## Sponsor

Novartis Pharma AG

## Generic Drug Name

Fingolimod

## Therapeutic Area of Trial

Neurodegenerative diseases

## Approved Indication

Relapsing multiple sclerosis (MS), including relapsing-remitting MS and secondary progressive MS

## Study Number

CFTY720D1201

## Title

A 6-month, double-blind, randomized, placebo-controlled, parallel-group, multicenter study comparing efficacy and safety of FTY720 0.5 mg and 1.25 mg administered orally once daily in patients with relapsing MS.

## Phase of Development

II

## Study Start/End Dates

24 Oct 2007 to 22 Feb 2010

## Study Design/Methodology

This was a 6-month double-blind, randomized, multicenter, placebo-controlled, parallel-group study in approximately 165 patients with relapsing MS. Patients were randomized in a ratio of 1:1:1 to receive treatment with FTY720 0.5 mg, FTY720 1.25 mg or placebo once daily for up to 6 months.

## Centres

A total of 43 study sites in Japan

## Publication

None

## Objectives

Primary objective(s)

- To evaluate the effect of two doses (0.5 mg and 1.25 mg) of FTY720 compared to placebo on the percentage of patients free of gadolinium (Gd-) enhanced T1 weighted magnetic resonance imaging (MRI) lesions at both 3 months and 6 months of treatment.

Secondary objective(s)

- To assess the effect of two doses (0.5 mg and 1.25 mg) of FTY720 compared to placebo on the percentage of patients free of clinical relapse during 6 months of treatment
- To assess the safety and tolerability of two doses (0.5 mg and 1.25 mg) of FTY720 compared to placebo in patients with MS during 6 months of treatment.

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

Capsules of FTY720 0.5 mg or 1.25 mg once a day in the morning as much as possible at the same time, with or without food.

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

Capsules of matching placebo once a day in the morning as much as possible at the same time, with or without food.

## Criteria for Evaluation

### Primary variables

- Proportion of patients free of Gd-enhanced T1 weighted MRI lesions (the patients without active lesions) at both Month 3 and Month 6.

### Secondary variables

- Proportion of relapse free patients at Month 6 (key secondary variable)
- Annualized relapse rate (ARR) at 6 months.

### Safety and tolerability

All adverse events (AEs), serious adverse events (SAE), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of laboratory values and regular assessments of vital signs, electrocardiogram, physical condition, and body weight. Additional safety assessments, as specified per protocol, included dermatologic and ophthalmic examinations, chest x-ray, and pulmonary function tests.

## Statistical Methods

### Efficacy - Primary analysis

The primary null hypotheses tested for the primary efficacy variable were: 1) there is no difference in the proportion of patients free of Gd-enhanced T1 weighted MRI lesions at both Month 3 and Month 6 between patients treated with the FTY720 1.25 mg and placebo, and 2) there is no difference in the proportion of patients free of Gd-enhanced T1 weighted MRI lesions at both Month 3 and Month 6 between patients treated with the FTY720 0.5 mg and placebo. The primary analysis used the Modified full analysis set (FAS).

The test of the hypotheses was based on a logistic regression model using treatment group and number of Gd-enhanced T1 weighted MRI lesions at screening.

To control the overall type-I error rate of the study, a multiplicity adjustment for two pair-wise treatment comparisons (FTY720 1.25 mg vs. placebo, FTY720 0.5 mg vs. placebo) was applied to the primary endpoint: the adjustment was done according to hierarchical closed testing procedure. The first test was to compare FTY720 1.25 mg (higher dose) with placebo, then the second test was to compare FTY720 0.5 mg (lower dose) with placebo if the result of the first test was statistically significant with the significance level of 0.05. The second hypothesis was not tested if the first test was not statistically significant. However the p-value for both tests was calculated.

### Efficacy – Secondary analysis

The key secondary analysis, the proportion of relapse free patients at Month 6, was analyzed using logistic regression adjusted for treatment, expanded disability status scale (EDSS) at screen-

ing, and baseline relapse rate (in previous 2 years).

The primary ARR analysis used confirmed relapses only. The relapse rates at Month 6 were analyzed using rank analysis of covariance and negative binominal regression model. The regression used the treatment, baseline number of relapses in previous 2 years, and EDSS score at screening as covariate. Logarithmic transformation of the time on study was used as the offset variable. The annualized relapse rate in each treatment group was calculated as the total number of relapses divided by the total number of days on study, multiplied by 365.25.

## Safety

Safety assessments were summarized based primarily on the frequency of AEs, SAEs and notable laboratory abnormalities with the safety population. Other safety data were summarized as appropriate.

## Study Population: Inclusion/Exclusion Criteria and Demographics

Male and female patients aged 18-60 years with a diagnosis of MS as defined by 2005 revised McDonald criteria, and a relapsing-remitting course with at least 2 relapses during the past 2 years, or at least 1 documented relapse during the last year prior to randomization, or at least 1 Gd-enhanced T1 weighted MRI lesion in brain at screening (in case the first MRI scan obtained at screening was negative, a second MRI scan could be obtained 1 month later).

Patients with EDSS score of 0 to 6.0, and neurologically stable with no evidence of relapse within 30 days prior to randomization.

## Number of Subjects

### Patient disposition (Randomized population)

| | FTY720 1.25 mg N = 57 n (%) | FTY720 0.5 mg N = 57 n (%) | Placebo N = 57 n (%) | Total N = 171 n (%) |
|---|---|---|---|---|
| Completed study phase[a] | 48 (84.2) | 48 (84.2) | 51 (89.5) | 147 (86.0) |
| Discontinued from the study phase after starting study medication | 6 (10.5) | 9 (15.8) | 6 (10.5) | 21 (12.3) |
| Adverse Event(s) | 6 (10.5) | 6 (10.5) | 3 (5.3) | 15 (8.8) |
| Protocol deviation | 0 (0.0) | 2 (3.5) | 1 (1.8) | 3 (1.8) |
| Unsatisfactory therapeutic effect | 0 (0.0) | 0 (0.0) | 2 (3.5) | 2 (1.2) |
| Subject withdrew consent | 0 (0.0) | 1 (1.8) | 0 (0.0) | 1 (0.6) |
| Administrative problems | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Death | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Lost to follow-up | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Subject's condition no longer requires study drug | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

"Study phase" denotes double-blinded treatment phase.
[a] Three patients were randomized in the FTY720 1.25 mg group, but did not take any study medication.
All percentages were calculated based on the number of randomized patients (N).

## Demographic and Background Characteristics

### Demographics by treatment group (Randomized population)

| | | FTY720 1.25 mg N = 57 | FTY720 0.5 mg N = 57 | Placebo N = 57 | Total N = 171 |
|---|---|---|---|---|---|
| Age (years) | Mean (SD) | 36.0 (9.31) | 35.0 (9.01) | 35.0 (8.93) | 35.3 (9.04) |
| | Median | 36.0 | 34.0 | 34.0 | 34.0 |
| | Range | (18-55) | (19-52) | (18-52) | (18-55) |
| Age group (years)-n (%) | 30 | 19 (33.3) | 23 (40.4) | 19 (33.3) | 61 (35.7) |
| | 31-40 | 20 (35.1) | 17 (29.8) | 25 (43.9) | 62 (36.3) |
| | 41-50 | 13 (22.8) | 14 (24.6) | 10 (17.5) | 37 (21.6) |
| | > 50 | 5 (8.8) | 3 (5.3) | 3 (5.3) | 11 (6.4) |
| Sex-n (%) | Male | 18 (31.6) | 17 (29.8) | 18 (31.6) | 53 (31.0) |
| | Female | 39 (68.4) | 40 (70.2) | 39 (68.4) | 118 (69.0) |
| Weight (kg) | Mean (SD) | 56.50 (10.760) | 57.89 (11.667) | 55.19 (9.923) | 56.53 (10.800) |
| | Median | 53.00 | 54.90 | 51.90 | 54.00 |

| | | | | | |
|---|---|---|---|---|---|
| | Range | (35.9-96.5) | (39.1-85.6) | (34.1-87.1) | (34.1-96.5) |
| Height (cm) | Mean (SD) | 160.9 (7.05) | 162.4 (7.93) | 162.5 (8.52) | 161.9 (7.84) |
| | Median | 161.0 | 161.0 | 161.0 | 161.0 |
| | Range | (141-174) | (147-183) | (143-181) | (141-183) |
| BMI (kg/m$^2$) | Mean (SD) | 21.79 (3.767) | 21.83 (3.338) | 20.83 (2.797) | 21.48 (3.337) |
| | Median | 20.83 | 21.45 | 20.45 | 20.86 |
| | Range | (17.2-36.2) | (15.1-32.6) | (13.8-28.8) | (13.8-36.2) |

BMI = body mass index (= body weight (kg)/height (m) $^2$), calculated using baseline body weight and height on Visit 1

## Primary Objective Result(s)

### Number of patients free of Gd-enhanced T1 weighted MRI lesions at both Month 3 and Month 6 (Modified FAS)

| | FTY720 1.25 mg N = 50 n (%) | FTY720 0.5 mg N = 50 n (%) | Placebo N = 52 n (%) |
|---|---|---|---|
| Total | 50 | 50 | 52 |
| Number (%) of patients free of Gd-enhanced T1 weighted MRI lesions at both Month 3 and 6 | 43 (86.0) | 35 (70.0) | 21 (40.4) |
| **Treatment comparison of FTY720 vs. Placebo** | | | |
| Odds ratio | 15.238 | 3.628 | - |
| (95% CI) | (4.717, 49.222) | (1.504, 8.753) | - |
| P-value | < 0.001* | 0.004* | - |

Total = Number of patients with the MRI data at Month 3 or Month 6. n = Number of patients free of Gd-enhanced T1 weighted MRI lesions. Percentage are calculated as n/Total*100.
Any Gd-enhanced T1 weighted MRI data obtained less than 14 days after the steroid used to treat MS relapses was invalid and excluded.
Odds ratio, 95% CI and p-value were calculated using logistic regression model adjusted by treatment group and the number of Gd-enhanced T1 weighted MRI lesions at screening.
* Indicates two-sided statistical significance at 0.05 level.

## Secondary Objective Result(s)

Key secondary objective results

### Number (%) of patients free of MS relapse up to Month 6 (confirmed relapse only) (FAS)

| | FTY720 1.25 mg N = 54 | FTY720 0.5 mg N = 57 | Placebo N = 57 |
|---|---|---|---|
| Number (%) of patients free of confirmed relapse up to Month 6 | 45 (83.3) | 45 (78.9) | 37 (64.9) |
| **Treatment comparison of FTY720 vs. Placebo** | | | |
| Odds ratio | 2.492 | 1.944 | - |
| (95% CI) | (0.988, 6.287) | (0.816, 4.631) | - |
| P-value | 0.053 | 0.133 | - |

Odds ratio, 95% CI and p-value were calculated using logistic regression model adjusted by treatment group, EDSS at screening, and baseline number of relapses in the previous 2 years.

Other results

### Aggregate annualized relapse rate (ARR) up to Month 6 (confirmed relapse only) (FAS)

| | FTY720 1.25 mg N = 54 | FTY720 0.5 mg N = 57 | Placebo N = 57 |
|---|---|---|---|
| Number of relapses | 10 | 13 | 30 |
| Time on study (days) | 8978 | 9269 | 9685 |
| Aggregated ARR | 0.407 | 0.512 | 1.131 |
| ARR estimate | 0.414 | 0.501 | 0.986 |
| (95% CI) | (0.223, 0.769) | (0.289, 0.868) | (0.670, 1.452) |
| ARR ratio for treatment comparison for FTY720 vs. placebo | 0.419 | 0.508 | |
| P-value for treatment comparison of FTY720 vs. placebo | 0.020* | 0.047* | |

ARR of the treatment group was calculated by taking the total number of confirmed relapses for all the patients in the treatment group divided by the total number of days on study for all patients in the group and multiplied by 365.25 to obtain the annual rate.
ARR estimate (95% CI), ARR ratio, and p-value were calculated using Negative Binomial regression adjusted by treatment group, number of relapses in the previous 2 years, and baseline EDSS.
* Indicates two-sided statistical significance at 0.05 level.

## Safety Results

## 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 1.25 mg N = 54 n (%) | FTY720 0.5 mg N = 57 n (%) | Placebo N = 57 n (%) |
|---|---|---|---|
| **Any primary system organ class** | 51 (94.4) | 52 (91.2) | 45 (78.9) |
| Infections and infestations | 31 (57.4) | 28 (49.1) | 23 (40.4) |
| Investigations | 25 (46.3) | 15 (26.3) | 8 (14.0) |
| Gastrointestinal disorders | 17 (31.5) | 23 (40.4) | 13 (22.8) |
| Nervous system disorders | 13 (24.1) | 11 (19.3) | 6 (10.5) |
| Skin and subcutaneous tissue disorders | 12 (22.2) | 11 (19.3) | 10 (17.5) |
| Cardiac disorders | 9 (16.7) | 7 (12.3) | 1 (1.8) |
| Blood and lymphatic system disorders | 8 (14.8) | 2 (3.5) | 1 (1.8) |
| Injury, poisoning and procedural complications | 7 (13.0) | 3 (5.3) | 3 (5.3) |
| General disorders and administration site conditions | 6 (11.1) | 7 (12.3) | 8 (14.0) |
| Musculoskeletal and connective tissue disorders | 5 (9.3) | 0 (0.0) | 5 (8.8) |
| Respiratory, thoracic and mediastinal disorders | 5 (9.3) | 4 (7.0) | 3 (5.3) |
| Eye disorders | 4 (7.4) | 6 (10.5) | 7 (12.3) |
| Psychiatric disorders | 3 (5.6) | 3 (5.3) | 0 (0.0) |
| Metabolism and nutrition disorders | 2 (3.7) | 0 (0.0) | 2 (3.5) |
| Reproductive system and breast disorders | 2 (3.7) | 3 (5.3) | 1 (1.8) |
| Renal and urinary disorders | 1 (1.9) | 1 (1.8) | 0 (0.0) |
| Vascular disorders | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Ear and labyrinth disorders | 0 (0.0) | 1 (1.8) | 0 (0.0) |
| Hepatobiliary disorders | 0 (0.0) | 2 (3.5) | 0 (0.0) |
| Surgical and medical procedures | 0 (0.0) | 0 (0.0) | 1 (1.8) |

All AEs with onset date within 45 days of last dose of study drug and all SAEs were included.
A subject with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment
Sorted in descending frequency in the FTY720 1.25 mg group.

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

### Number of patients with AEs (at least 7% in any group) by preferred term and treatment (Safety population)

| Preferred term | FTY720 1.25 mg N = 54 n (%) | FTY720 0.5 mg N = 57 n (%) | Placebo N = 57 n (%) |
|---|---|---|---|
| **Any preferred term(s)** | 51 (94.4) | 52 (91.2) | 45 (78.9) |
| Nasopharyngitis | 21 (38.9) | 24 (42.1) | 19 (33.3) |
| Liver function test abnormal | 18 (33.3) | 12 (21.1) | 3 (5.3) |
| Bradycardia | 8 (14.8) | 3 (5.3) | 0 (0.0) |
| Diarrhea | 6 (11.1) | 3 (5.3) | 3 (5.3) |
| Headache | 5 (9.3) | 5 (8.8) | 4 (7.0) |
| Nausea | 4 (7.4) | 4 (7.0) | 2 (3.5) |
| Dizziness | 3 (5.6) | 4 (7.0) | 1 (1.8) |
| Constipation | 2 (3.7) | 4 (7.0) | 1 (1.8) |
| Pyrexia | 2 (3.7) | 2 (3.5) | 4 (7.0) |

All AEs with onset date within 45 days of last dose of study drug and all SAE were included.
A subject with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.
Preferred terms are sorted in descending frequency in the FTY720 1.25 mg group.

## Serious Adverse Events and Deaths

### Number (%) of patients who died or experienced other serious or clinically significant AEs (Safety population)

| | FTY720 1.25 mg N = 54 n (%) | FTY720 0.5 mg N = 57 n (%) | Placebo N = 57 n (%) |
|---|---|---|---|
| Death | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| SAE(s) | 11 (20.4) | 5 (8.8) | 3 (5.3) |
| SAE(s) leading to study drug discontinuation | 3 (5.6) | 1 (1.8) | 1 (1.8) |
| AE(s) leading to study drug discontinuation | 6 (11.1) | 6 (10.5) | 3 (5.3) |
| AE(s) leading to study drug interruption | 6 (11.1) | 6 (10.5) | 1 (1.8) |

These categories are not mutually exclusive.

### Number (%) of patients with SAEs, regardless of study drug relationship, by primary system organ class, preferred term and treatment (Safety population)

| System organ class / Preferred term | FTY720 1.25 mg N = 54 n (%) | FTY720 0.5 mg N = 57 n (%) | Placebo N = 57 n (%) |
|---|---|---|---|
| **Any primary system organ class(s)** | 11 (20.4) | 5 (8.8) | 3 (5.3) |
| **Cardiac disorders** | 9 (16.7) | 4 (7.0) | 1 (1.8) |
| Bradycardia | 8 (14.8) | 3 (5.3) | 0 (0.0) |
| Atrioventricular block second degree | 2 (3.7) | 0 (0.0) | 0 (0.0) |
| Sinus bradycardia | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Atrioventricular block first degree | 0 (0.0) | 1 (1.8) | 0 (0.0) |

| | | | |
|---|---|---|---|
| Stress cardiomyopathy | 0 (0.0) | 0 (0.0) | 1 (1.8) |
| **Nervous system disorders** | 2 (3.7) | 0 (0.0) | 0 (0.0) |
| Facial palsy | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Multiple sclerosis relapse | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| **Investigations** | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Heart rate decreased | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Liver function test abnormal | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| **Vascular disorders** | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| Hypotension | 1 (1.9) | 0 (0.0) | 0 (0.0) |
| **Gastrointestinal disorders** | 0 (0.0) | 0 (0.0) | 1 (1.8) |
| Enterocolitis | 0 (0.0) | 0 (0.0) | 1 (1.8) |
| **General disorders and administration site conditions** | 0 (0.0) | 2 (3.5) | 0 (0.0) |
| Chest discomfort | 0 (0.0) | 1 (1.8) | 0 (0.0) |
| Malaise | 0 (0.0) | 1 (1.8) | 0 (0.0) |
| **Surgical and medical procedures** | 0 (0.0) | 0 (0.0) | 1 (1.8) |
| Abortion induced | 0 (0.0) | 0 (0.0) | 1 (1.8) |

Primary system organ class (SOC) is sorted by descending frequency in the FTY720 1.25 mg group.
Preferred terms are sorted within each primary SOC by descending frequency in the FTY720 1.25 mg group.
A patient with multiple occurrences of a SAE for a preferred term or SOC under one treatment was counted only once in each specific category for that treatment.

## Other Relevant Findings

Not applicable.

## Date of Clinical Trial Report

16-November-2010

## Date Inclusion on Novartis Clinical Trial Results Database

18 February 2011

## Date of Latest Update

8 February 2011