Sponsor

Novartis

Generic Drug Name

Fingolimod (FTY720)

Therapeutic Area of Trial

Neuroinflammation - Relapsing-remitting multiple sclerosis (RRMS)

Approved Indication

Investigational

Study Number

CFTY720D2301

Title

A 24-month double-blind, randomized, multicenter, active-controlled, parallel group study comparing the efficacy and safety of FTY720 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis.

Phase of Development

Phase III

Study Start/End Dates

26 Jan 2006 to 29 Jul 2009

Study Design/Methodology

This was a double-blind, randomized, multicenter, parallel-group using a placebo-control to evaluate the efficacy and safety of two doses of FTY720, 0.5 mg and 1.25 mg capsules administered once daily for a period of 24 months in patients with RRMS. The study consisted of two phases: a pre-randomization phase (Screening and Baseline [Days -45 to Day -1]) and a double-blind treatment phase (Core treatment phase [Day 1 to Day 720]). After pre-randomization phase, patients were randomized to 1 of the 3 treatment arms (FTY720 0.5 mg or 1.25 mg or placebo) in a 1:1:1 fashion. Eligible patients who completed the 24-month double-blind treatment phase could enter an optional long-term extension study under a separate protocol (FTY720D2301E1).

Centers

138 centers in 22 countries: 5 centers in Australia, 7 centers in Belgium, 9 centers in Canada, 10 centers in Czech Republic, 1 center in Estonia, 5 centers in Finland, 11 centers in France, 17 centers in Germany, 4 centers in Greece, 3 centers in Hungary, 1 center in Ireland, 4 centers in Israel, 6 centers in Netherlands, 10 centers in Poland, 7 centers in Romania, 8 centers in Russia, 3 centers in Slovakia, 3 centers in South Africa, 3 centers in Sweden, 3 centers in Switzerland, 12 centers in Turkey, and 6 centers in United Kingdom.

Publication

Kappos L, Radue EW, O'Connor P, et al. A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis. N Engl J Med 2010; 362:387-401.

Objectives

Primary objective(s)

- The primary objective was to compare two doses of FTY720 (1.25 mg and 0.5 mg) with placebo and to demonstrate that at least 1.25 mg FTY720 is superior to placebo in terms of annualized relapse rate (ARR) in patients with RRMS treated for up to 24 months.

Secondary objective(s)

Key secondary objective

- To evaluate the effect of FTY720 1.25 mg and 0.5 mg relative to placebo on disability progression as measured by the time to 3-month confirmed disability progression as measured by EDSS in patients treated for up to 24 months.

Other secondary objectives:

- To evaluate the safety and tolerability of FTY720 compared to placebo in patients with RRMS treated up to 24 months
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months with respect to MRI parameters of inflammatory disease activity, burden of disease, and brain volume (atrophy)
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months with respect to relapse-related parameters:
  - time to the first relapse
  - proportion of relapse-free patients
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months on disability progression with respect to:
  - time to 6-month confirmed disability progression as measured by EDSS
  - proportion of patients with confirmed disability progression
  - change from baseline to the end of the study on the MSFC z-score
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo on multidimensional health status as measured by the Patient Utility Index derived from patients responses on the EuroQoL (EQ-5D)
- To evaluate the pharmacokinetics of FTY720
- To evaluate the pharmacokinetic/pharmacodynamic relationship of FTY720 1.25 mg and 0.5 mg for main efficacy and safety outcomes in patients with RRMS

Exploratory objective(s):

- To conduct pharmacogenetics studies to identify inherited genetic factors that may (1) be related to multiple sclerosis, (2) predict response to treatment with FTY720, (3) predict relative susceptibility to drug-drug interactions, or (4) predict genetic predisposition to side effects.
- To conduct proteomic/metabonomic studies in plasma and CSF (in selected centers) to monitor the products of gene expression at pre-treatment and post-treatment with FTY720 as well as to identify proteins, and metabolites in plasma that are associated with the treatment re-

sponse to FTY720.

- To explore possible relationships between FTY720/FTY720-P concentrations in CSF and relevant biomarkers.

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

FTY720 1.25 mg or FTY720 0.5 mg capsules for oral administration once daily.

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

Matching FTY720 placebo in capsules for oral administration once daily

Criteria for Evaluation

Primary variables

- Confirmed MS relapse: Appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. A relapse was confirmed when it was accompanied by an increase of at least half a step (0.5) on the EDSS or an increase of 1 point on two different Functional Systems (FS) of the EDSS or 2 points on one of the FS (excluding Bowel/Bladder or Cerebral FS).

Secondary variables

- Key secondary efficacy: disability progression by EDSS.
- Other efficacy: MRI parameters of inflammatory disease activity, time to first and second relapse and proportion of relapse free patients for confirmed relapses and for all relapses, and Multiple Sclerosis Functional Composite (MSFC) measures.

Health-related quality of life: EQ-5D was performed at all sites.

Safety and tolerability

Safety assessments consisted of collecting all AEs, SAEs, with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of laboratory values and regular assessments of vital signs, ECG, physical condition, and body weight. Additional safety assessments as specified per protocol included dermatologic examinations, ophthalmic examinations, chest x-ray/HRCT, and pulmonary function tests.

MS relapses were reported on the MS relapse CRF. If, in the judgment of the investigator, a MS relapse was unusually severe or unexpected and warranted specific notification, then an SAE form was completed and submitted in addition.

Special safety guidances were provided for elevated blood pressure, elevated liver function tests, notable lymphopenia, symptoms of neurological deterioration inconsistent with MS course, infections, pulmonary function monitoring, and ophthalmic monitoring.

Other (Bioanalytics):

Blood samples for pharmacokinetic (PK) analysis were collected in all patients at every scheduled visit, post-randomization.

Statistical Methods

Efficacy:

The primary efficacy variable was aggregate annualized relapse rate (ARR). Only confirmed re-

lapses were considered for the primary analysis.

The primary null hypotheses to be tested were: 1) there is no difference in the ARRs between patients treated with the FTY720 1.25 mg and placebo, and 2) there is no difference in the ARRs between patients treated with the FTY720 0.5 mg and placebo.

The test of the hypotheses (p-value) was performed based on a negative binomial regression model adjusting for treatment group, country, baseline number of relapses in the previous 2 years, and baseline EDSS as covariates, in the intent-to-treat (ITT) population.

Two types of supportive analyses were provided for the primary endpoint: 1) negative binomial regression model using the per-protocol population and 2) rank analysis of covariance (ANCOVA) on patient-level ARR using ITT population. Both models used the same covariates as the primary efficacy analysis.

The key secondary efficacy endpoint, the time to 3-month confirmed disability progression as measured by EDSS during 24 months, was compared by means of the log-rank test. Cox regression with covariates of treatment, country, baseline EDSS and age was performed as well. Proportions of disability free patients at 12 and 24 months were obtained using the Kaplan–Meier method.

To control the overall type-I error rate of the study, a multiplicity adjustment was applied to the primary and key secondary endpoints. There was one primary endpoint and one key secondary endpoint with two doses, yielding four FTY720 (1.25 mg and 0.5 mg) comparisons vs. placebo. The testing of FTY720 comparisons vs. placebo was performed in a hierarchical order as follows:

1. FTY720 1.25 mg, aggregate ARR

2. FTY720 0.5 mg, aggregate ARR

3. FTY720 1.25 mg, 3-month disability progression

4. FTY720 0.5 mg, 3-month disability progression.

Each testing was performed at a significant level of 0.05 for these four comparisons. However, the lower-rank testing was performed only when every high-rank testing was statistically significant.

ARR for all relapses (confirmed and unconfirmed) was analyzed similarly to the primary efficacy variable. For time to first relapse and time to second relapse, log-rank test and Cox regression with the same covariates as in the primary analysis were used. The proportion of relapse-free patients was obtained from the Kaplan–Meier method. Fisher's exact test and Wilcoxon rank sum test were used for testing treatment differences for relapse characteristics.

For other efficacy disability-related and EDSS variables (time to 6-month confirmed disability progression, time to 3-month and 6-month confirmed disability progression sustained until last observation), log-rank test and Cox regression with the same covariates as in the key secondary analysis were used. The proportion of disability progression-free patients was obtained from the Kaplan–Meier method. Change from baseline to the end of study for EDSS, and change from baseline to the end of study for the MSFC z-score and subscales were analyzed using rank ANCOVA with covariates of treatment, country, the corresponding baseline value, and age.

For the proportion type of MRI endpoints (proportion of patients free of new/newly enlarged T2

lesions, proportion of patients free of Gd-enhanced T1 lesions, proportion of patients free of new MRI activity), the treatment comparisons were performed using the logistic regression model adjusting for treatment, country, and the corresponding baseline value (when available). The number of new/newly enlarged T2 lesions was analyzed using negative binomial model adjusted for treatment and country. For the other MRI endpoints (number and total volume of Gd-enhanced T1 lesions, change and percent change from baseline in total volume of T2 lesions, change and percent change from baseline in total volume of T1 hypointense lesions, percent change from baseline in brain volume), rank ANCOVA with covariates treatment, country, and corresponding baseline values (when available) were used for treatment comparisons.

Health-related quality of life:

The changes from baseline in EQ-5D utility and Visual Analog Scale scores were tabulated and compared between treatment groups using ANCOVA (with covariates treatment, country, baseline value, and age).

Safety:

Summary statistics were used for safety variables; summaries were presented by treatment group using the safety population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Males or females aged 18 to 55 years inclusive. Female participants of childbearing potential who had a negative pregnancy test prior to entry into the double-blind treatment phase and agreed to use simultaneously two forms of effective contraception (either partner) during treatment and for 3 months after discontinuation of the study medication. Females participants who were either post-menopausal for 12 months prior to randomization or were surgically sterile (through hysterectomy or bilateral oophorectomy) were exempted from using birth control.
- Provided written informed consent prior to participating in the study
- Diagnosis of MS as defined by 2005 revised McDonald criteria
- A relapsing-remitting course with at least one documented relapse during the previous year or two documented relapses during the previous 2 years, prior to randomization.
- Expanded Disability Status Scale (EDSS) score of 0 to 5.5 inclusive
- Patients who explicitly declined initiation or continuation of treatment with available disease-modifying drugs for whatever reason after having been informed about their respective benefits and possible adverse events by the investigator
- Patients who were neurologically stable with no evidence of relapse or corticosteroid treatment within 30 days prior to randomization.

Exclusion Criteria

- Manifestation of MS other than RRMS
- History of chronic disease of the immune system other than MS or a known immunodeficiency syndrome

- History or presence of malignancy (except for successfully treated basal or squamous cell carcinoma of skin)
- Known or 'new' diagnosis of diabetes mellitus (if screening blood glucose was suspicious for diabetes (= 126 mg/dL or = 7 mmol/L if fasting; = 200 mg/dL or 11.1 mmol/L if random testing) the patient was to be further evaluated for diabetes mellitus)
- Diagnosis of macular edema during the pre-randomization phase (patients with a history of macular edema were allowed to enter the study provided that they did not have macular edema at the ophthalmic screening visit)
- Active systemic bacterial, viral, or fungal infections, or diagnosis of AIDS, hepatitis B, or hepatitis C infection (defined as a positive HIV antibody, hepatitis B surface antigen, or hepatitis C antibody test, respectively)
- Received total lymphoid irradiation or bone marrow transplantation
- Had been treated with systemic corticosteroids or adrenocorticotropic hormones (ACTH) within 1 month prior to randomization; immunosuppressive medications such as azathioprine or methotrexate within 6 months prior to randomization; immunoglobulins and/or monoclonal antibodies (including natalizumab) within 6 months prior to randomization; IFN-ß or glatiramer acetate within 3 months prior to randomization; or cladribine, cyclophosphamide, or mitoxantrone at any time
- Any medically unstable condition, as assessed by the primary treating physician
- Any of the following cardiovascular conditions:
  - Myocardial infarction within the 6 months prior to enrollment or current unstable ischemic heart disease
  - History of angina pectoris due to coronary spasm or history of Raynaud's phenomenon
  - Cardiac failure at time of screening (Class III according to New York Heart Association Classification) (see Appendix 5 of the study protocol) or any severe cardiac disease as determined by the investigator
  - History of cardiac arrest, symptomatic bradycardia, sick sinus syndrome or sino-atrial heart block, or positive tilt test from workup for vasovagal syncope
  - Resting pulse rate < 55 bpm prior to randomization
  - History or presence of a second degree AV block or a third degree AV block or an increased QTc interval > 440 ms on screening ECG
  - Arrhythmia requiring current treatment with Class III anti-arrhythmic drugs (e.g., amiodarone, bretylium, sotalol, ibulitide, azimilide, dofelitide)
  - Hypertension uncontrolled by medication
- Any of the following pulmonary conditions:
  - Severe respiratory disease or pulmonary fibrosis
  - Tuberculosis, except for history of successfully treated tuberculosis or history of prophylactic treatment after positive PPD skin reaction
  - Abnormal chest x-ray or High Resolution Computer Tomography (HRCT) (at selected sites) suggestive of active pulmonary disease

- Abnormal pulmonary function tests: FEV_1, FVC values lower than 70% of predicted value, D_LCO values lower than 60% of predicted value
- Asthma requiring daily (chronic) therapies

- Any of the following hepatic conditions:
  - Known history of alcohol abuse, chronic liver or biliary disease
  - Total bilirubin greater than the upper limit of the normal (ULN) range, unless in context of Gilbert's syndrome
  - Conjugated bilirubin greater than ULN range
  - Alkaline phosphatase greater than 1.5 times ULN range
  - Aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT) greater than 2 times ULN (Canada only: ALT/SGPT greater than 1.5 times ULN)
  - Gamma-glutamyl-transferase (GGT) greater than 3 times ULN range
- Any of the following abnormal laboratory values:
  - Serum creatinine > 1.7 mg/dL (150 µmol/L)
  - White blood cell (WBC) count < 3,500/mm3 (< 3.5 x 109/ L)
  - Lymphocyte count < 800/mm3 (< 0.8 x 109/ L)
- Any of the following neurologic/psychiatric disorders:
  - History of substance abuse (drug or alcohol) or any other factor (i.e., serious psychiatric condition) that could interfere with the subject's ability to cooperate and comply with the study procedures
  - Progressive neurological disorder, other than MS, which could affect participation in the study or require the use of medications not allowed by the protocol
- Unable to undergo MRI scans, including claustrophobia or history of hypersensitivity to gadolinium-DTPA
- Participation in any clinical research study evaluating another investigational drug or therapy within 6 months prior to randomization
- Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL)
- History of FTY720 therapy

Number of Subjects

Patient disposition (study phase completion) – All randomized patients

	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)	Total N=1272 n (%)
Completed study	332 (77.4)	369 (86.8)	332 (79.4)	1033 (81.2)
On study drug [1]	297 (69.2)	345 (81.2)	303 (72.5)	945 (74.3)
Off study drug [2]	35 (8.2)	24 (5.6)	29 (6.9)	88 (6.9)
Discontinued from the study	97 (22.6)	56 13.2)	86 (20.6)	239 (18.8)
Subject withdrew consent	31 (7.2)	17 (4.0)	28 (6.7)	76 (6.0)
Adverse event(s)	22 (5.1)	13 (3.1)	18 (4.3)	53 (4.2)
Unsatisfactory therapeutic effect	13 (3.0)	6 (1.4)	25 (6.0)	44 (3.5)
Abnormal laboratory value(s)	20 (4.7)	9 (2.1)	1 (0.2)	30 (2.4)
Lost to follow-up	3 (0.7)	5 (1.2)	7 (1.7)	15 (1.2)
Protocol violation	5 (1.2)	5 (1.2)	4 (1.0)	14 (1.1)
Abnormal test procedure result(s)	2 (0.5)	1 (0.2)	1 (0.2)	4 (0.3)
Death	1 (0.2)	0 (0.0)	2 (0.5)	3 (0.2)
Discontinued study drug	131 (30.5)	80 (18.8)	115 (27.5)	326 (25.6)
Subject withdrew consent	30 (7.0)	17 (4.0)	31 (7.4)	78 (6.1)
Adverse event(s)	31 (7.2)	15 (3.5)	24 (5.7)	70 (5.5)
Unsatisfactory therapeutic effect	18 (4.2)	8 (1.9)	36 (8.6)	62 (4.9)
Abnormal laboratory value(s)	32 (7.5)	20 (4.7)	5 (1.2)	57 (4.5)
Protocol violation	8 (1.9)	8 (1.9)	5 (1.2)	21 (1.7)
Lost to follow-up	2 (0.5)	6 (1.4)	5 (1.2)	13 (1.0)
Abnormal test procedure result(s)	6 (1.4)	3 (0.7)	3 (0.7)	12 (0.9)
Administrative problems	3 (0.7)	3 (0.7)	4 (1.0)	10 (0.8)
Death	1 (0.2)	0 (0.0)	2 (0.5)	3 (0.2)

[1] 'On study drug': Patients who took study drug until the study completion.
[2] 'Off study drug': Patients who completed the study but discontinued study drug prematurely.
Note: This table displays the number of patients with the primary reason for discontinuation recorded as 'adverse event'. Reasons for discontinuation are sorted in descending frequency in the Total column.

Demographic and Background Characteristics

Demographic summary by treatment group (Randomized population)

		FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418	Total N=1272
Age (years)	Mean (SD)	37.4 (8.91)	36.6 (8.77)	37.2 (8.60)	37.1 (8.76)
	Median	38.0	36.0	37.0	37.0
	Range	17 - 55	18 - 55	18 - 55	17 - 55
Age group	<18	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
(years) - n (%)	18-30	107 (24.9)	120 (28.2)	97 (23.2)	324 (25.5)
	31-40	147 (34.3)	162 (38.1)	165 (39.5)	474 (37.3)

	41-55	174 (40.6)	143 (33.6)	156 (37.3)	473 (37.2)
Sex - n (%)	Male	134 (31.2)	129 (30.4)	120 (28.7)	383 (30.1)
	Female	295 (68.8)	296 (69.6)	298 (71.3)	889 (69.9)
Race - n (%)	Caucasian	408 (95.1)	406 (95.5)	399 (95.5)	1213 (95.4)
	Black	0 (0.0)	1 (0.2)	2 (0.5)	3 (0.2)
	Asian	0 (0.0)	3 (0.7)	3 (0.7)	6 (0.5)
	Other	21 (4.9)	15 (3.5)	14 (3.3)	50 (3.9)
Weight (kg)	Mean (SD)	70.81 (16.296)	71.63 (15.210)	70.70 (14.573)	71.05 (15.377)
	Median	68.00	70.00	69.00	69.00
	Range	40.1-154.3	40.0-128.8	40.0-118.0	40.0-154.3
Height (cm)	Mean (SD)	169.8 (9.05)	169.6 (9.09)	169.0 (8.76)	169.5 (8.97)
	Median	170.0	168.0	168.0	169.0
	Range	148 - 203	144 - 197	148 - 195	144 - 203
BMI (kg/m^2)	Mean (SD)	24.44 (4.748)	24.87 (4.822)	24.67 (4.409)	24.66 (4.664)
	Median	23.53	24.07	23.91	23.83
	Range	16.7- 48.8	17.2- 49.1	15.6- 43.4	15.6- 49.1

N: number of enrolled patients, n: number of patients

Clinical MS baseline characteristics by treatment group (Randomized population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418	Total N=1272
Duration of MS since first symptom, years				
n	429	425	418	1272
Mean (SD)	8.4 (6.86)	8.0 (6.60)	8.1 (6.35)	8.2 (6.60)
Median	6.9	6.6	7.0	6.7
Range	0 - 37	0 - 35	0 - 32	0 - 37
Number of relapses in the last year				
n	429	425	418	1272
Mean (SD)	1.5 (0.81)	1.5 (0.76)	1.4 (0.73)	1.5 (0.77)
Median	1.0	1.0	1.0	1.0
Range	0 - 6	0 - 5	0 - 6	0 - 6
Number of relapses in the last 2 years				
n	429	424	418	1271
Mean (SD)	2.1 (1.25)	2.1 (1.13)	2.2 (1.19)	2.1 (1.19)
Median	2.0	2.0	2.0	2.0
Range	1 - 10	1 - 11	1 - 10	1 - 11
EDSS				
n	429	425	418	1272
Mean (SD)	2.41 (1.36)	2.30 (1.29)	2.49 (1.29)	2.40 (1.32)
Median	2.00	2.00	2.00	2.00
Range	0.0 - 5.5	0.0 - 5.5	0.0 - 5.5	0.0 - 5.5
MSFC z-score				
n	424	422	413	n/a

Mean (SD)	-0.02 (0.75)	0.06 (0.60)	-0.04 (0.76)	n/a
Median	0.13	0.13	0.09	n/a
Range	-5.9 – 1.3	-2.9 – 1.6	-6.4 – 1.9	n/a

n/a=not available.

N: number of enrolled patients, n: number of patients

Primary Objective Result(s)

Aggregate annualized relapse rate (ARR) up to Month 24 (confirmed relapses only) (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Aggregate ARR estimate	0.16	0.18	0.40
(95% CI)	(0.13,0.19)	(0.15,0.22)	(0.34,0.47)
Treatment comparison of FTY720 vs. placebo			
ARR ratio	0.40	0.46	---
P-value	<0.001*	<0.001*	---

Aggregate ARR related to group-level annualized relapse rate.

Aggregate ARR estimate (95% CI), ARR ratio, and p-value are calculated using negative binomial regression adjusted by treatment, country, number of relapses in the previous 2 years, and baseline EDSS.

Log (time of study) is the offset variable.

* Indicates two-sided statistical significance at 0.05 level.

Secondary Objective Result(s)

Key secondary efficacy endpoint

Confirmed 3-month disability progression up to Month 24 based on EDSS (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Kaplan-Meier estimate (SE) of % free of 3-month disability progression at Month 24 (720 days)	83.4 (1.87)	82.3 (1.89)	75.9 (2.17)
(95% CI)	(79.7, 87.1)	(78.6, 86.1)	(71.7, 80.2)
Treatment comparison of FTY720 vs. placebo			
p-value (log-rank test)1	0.012*	0.026*	---
Hazard ratio (FTY720 vs. placebo)	0.68	0.70	---
(95% CI)	(0.50, 0.93)	(0.52, 0.96)	---
Cox PH regression p-value2	0.017*	0.024*	---

SE = standard error.
[1] Primary analysis method. P-value from log-rank test was used to compare the survival distributions between treatment groups.
[2] P-value from Cox proportional hazard model for time to 3-month confirmed disability progression, adjusted for treatment, country, baseline EDSS, and age.
* Indicates two-sided statistical significance at 0.05 level.

Other secondary efficacy endpoints

Inflammatory activity

Inflammatory activity based on MRI measurement of number of new/newly enlarged T2 lesions (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Month 0 to 24 [1]			
n	337	370	339
Mean (SD)	2.5 (5.52)	2.5 (7.19)	9.8 (13.17)
Median	0.0	0.0	5.0
Range	0 to 41	0 to 107	0 to 99
P-value for treatment comparison of FTY720 vs. placebo (negative binomial regression with covariates)	<0.001*	<0.001*	---
Number (%) of patients free of new/newly enlarged T2 lesions	175 (51.93)	187 (50.54)	72 (21.24)

n=the number of patients who had the specific MRI value at a visit.
[1] For each patient, the number of new or newly-enlarged T2 lesions at Month 0 to 24 was obtained by adding Month 0 to 12 results and Month 12 to 24 results.
P-value is calculated using a negative binomial model adjusted for treatment and country.
* Indicates two-sided statistical significance at 0.05 level.

Inflammatory activity based on MRI measurement of the number of Gd-enhancing T1 lesions (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Month 24 [1]			
n	343	369	332
Mean (SD)	0.2 (1.08)	0.2 (0.84)	1.1 (2.37)
Median	0.0	0.0	0.0
Range	0 to 11	0 to 8	0 to 21
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	<0.001*	---
Number (%) of patients free of Gd-enhancing T1 lesions	308 (89.80)	331 (89.70)	216 (65.06)

n=the number of patients who had the specific MRI value at a visit.
[1] Any Gd-enhancing T1 data obtained less than 30 days after the steroid used to treat MS relapses were excluded from the analysis.
P-value is calculated using a rank ANCOVA model adjusted for treatment, country, and baseline number of Gd-enhancing T1 lesions.
* Indicates two-sided statistical significance at 0.05 level.

Lesion volume

Change from baseline in lesion volume at Month 24 (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Change from baseline in total volume of T2 lesions (mm^3) at Month 24			
n	345	372	342
Mean (SD)	-95.65 (2167.220)	-23.46 (2360.073)	1045.31 (2716.132)
Median	-60.10	-42.40	357.00
Range	-15253.4 to 17508.0	-27656.7 to 22893.0	-5141.7 to 33170.4
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	<0.001*	---
Percent change from baseline in total volume of T2 lesions (mm^3) at Month 24			
n	343	368	339
Mean (SD)	1.58 (30.71)	10.61 (103.46)	33.82 (106.90)
Median	-3.10	-1.69	8.61
Range	-68.2 to 221.5	-100.0 to 1828.5	-84.5 to 1378.7
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	<0.001*	---
Change from baseline in total volume of T1 hypointense lesions (mm^3) at Month 24			
n	343	372	340

Mean (SD)	30.23 (674.253)	32.93 (536.327)	172.63 (690.229)
Median	0.00	0.00	2.90
Range	-2403.4 to 7811.2	-4912.7 to 3462.1	-3440.4 to 5857.0
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	0.008*	---
Percent change from baseline in total volume of T1 hypointense lesions (mm^3) at Month 24			
n	317	346	305
Mean (SD)	12.24 (85.49)	8.80 (76.27)	50.68 (388.26)
Median	-0.20	0.00	1.59
Range	-100 to 888.4	-100.0 to 1037.1	-100.0 to 5285.3
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	0.015*	0.012*	---

n = the number of patients with non-missing baseline and post-baseline values.
P-values are from rank ANCOVA with covariates of treatment, country, and the baseline volume of T2 (for total volume of T2 lesions) or T1 hypointensive lesions (for total volume of T1 hypointensive lesions).
* Indicates two-sided statistical significance at 0.05 level.

Brain volume (atrophy)

Percent change in brain volume by visit (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Percent change from baseline to Month 24			
n	334	357	331
Mean (SD)	-0.885 (1.3857)	-0.843 (1.3120)	-1.306 (1.5000)
Median	-0.700	-0.670	-0.980
Range	-6.33 to 3.04	-13.50 to 2.16	-7.58 to 2.38
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	<0.001*	---

n = the number of patients with non-missing baseline and post-baseline values.
P-values are from rank ANCOVA with covariates of treatment, country, and baseline normalized brain volume.
* Indicates two-sided statistical significance at 0.05 level.

MS relapse-related secondary parameters

First confirmed MS relapse up to Month 24 (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Kaplan–Meier estimate (SE) of % relapse-free (720 days)	74.7 (2.17)	70.4 (2.26)	45.6 (2.52)
(95% CI)	(70.40, 78.90)	(65.95, 74.80)	(40.70, 50.57)
Treatment comparison of FTY720 vs. placebo			
p-value (log-rank test)1	<0.001*	<0.001*	---

Hazard ratio (FTY720 vs. placebo)	0.38	0.48	---
(95% CI)	(0.30, 0.48)	(0.39, 0.61)	---
Cox PH regression p-value2	<0.001*	<0.001*	---

SE= standard error.
[1] P-value from log-rank test was used to compare the survival distributions between treatment groups.
[2] Hazard ratio and p-value derived from Cox's proportional hazards model adjusted for treatment, country, number of relapses in previous 2 years, and baseline EDSS.
* Indicates two-sided statistical significance at 0.05 level.

Confirmed MS relapse characteristics for 0 to 24 months (ITT population)

MS relapse characteristics	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Total number of relapses	148	172	359
Relapse severity			
Mild, n (%)	43 (29.1)	60 (34.9)	119 (33.1)
Moderate, n (%)	86 (58.1)	102 (59.3)	205 (57.1)
Severe, n (%)	19 (12.8)	10 (5.8)	35 (9.7)
Affects daily activities, n (%)	107 (72.3)	130 (75.6)	256 (71.3)
Steroid used, n (%)	120 (81.1)	140 (81.4)	303 (84.4)
Median (range) accumulated steroid dose (mg/kg) [1]	114.53 (6.2 to 1257.9)	117.92 (4.8 to 2528.1)	158.90 (8.4 to 775.0)
Total steroid dose (all patients) (g)	1633	2426	3945
Recovery status			
None, n (%)	13 (8.8)	12 (7.0)	18 (5.0)
Partial, n (%)	56 (37.8)	51 (29.7)	119 (33.1)
Complete, n (%)	78 (52.7)	108 (62.8)	212 (59.1)
Missing, n (%)	1 (0.7)	1 (0.6)	10 (2.8)
Hospitalization due to MS relapse, n (%)	60 (40.5)	63 (36.6)	146 (40.7)
Median (range) duration of relapse (days)	42.0 (5 to 153)	37.0 (4 to 161)	39.0 (3 to 156)

Percentages are calculated using the total number of relapses as the denominator.
[1] Steroid dose for both confirmed and unconfirmed relapses.

Other disability progression-related secondary clinical parameters

Confirmed 6-month disability progression up to Month 24 based on EDSS (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Kaplan-Meier estimate (SE) of % free of 6-month disability progression at Month 24 (720 days)	88.5 (1.60)	87.5 (1.64)	81.0 (1.99)
(95% CI)	(85.33, 91.61)	(84.26, 90.70)	(77.11, 84.92)
Treatment comparison of FTY720 vs. placebo			
p-value (log-rank test)1	0.004*	0.011*	---

Hazard ratio (FTY720 vs. placebo)	0.60	0.63	---
(95% CI)	(0.41, 0.86)	(0.44, 0.90)	---
Cox PH regression p-value2	0.006*	0.012*	---

SE = standard error.
[1] P-value from log-rank test is used to compare the survival distributions between treatment groups.
[2] P-value from Cox proportional hazard model for time to 6-month confirmed disability progression, adjusted for treatment, country, baseline EDSS, and age.
* Indicates two-sided statistical significance at 0.05 level.

Change from baseline in EDSS at Month 24 (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Month 24			
n	338	374	332
Mean (SD)	-0.03 (0.875)	0.00 (0.878)	0.13 (0.936)
Median	0.00	0.00	0.00
Range	-3.0 to 4.0	-3.0 to 3.5	-3.0 to 3.5
P-value for treatment comparison of FTY720 vs. placebo	0.002*	0.002*	

n = the number of patients who had EDSS values at both baseline and Month 24.
P-value is calculated using rank ANCOVA with covariates of treatment, country, the corresponding baseline value, and age.
* Indicates two-sided statistical significance at 0.05 level.

Change from baseline in MSFC z-score at Month 24 (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
MSFC z-score			
n	332	361	316
Mean (SD)	0.01 (0.403)	0.03 (0.394)	-0.06 (0.570)
P-value for treatment comparison of FTY720 vs. placebo	0.022*	0.010*	

n = the number of patients who had MSFC values at both baseline and Month 24.
P-value is calculated using rank ANCOVA with covariates of treatment, country, the corresponding baseline value, and age.
* Indicates two-sided statistical significance at 0.05 level

Safety Results

The overall incidence of AEs by proportion of patients was comparable for the two FTY720 treatment groups and the placebo treatment group. The most frequently reported AEs were infections, followed by nervous system and gastrointestinal disorders, with an even distribution by treatment group. The incidence of AEs was notably higher in both FTY720 groups than the placebo group for investigations (mainly driven by liver enzymes elevation), and blood and lymphatic disorders (mainly driven by leukopenia). SAEs were reported in comparable proportions of patients from all treatment groups, being slightly higher in the placebo group (13.4%), followed by the FTY720 1.25 mg (11.9%) and FTY720 0.5 mg (10.1%) treatment groups. Three patients died in the study; one patient on placebo due to a pulmonary embolism, one patient on placebo due to a traffic accident, and one patient on FTY720 1.25 mg who committed suicide. All deaths were considered as unrelated to study drug by the investigators.

Adverse Events by System Organ Class

Number (%) of patients with AEs by primary system organ class and treatment (Safety population)

Primary system organ class	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
Any primary system organ class	**404 (94.2)**	**401(94.4)**	**387(92.6)**
Infections and infestations	294 (68.5)	304 (71.5)	301 (72.0)
Nervous system disorders	183 (42.7)	173 (40.7)	172 (41.1)
Gastrointestinal disorders	157 (36.6)	146 (34.4)	144 (34.4)
Investigations	152 (35.4)	138 (32.5)	105 (25.1)
Musculoskeletal and connective tissue disorders	125 (29.1)	140 (32.9)	128 (30.6)
General disorders and administration site conditions	110 (25.6)	108 (25.4)	107 (25.6)
Skin and subcutaneous tissue disorders	106 (24.7)	131 (30.8)	122 (29.2)
Respiratory, thoracic and mediastinal disorders	103 (24.0)	107 (25.2)	95 (22.7)
Eye disorders	80 (18.6)	81 (19.1)	72 (17.2)
Psychiatric disorders	72 (16.8)	91 (21.4)	81 (19.4)
Injury, poisoning and procedural complications	50 (11.7)	61 (14.4)	65 (15.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	45 (10.5)	49 (11.5)	55 (13.2)
Reproductive system and breast disorders	45 (10.5)	39 (9.2)	26 (6.2)
Vascular disorders	43 (10.0)	46 (10.8)	42 (10.0)
Metabolism and nutrition disorders	41 (9.6)	43 (10.1)	44 (10.5)
Cardiac disorders	38 (8.9)	25 (5.9)	23 (5.5)
Blood and lymphatic system disorders	35 (8.2)	34 (8.0)	17 (4.1)
Ear and labyrinth disorders	35 (8.2)	31 (7.3)	32 (7.7)
Renal and urinary disorders	31 (7.2)	20 (4.7)	40 (9.6)
Hepatobiliary disorders	12 (2.8)	9 (2.1)	7 (1.7)
Immune system disorders	6 (1.4)	12 (2.8)	16 (3.8)
Endocrine disorders	3 (0.7)	3 (0.7)	3 (0.7)
Congenital, familial and genetic disorders	2 (0.5)	3 (0.7)	2 (0.5)
Social circumstances	2 (0.5)	0 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	7 (1.7)
Surgical and medical procedures	0 (0.0)	1 (0.2)	0 (0.0)

Primary system organ classes are sorted in descending frequency in the FTY720 1.25 mg group.

Number (%) of patients with AEs (at least 5% in any treatment group) by preferred term and treatment (Safety population)

Preferred term	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
Any preferred term	**404 (94.2)**	**401 (94.4)**	**387 (92.6)**

Headache	114 (26.6)	107 (25.2)	96 (23.0)
Nasopharyngitis	112 (26.1)	115 (27.1)	115 (27.5)
Upper respiratory tract infection	62 (14.5)	73 (17.2)	73 (17.5)
Alanine aminotransferase increased	50 (11.7)	43 (10.1)	16 (3.8)
Fatigue	47 (11.0)	48 (11.3)	45 (10.8)
Back pain	45 (10.5)	50 (11.8)	29 (6.9)
Diarrhoea	40 (9.3)	50 (11.8)	31 (7.4)
Influenza	40 (9.3)	55 (12.9)	41 (9.8)
Bronchitis	39 (9.1)	34 (8.0)	15 (3.6)
Nausea	38 (8.9)	38 (8.9)	36 (8.6)
Cough	37 (8.6)	43 (10.1)	34 (8.1)
Gamma-glutamyltransferase increased	32 (7.5)	22 (5.2)	4 (1.0)
Dizziness	30 (7.0)	31 (7.3)	23 (5.5)
Arthralgia	27 (6.3)	30 (7.1)	33 (7.9)
Hypertension	27 (6.3)	26 (6.1)	16 (3.8)
Sinusitis	27 (6.3)	28 (6.6)	19 (4.5)
Depression	26 (6.1)	33 (7.8)	28 (6.7)
Hypercholesterolaemia	26 (6.1)	24 (5.6)	26 (6.2)
Pharyngitis	25 (5.8)	27 (6.4)	24 (5.7)
Pain in extremity	24 (5.6)	28 (6.6)	28 (6.7)
Dyspnoea	23 (5.4)	30 (7.1)	19 (4.5)
Hepatic enzyme increased	22 (5.1)	14 (3.3)	1 (0.2)
Urinary tract infection	21 (4.9)	34 (8.0)	47 (11.2)
Rhinitis	18 (4.2)	25 (5.9)	25 (6.0)
Vertigo	18 (4.2)	18 (4.2)	21 (5.0)
Oropharyngeal pain	17 (4.0)	29 (6.8)	29 (6.9)
Paraesthesia	17 (4.0)	23 (5.4)	18 (4.3)
Insomnia	16 (3.7)	21 (4.9)	25 (6.0)
Weight increased	14 (3.3)	14 (3.3)	22 (5.3)

Preferred terms are sorted in descending frequency in the FTY720 1.25 mg group.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Percentage of patients with adverse events reported at 2% or greater difference between either FTY720 group and placebo by preferred term and treatment (Safety population)

Preferred term	FTY720 1.25mg N=429 (%)	FTY720 0.5mg N=425 (%)	Placebo N=418 (%)
Headache	114 (26.6)	107 (25.2)	96 (23.0)
Upper respiratory tract infection	62 (14.5)	73 (17.2)	73 (17.5)
ALT increased	50 (11.7)	43 (10.1)	16 (3.8)
Back pain	45 (10.5)	50 (11.8)	29 (6.9)
Influenza	40 (9.3)	55 (12.9)	41 (9.8)
Diarrhea	40 (9.3)	50 (11.8)	31 (7.4)
Bronchitis	39 (9.1)	34 (8.0)	15 (3.6)
Cough	37 (8.6)	43 (10.1)	34 (8.1)
Gamma-glutamyltransferase increased	32 (7.5)	22 (5.2)	4 (1.0)
Hypertension	27 (6.3)	26 (6.1)	16 (3.8)

Terms are listed in descending frequency in the FTY720 1.25 mg group.

Summary of Serious Adverse Events, deaths and discontinuations

Number (%) of patients who died or experienced SAEs or conditions leading to study drug discontinuation (Safety population)

	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
Any AE(s)	404 (94.2)	401 (94.4)	387 (92.6)
Death	1 (0.2)	0	2 (0.5)
SAE(s)	51 (11.9)	43 (10.1)	56 (13.4)
AE(s) leading to study drug discontinuation#	61 (14.2)	32 (7.5)	32 (7.7)
Abnormal lab value leading to study drug discontinuation	32 (7.5)	20 (4.7)	5 (1.2)

#Note this counts any patient with an AE leading to discontinuation and is different from disposition which summarizes only those patients who discontinued study drug for AEs as the primary reason for discontinuation.

Most frequent SAEs by system organ class were: infections and infestations (11 patients corresponding to 2.6% for FTY720 1.25 mg, 7 patients (1.6%) for FTY720 0.5 mg and 8 patients (1.9%) for placebo); nervous system disorders (11 patients (2.6%) for FTY720 1.25 mg, 10 patients (2.4%) for FTY720 0.5 mg and 4 patients (1.0%) for placebo); neoplasms benign, malignant and unspecified (including cysts and polyps (5 patients (1.2%) for FTY720 1.25 mg, 5 patients (1.2%) for FTY720 0.5 mg and 11 patients (2.6%) for placebo) and cardiac disorder (7 pa-

tients (1.6%) for FTY720 1.25 mg, 7 patients (1.6%) for FTY720 0.5 mg and 4 patients (1.0%) for placebo). The most common AE leading to discontinuation of FTY720 was ALT increased (3.7% of FTY720 1.25 mg patients, 2.8% of FTY720 0.5 mg patients, and 0.7% of placebo patients).

Clinical laboratory evaluation

Frequency (%) distribution of absolute lymphocytes by treatment (Safety population)

Parameter	Criterion	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
Absolute lymphocytes (x 10^9/L)	n	425	424	414
	> ULN	0 (0.0)	0 (0.0)	0 (0.0)
	< 0.8 x 10^9/L	415 (97.6)	418 (98.6)	30 (7.2)
	< 0.6 x 10^9/L	402 (94.6)	398 (93.9)	11 (2.7)
	< 0.4 x 10^9/L	359 (84.5)	315 (74.3)	6 (1.4)
	< 0.2 x 10^9/L	128 (30.1)	78 (18.4)	0 (0.0)
	< 0.1 x 10^9/L	9 (2.1)	3 (0.7)	0 (0.0)

ULN=upper limit of normal; normal range is specified by study laboratory.

The lowest post-baseline value is used. The results are presented in cumulative form, i.e., the lowest actual laboratory value/upper limit value was used.

Except for the n values, patients with values not classified as abnormal are not shown.

Number (%) of patients with clinically notable hematological abnormalities (Safety population)

Parameter	Criterion	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
WBC (total)	n	425	424	414
	= 2 x 10^9/L	55 (12.9)	43 (10.1)	0 (0.0)
	= 15 x 10^9/L	5 (1.2)	0 (0.0)	12 (2.9)
Absolute lymphocytes	n	425	424	414
	< 0.2 x 10^9/L	128 (30.1)	78 (18.4)	0 (0.0)
	= 8 x 10^9/L	0 (0.0)	0 (0.0)	0 (0.0)
Absolute neutrophils (seg. + bands)	n	425	424	414
	= 1 x 10^9/L	19 (4.5)	11 (2.6)	5 (1.2)
	= 12 x 10^9/L	8 (1.9)	3 (0.7)	12 (2.9)
RBC	n	425	424	414
	< 3.3 x 10^{12}/L	2 (0.5)	0 (0.0)	1 (0.2)
	> 6.8 x 10^{12}/L	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin	n	425	424	414
	= 100 g/L	8 (1.9)	10 (2.4)	11 (2.7)
Platelet count (direct)	n	425	424	414
	= 100 x 10^9/L	1 (0.2)	3 (0.7)	3 (0.7)
	= 600 x 10^9/L	0 (0.0)	0 (0.0)	3 (0.7)

The highest post-baseline value is used for high ranges. The lowest post-baseline value is used for low ranges.

Frequency (%) distribution of ALT values (Safety population)

Liver parameter	Criterion	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
ALT (U/L)	n	425	424	414
	No abnormality	226 (53.2)	214 (50.5)	314 (75.8)
	> ULN	199 (46.8)	210 (49.5)	100 (24.2)
	= 2 x ULN	88 (20.7)	80 (18.9)	23 (5.6)
	= 3 x ULN	53 (12.5)	36 (8.5)	7 (1.7)
	= 5 x ULN	13 (3.1)	8 (1.9)	4 (1.0)
	= 10 x ULN	0 (0.0)	1 (0.2)	0 (0.0)
	= 20 x ULN	0 (0.0)	0 (0.0)	0 (0.0)

ULN=upper limit of normal; normal range is specified by study laboratory.

The results are presented in cumulative form, i.e., the highest actual laboratory value/upper limit value was used. If the value was = 20 x ULN, it was also included in the = 10 x ULN and all preceding categories.

Number (%) of patients with clinically notable liver parameters abnormalities (Safety population)

	Criterion	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
Liver parameters				
SGPT (ALT)	n	425	424	414
	> 90 U/L	88 (20.7)	75 (17.7)	21 (5.1)
SGOT (AST)	n	425	424	414
	> 82 U/L	30 (7.1)	14 (3.3)	8 (1.9)
Gamma glutamyltransferase (GGT)	n	425	424	414
	> 130 U/L	80 (18.8)	63 (14.9)	9 (2.2)
Bilirubin (total)	n	425	424	414
	= 34.2 µmol/L	7 (1.6)	6 (1.4)	9 (2.2)
Alkaline phosphatase, serum	n	425	424	414
	> 280 U/L	3 (0.7)	0 (0.0)	0 (0.0)

Number (%) of patients with clinically notable vital sign abnormalities during the first dose administration monitoring (Safety population)

Vital Signs (units)	Criterion	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
Sitting pulse (bpm)	Low: < 50	49 (11.4)	22 (5.2)	9 (2.2)
	= 15 decrease from baseline	171 (39.9)	118 (27.8)	48 (11.5)
	High: > 120	0	0	0
	= 15 increase from baseline	12 (2.8)	17 (4.0)	54 (12.9)
Sitting systolic BP (mmHg)	Low: = 90	56 (13.1)	38 (8.9)	30 (7.2)
	= 20 decrease from baseline	67 (15.6)	70 (16.5)	47 (11.2)
	High: = 180	1 (0.2)	0	1 (0.2)
	= 160	10 (2.3)	10 (2.4)	8 (1.9)
	=20 increase from baseline	38 (8.9)	40 (9.4)	46 (11.0)
Sitting diastolic BP (mmHg)	Low: = 50	33 (7.7)	20 (4.7)	13 (3.1)
	= 15 decrease from baseline	120 (28.0)	100 (23.5)	67 (16.0)

High: = 105	5 (1.2)	1 (0.2)	6 (1.4)
= 100	11 (2.6)	11 (2.6)	18 (4.3)
= 15 increase from baseline	26 (6.1)	24 (5.6)	35 (8.4)

Other Relevant Findings

A transient decrease in heart rate and an effect on atrioventricular conduction upon treatment initiation was observed in this study. The majority of cardiac events (including bradycardia and first degree AV block) occurred during the first dose administration, were asymptomatic, without treatment, and recovered within 24 hours. First degree AV block occurred in 8.3%, 4.8% and 1.5% of patients on 1.25mg FTY720, 0.5mg FTY720 and placebo respectively. Mobitz Type 1 second degree AV block occurred in 0.5% of those receiving 1.25mg FTY720 and 0.2% receiving 0.5mg FTY720.Seven (1.6%) confirmed cases of macular edema were observed in the FTY720 1.25 mg group.

Date of Clinical Trial Report

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Date Inclusion on Novartis Clinical Trial Results Database

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Date of Latest Update

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