (0.4)	0.1 (0.03; 0.33)	0.48 (0.07; 2.84)
ABDOMINAL PAIN UPPER	1 (<0.1)	<0.1 (<0.01; 0.11)	4 (0.4)	0.1 (0.03; 0.33)	0.16 (<.01; 1.62)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
-Total	25 (1.2)	0.5 (0.33; 0.76)	16 (1.4)	0.5 (0.29; 0.83)	1.00 (0.51; 2.01)
NON-CARDIAC CHEST PAIN	5 (0.2)	0.1 (0.03; 0.24)	3 (0.3)	0.1 (0.02; 0.28)	1.07 (0.21; 6.89)
PYREXIA	4 (0.2)	0.1 (0.02; 0.21)	4 (0.4)	0.1 (0.03; 0.33)	0.64 (0.12; 3.44)
HEPATOBILIARY DISORDERS					
-Total	6 (0.3)	0.1 (0.05; 0.27)	4 (0.4)	0.1 (0.03; 0.33)	0.96 (0.23; 4.62)
INFECTIONS AND INFESTATIONS					
-Total	68 (3.2)	1.4 (1.10; 1.79)	34 (3.0)	1.1 (0.76; 1.54)	1.28 (0.84; 2.00)
PNEUMONIA	18 (0.9)	0.4 (0.22; 0.58)	6 (0.5)	0.2 (0.07; 0.42)	1.92 (0.73; 5.92)
URINARY TRACT INFECTION	13 (0.6)	0.3 (0.14; 0.46)	13 (1.1)	0.4 (0.22; 0.71)	0.64 (0.27; 1.50)
SEPSIS	7 (0.3)	0.1 (0.06; 0.29)	3 (0.3)	0.1 (0.02; 0.28)	1.50 (0.34; 8.97)
CELLULITIS	4 (0.2)	0.1 (0.02; 0.21)	5 (0.4)	0.2 (0.05; 0.37)	0.51 (0.10; 2.38)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS					
-Total	18 (0.9)	0.4 (0.22; 0.58)	26 (2.3)	0.8 (0.55; 1.23)	0.44 (0.23; 0.84)
FALL	9 (0.4)	0.2 (0.08; 0.35)	10 (0.9)	0.3 (0.15; 0.59)	0.58 (0.21; 1.58)
INVESTIGATIONS					
-Total	22 (1.0)	0.5 (0.28; 0.69)	8 (0.7)	0.3 (0.11; 0.50)	1.77 (0.76; 4.59)
LYMPHOCYTE COUNT DECREASED	7 (0.3)	0.1 (0.06; 0.30)	0	0.0 (0.00; 0.12)	
METABOLISM AND NUTRITION DISORDERS					
-Total	12 (0.6)	0.2 (0.13; 0.43)	7 (0.6)	0.2 (0.09; 0.46)	1.10 (0.40; 3.30)
DEHYDRATION	6 (0.3)	0.1 (0.05; 0.27)	2 (0.2)	0.1 (0.01; 0.23)	1.93 (0.34; 19.50)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS					
-Total	19 (0.9)	0.4 (0.24; 0.61)	15 (1.3)	0.5 (0.27; 0.79)	0.81 (0.39; 1.72)
MUSCULAR WEAKNESS	3 (0.1)	0.1 (0.01; 0.18)	5 (0.4)	0.2 (0.05; 0.37)	0.38 (0.06; 1.98)
MUSCULOSKELETAL CHEST PAIN	2 (0.1)	<0.1 (<0.01; 0.15)	4 (0.4)	0.1 (0.03; 0.33)	0.32 (0.03; 2.24)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)					
-Total	40 (1.9)	0.8 (0.59; 1.13)	24 (2.1)	0.8 (0.50; 1.15)	1.07 (0.63; 1.85)
BASAL CELL CARCINOMA	11 (0.5)	0.2 (0.11; 0.40)	4 (0.4)	0.1 (0.03; 0.33)	1.77 (0.52; 7.61)
MALIGNANT MELANOMA	5 (0.2)	0.1 (0.03; 0.24)	0	0.0 (0.00; 0.12)	
NERVOUS SYSTEM DISORDERS					
-Total	71 (3.4)	1.5 (1.16; 1.87)	32 (2.8)	1.0 (0.71; 1.46)	1.43 (0.93; 2.24)
MULTIPLE SCLEROSIS RELAPSE	14 (0.7)	0.3 (0.16; 0.48)	5 (0.4)	0.2 (0.05; 0.37)	1.80 (0.61; 6.38)
SEIZURE	12 (0.6)	0.2 (0.13; 0.43)	2 (0.2)	0.1 (0.01; 0.23)	3.85 (0.86; 35.44)
MIGRAINE	7 (0.3)	0.1 (0.06; 0.29)	1 (0.1)	<0.1 (<0.01; 0.18)	4.50 (0.58; 202.65)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS					
-Total	9 (0.4)	0.2 (0.08; 0.35)	5 (0.4)	0.2 (0.05; 0.37)	1.15 (0.35; 4.37)

Primary system organ class Preferred term	FTY720 N=2112 n (%)	IR (95% CI)	Other DMTs N=1138 n (%)	IR (95% CI)	Incidence rate ratio IRR (95% CI)
ABORTION SPONTANEOUS	5 (0.2)	0.1 (0.03; 0.24)	4 (0.4)	0.1 (0.03; 0.33)	0.80 (0.17; 4.03)
PSYCHIATRIC DISORDERS					
-Total	22 (1.0)	0.5 (0.28; 0.68)	13 (1.1)	0.4 (0.22; 0.71)	1.08 (0.52; 2.34)
DEPRESSION	1 (<0.1)	<.1 (<.01; 0.11)	4 (0.4)	0.1 (0.03; 0.33)	0.16 (<.01; 1.62)
RENAL AND URINARY DISORDERS					
-Total	16 (0.8)	0.3 (0.19; 0.53)	9 (0.8)	0.3 (0.13; 0.55)	1.14 (0.47; 2.93)
ACUTE KIDNEY INJURY	5 (0.2)	0.1 (0.03; 0.24)	1 (0.1)	<0.1 (<0.01; 0.18)	3.21 (0.36; 151.67)
NEPHROLITHIASIS	5 (0.2)	0.1 (0.03; 0.24)	3 (0.3)	0.1 (0.02; 0.28)	1.07 (0.21; 6.89)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS					
-Total	5 (0.2)	0.1 (0.03; 0.24)	3 (0.3)	0.1 (0.02; 0.28)	1.07 (0.21; 6.87)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
-Total	24 (1.1)	0.5 (0.32; 0.73)	10 (0.9)	0.3 (0.15; 0.59)	1.54 (0.71; 3.61)
DYSPNOEA	8 (0.4)	0.2 (0.07; 0.32)	4 (0.4)	0.1 (0.03; 0.33)	1.28 (0.34; 5.83)
PULMONARY EMBOLISM	6 (0.3)	0.1 (0.04; 0.27)	2 (0.2)	0.1 (0.01; 0.23)	1.92 (0.34; 19.45)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
-Total	3 (0.1)	0.1 (0.01; 0.18)	4 (0.4)	0.1 (0.03; 0.33)	0.48 (0.07; 2.84)
VASCULAR DISORDERS					
-Total	15 (0.7)	0.3 (0.17; 0.51)	8 (0.7)	0.3 (0.11; 0.50)	1.20 (0.48; 3.27)
DEEP VEIN THROMBOSIS	2 (0.1)	<0.1 (<0.01; 0.15)	4 (0.4)	0.1 (0.03; 0.33)	0.32 (0.03; 2.24)

Data as per Group G general safety rules are used.
Primary system organ classes and preferred terms with an occurrence of at least 0.1 per 100 patient years in any cohort are displayed.
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by frequency from highest to lowest in the FTY720 column.
A patient with multiple occurrences of an SAE for a preferred term or primary system organ class is counted only once in each specific category.
Incidence rate: The number of patients who reported at least one SAE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
Incidence rate ratio: The incidence rate of the FTY720 cohort divided by the incidence rate of the Other DMT cohort for a particular AE term/category. It is only calculated if both incidence rates are >0.
MedDRA Version 22.1 has been used for the reporting of adverse events.

Table 10-25 IR of SAEs per 100 PTY, by primary SOC and PT with cut-off 0.1 per 100 PTY, Group F, Safety set

Primary system organ class Preferred term	FTY720 N=2189	
	n (%)	IR (95% CI)
-Any primary system organ class		

Primary system organ class Preferred term	FTY720 N=2189 n (%)	IR (95% CI)
-Total	285 (13.0)	6.1 (5.41; 6.85)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
-Total	9 (0.4)	0.2 (0.08; 0.34)
CARDIAC DISORDERS		
-Total	33 (1.5)	0.7 (0.45; 0.92)
EYE DISORDERS		
-Total	10 (0.5)	0.2 (0.09; 0.36)
GASTROINTESTINAL DISORDERS		
-Total	28 (1.3)	0.6 (0.37; 0.80)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
-Total	27 (1.2)	0.5 (0.35; 0.78)
NON-CARDIAC CHEST PAIN	6 (0.3)	0.1 (0.04; 0.26)
HEPATOBILIARY DISORDERS		
-Total	8 (0.4)	0.2 (0.07; 0.31)
INFECTIONS AND INFESTATIONS		
-Total	76 (3.5)	1.5 (1.20; 1.90)
PNEUMONIA	19 (0.9)	0.4 (0.23; 0.58)
URINARY TRACT INFECTION	15 (0.7)	0.3 (0.17; 0.49)
SEPSIS	7 (0.3)	0.1 (0.06; 0.28)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
-Total	24 (1.1)	0.5 (0.30; 0.70)
FALL	14 (0.6)	0.3 (0.15; 0.46)
INVESTIGATIONS		
-Total	25 (1.1)	0.5 (0.32; 0.73)
LYMPHOCYTE COUNT DECREASED	7 (0.3)	0.1 (0.06; 0.28)
METABOLISM AND NUTRITION DISORDERS		
-Total	15 (0.7)	0.3 (0.17; 0.49)
DEHYDRATION	7 (0.3)	0.1 (0.06; 0.28)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
-Total	21 (1.0)	0.4 (0.26; 0.63)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
-Total	47 (2.1)	0.9 (0.69; 1.24)
BASAL CELL CARCINOMA	14 (0.6)	0.3 (0.15; 0.46)
NERVOUS SYSTEM DISORDERS		
-Total	78 (3.6)	1.6 (1.24; 1.95)
MULTIPLE SCLEROSIS RELAPSE	15 (0.7)	0.3 (0.17; 0.49)
SEIZURE	13 (0.6)	0.3 (0.14; 0.44)
MIGRAINE	7 (0.3)	0.1 (0.06; 0.28)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS		
-Total	9 (0.4)	0.2 (0.08; 0.34)
PSYCHIATRIC DISORDERS		
-Total	27 (1.2)	0.5 (0.35; 0.77)
MENTAL STATUS CHANGES	6 (0.3)	0.1 (0.04; 0.26)
RENAL AND URINARY DISORDERS		

Primary system organ class Preferred term	FTY720 N=2189 n (%)	IR (95% CI)
-Total	19 (0.9)	0.4 (0.23; 0.58)
ACUTE KIDNEY INJURY	6 (0.3)	0.1 (0.04; 0.26)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
-Total	7 (0.3)	0.1 (0.06; 0.28)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
-Total	28 (1.3)	0.6 (0.37; 0.80)
DYSPNOEA	9 (0.4)	0.2 (0.08; 0.34)
PULMONARY EMBOLISM	6 (0.3)	0.1 (0.04; 0.26)
VASCULAR DISORDERS		
-Total	16 (0.7)	0.3 (0.18; 0.51)

Data as per Group F general safety rules are used.
Primary system organ classes and preferred terms with an occurrence of at least 0.1 per 100 patient years are displayed.
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by frequency from highest to lowest.
A patient with multiple occurrences of an SAE for a preferred term or primary system organ class is counted only once in each specific category.
Incidence rate: The number of patients who reported at least one SAE in this category, over the total patient-years of the population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed. Incidence rate is expressed per 100 patient-years of the population.
MedDRA Version 22.1 has been used for the reporting of adverse events.

Other Relevant Findings

Not Applicable

Conclusion:

- In conclusion, the overall safety profile from Study D2403 remains consistent with the known safety profile of fingolimod, the findings were consistent with the observation seen in the clinical trials and post-marketing setting till date and no new safety findings were noted.
- No indication of increased risk was noted for some of the potential safety risks related to long-term exposure with fingolimod, such as opportunistic infections, cardiovascular safety risk, or respiratory system-related safety risk.
- Study patients over the period of time remained stable in fingolimod cohort, fingolimod continued to be effective over the long term study duration, however, study was not designed for efficacy analysis.

Date of Clinical Study Report

04 February 2021