Sponsor

Novartis

Generic Drug Name

Fingolimod

Therapeutic Area of Trial

Relapsing forms of multiple sclerosis

Approved Indication(s)

United States (US Package Insert)

- Fingoliomod is indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

European Union (Summary of Product Characteristics)

Fingolomod is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

- Patients with high disease activity despite treatment with a beta-interferon.

  or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Protocol Number

CFTY720D2316

EudraCT no. 2010-019029-32

ClinicalTrials.gov Identifier: NCT01127750

Title

A 4-month, open-label, multi-center study to explore tolerability and safety and health outcomes of FTY720 in patients with relapsing forms of multiple sclerosis.

Phase of Development

Phase IIIB

Study Start/End Dates

10-May-2010 (first patient first visit) to 13-Oct-2011 (last patient last visit)

Study Design/Methodology

This was a multi-center, open-label, single treatment arm study in 2417 patients with relapsing forms of multiple sclerosis. The study was of 4 month duration consisting of a Screening phase of 1-2 week and an open-label Treatment phase with fingolimod for 16 weeks. On completion of the open-label treatment phase, patients had an option of entering an extension study to receive continuous treatment with fingolimod. Patients who did not continue on fingolimod (prescribed either in the extension study or from the commercial supply) were required to return for a Follow-up visit 12 weeks after the last dose of study drug.

Centres

A total of 285 study centers in 23 countries; 5 centers (Australia), 3 centers (Austria), 10 centers (Belgium), 3 centers (Canada), 2 centers (Czech Republic), 2 centers (Denmark), 2 centers (Finland), 146 centers (Germany), 5 centers (Greece), 5 centers (Hungary), 2 centers (Ireland), 24 centers (Italy), 7 centers (Netherlands), 3 centers (Norway), 3 centers (Poland), 3 centers (Portugal), 12 centers (Russia), 3 centers (Slovakia), 8 centers (Spain), 3 centers (Sweden), 8 centers (Switzerland), 6 centers (Turkey) and 20 centers (United Kingdom).

Publication

None.

Outcome measures

Primary outcome measures(s)

- The primary objective was to evaluate the safety and tolerability profile of fingolimod 0.5 mg in patients with relapsing forms of multiple sclerosis (MS) including a broader patient population than has been previously studied in clinical trials with fingolimod.

Secondary outcome measures(s)

The study had no secondary objectives.

Test Product, Dose, and Mode of Administration

Fingolimod 0.5 mg for oral administration once daily.

Statistical Methods

Safety

Statistical summary is provided as frequency summary (count number and percentage) for categorical variables and descriptive summary (n, mean, SD, minimum, median, maximum) for continuous variables. All safety analyses were performed in the safety set.

The incidence of death, serious adverse events (SAEs), AEs leading to discontinuation, and other significant AEs were summarized separately by primary system organ class and preferred term. Adverse events were summarized by cardiac risk criteria and by subgroup of patients receiving beta blockers or calcium channel blockers.

Laboratory data was summarized by presenting summary statistics of actual values and change from baseline values, by presenting shift tables using clinically notable ranges (baseline to most extreme post-baseline value), and by flagging notable values in data listings. For liver function tests, the frequencies and percentages of patients with elevations of 1, 2, 3, 5, and 10 times upper limit of normal were summarized by visit.

Vital sign data were summarized as descriptive statistics for change from baseline value. The incidence rates of notable vital sign abnormalities were summarized.

The 1st dose Holter-ECGs data were summarized as descriptive statistics for change from screening by post-dose 6 hours. In addition, incidence rate of abnormal Holter-ECGs and abnormal Holter-ECGs by type of abnormality was summarized. The pre-dose ECGs were summarized as well.

The ophthalmic data in visual acuity and central foveal thickness was summarized as frequency distributions, summary statistics, and change from baseline by visit. The incidence of macular edema events after treatment initiation with fingolimod 0.5 mg was summarized as frequency distributions.

The skin assessments were summarized based on normal and abnormal findings.

For the supportive safety analysis purpose, the safety data were summarized by subgroups of gender, age group, treated and untreated patients with prior disease-modifying MS therapies, on-site and off-site patients, cardiac risk and no-risk patients and diabetic and non-diabetic patients.

Sample size calculation

The incidence of AV blocks and conduction abnormalities from 1st dose 6-hour ECG, liver function test ALT elevations, and macular edema were selected for the consideration of the sample size calculation.

Interim analysis

No interim analyses were planned or performed for this study.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Patients eligible for inclusion in this study had to fulfill all of the following criteria:

- Provide written informed consent before any assessment was performed.
- Male or female aged 18-65 years (inclusive).
- Relapsing forms of MS, defined by 2005 revised McDonald criteria.
- Expanded Disability Status Scale (EDSS) score of 0-6.5.

Exclusion criteria

Patients fulfilling any of the following criteria were not eligible for inclusion in this study:

- Manifestation of MS other than relapsing MS.
- A history of chronic disease of the immune system other than MS.
- History or presence of malignancy.
- Diabetic with moderate or severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy and uncontrolled diabetic patients with HbA1c > 8%.
- Diagnosis of macular edema during Screening.
- Active systemic bacterial, viral or fungal infections, or known to have AIDS, Hepatitis B, Hepatitis C infection or to have positive HIV antibody, Hepatitis B surface antigen or Hepatitis C antibody tests.
- Negative for varicella-zoster virus IgG antibodies at Screening.
- Received any live or live attenuated vaccines (including for varicella-zoster virus or measles) within 1 month prior to baseline.
- Received total lymphoid irradiation or bone marrow transplantation.
- Had been treated with:
    - corticosteroids or adrenocorticotropic hormones (ACTH) within 1 month prior to baseline;
    - immunosuppressive medications such as azathioprine or methotrexate within 3 months prior to baseline;
    - immunoglobulins and/or monoclonal antibodies (including natalizumab) within 3 months prior to baseline;
    - cladribine, cyclophosphamide or mitoxantrone at any time.
- Any medically unstable condition, as assessed by the primary treating physician at each site.
- Any of the following cardiovascular conditions and/or findings in the screening ECG-recordings:
    - history of cardiac arrest;
    - myocardial infarction within the past 6 months prior to enrollment or with current unstable ischemic heart disease;
    - known 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) or any severe cardiac disease as determined by the investigator;
- history or presence of a Mobitz 2 second degree AV block or a third degree AV block or an increased QTc interval >450 ms in males and >470 ms in females corrected using Bazett's formula;
- receiving Class Ia (ajmaline, disopyramide, procainamide, quinidine) and III antiarrhythmic drugs (e.g., amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide).
- resting pulse rate <45 bpm prior to baseline;
- bradycardia measured by continuous ambulatory ECG of <40 bpm at any hour (mean) or of <30 bpm at any time (beat to beat)
- proven history of sick sinus syndrome or sino-atrial heart block;
- hypertension, not controlled by prescribed medications

- Any of the following hepatic conditions
  - chronic liver or biliary disease;
  - total bilirubin greater than 2 times the upper limit of the normal range, unless in context of Gilbert's syndrome
  - conjugated bilirubin greater than 2 times the upper limit of the normal range
  - AST (SGOT), ALT (SGPT) greater than 2 times the upper limit of the normal range;
  - alkaline phosphatase (AP) greater than 1.5 times the upper limit of the normal range;
  - gamma-glutamyl-transferase (GGT) greater than 3 times the upper limit of the normal range;
- Pregnant or nursing (lactating) women.
- Prior participation in a trial with fingolimod.

Other protocol defined exclusion criteria were applicable.

Participant Flow

Patient disposition (Enrolled Set)

Disposition	FTY720 0.5 mg n (%)
Enrolled	2417
Completed	2282 (94.4)
Discontinued	135 (5.6)
Reason for discontinuation	
Abnormal laboratory value(s)	27 (1.1)
Abnormal test procedure result(s)	4 (0.2)
Administrative problems	1 (0.0)
Adverse Event(s)	68 (2.8)
Death	1 (0.0)
Lost to follow-up	6 (0.2)
Other	0 (0.0)
Protocol deviation	8 (0.3)
Subject withdrew consent	13 (0.5)
Subject's condition no longer requires study drug	0 (0.0)
Unsatisfactory therapeutic effect	7 (0.3)

Reasons for discontinuation are sorted alphabetically.
Percentage (%) is calculated using the Enrolled Set as the denominator.

Baseline Characteristics

Patient demographics summary (Enrolled Set)

Demographic Characteristic Category / statistic	FTY720 0.5 mg N=2417
Age (years)	
n	2417
Mean	38.4
SD	9.50
Median	39.0
Minimum	18
Maximum	65
Age group (years) n (%)	
18-30	552 (22.8)
31-40	804 (33.3)
41-55	981 (40.6)
56-65	80 (3.3)
Sex n (%)	

Male	644 (26.6)
Female	1773 (73.4)
Race n (%)	
Caucasian	2381 (98.5)
Black	2 (0.1)
Asian	4 (0.2)
Native American	3 (0.1)
Other	27 (1.1)
Ethnicity n (%)	
Hispanic/Latino	87 (3.6)
Chinese	1 (0.0)
Mixed Ethnicity	34 (1.4)
Other	2295 (95.0)
Weight (kg)	
n	2398
Mean	72.1
SD	16.10
Median	70.0
Minimum	41
Maximum	155
Height (cm)	
n	2388
Mean	170.2
SD	8.99
Median	170.0
Minimum	144
Maximum	202
BMI (kg/m^2)	
n	2385
Mean	24.8
SD	4.75
Median	23.9
Minimum	15
Maximum	48
Subject met cardiac risk criteria for on-site monitoring n (%)	
Yes	296 (12.2)
No	2121 (87.8)

Type of monitoring n (%)	
On-site	1221 (50.5)
Off-site	1196 (49.5)
Diabetic*	
Yes	26 (1.1)
No	2391 (98.9)

SD = standard deviation; BMI: Body Mass Index

N = Number of patients in the Enrolled Set.

n = Number of patients meeting the criterion (for categorical variables) or the number of patients with a measurement (for continuous variable).

*Diabetic status based on patient's history with high level term "Diabetes mellitus" (incl subtypes).

BMI (kg/m^2) = Weight (kg)/ {Height (m)}^{2}.

Outcome measures

Primary Outcome Result(s)

Safety and tolerability was the primary objective in the study and the results are presented under Safety results.

Safety Results

Adverse Events by System Organ Class

Number (%) of patients with adverse events by primary system organ class (Safety Set)

Primary system organ class	FTY720 0.5 mg N=2415 n (%)
Any primary system organ class	1819 (75.3)
Infections and infestations	828 (34.3)
Nervous system disorders	561 (23.2)
Gastrointestinal disorders	396 (16.4)
General disorders and administration site conditions	311 (12.9)
Investigations	277 (11.5)
Musculoskeletal and connective tissue disorders	272 (11.3)
Blood and lymphatic system disorders	264 (10.9)
Skin and subcutaneous tissue disorders	259 (10.7)
Psychiatric disorders	177 (7.3)
Respiratory, thoracic and mediastinal disorders	160 (6.6)
Eye disorders	140 (5.8)
Vascular disorders	113 (4.7)
Cardiac disorders	96 (4.0)
Ear and labyrinth disorders	94 (3.9)
Injury, poisoning and procedural complications	88 (3.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	86 (3.6)
Reproductive system and breast disorders	58 (2.4)
Metabolism and nutrition disorders	50 (2.1)
Renal and urinary disorders	46 (1.9)
Immune system disorders	12 (0.5)
Hepatobiliary disorders	8 (0.3)
Endocrine disorders	5 (0.2)
Congenital, familial and genetic disorders	3 (0.1)
Pregnancy, puerperium and perinatal conditions	2 (0.1)
Social circumstances	1 (0.0)

System organ classes are sorted in descending frequency.

A patient with multiple adverse events within a primary system organ class is counted only once.

A patient with multiple adverse events within a primary system organ class is counted only once in the any system organ class row.

Most Frequently Reported AEs Overall by Preferred Term

Number (%) of patients with adverse events (at least 5%) by preferred term (Safety Set)

Preferred term	FTY720 0.5 mg N=2415 n (%)
Any Preferred term (s)	1819 (75.3)
Nasopharyngitis	358 (14.8)
Headache	273 (11.3)
Lymphopenia	228 (9.4)
Fatigue	160 (6.6)

Preferred terms are sorted in descending frequency.

Serious Adverse Events, deaths and adverse events leading to study drug discontinuation

Number (%) of patients who died or experienced serious adverse events and other adverse events leading to study drug discontinuations (Safety Set)

	FTY720 0.5 mg N=2415 n (%)
Any adverse events	1819 (75.3)
Deaths	1 (0.0)
SAE(s)	99 (4.1)
AE discontinuations	98 (4.1)
Drug-related AE discontinuations	84 (3.5)
SAE discontinuations	26 (1.1)
Discontinuations for abnormal lab values	27 (1.1)
AE(s) leading to study drug interruption	145 (6.0)

Holter-ECG

Number (%) of pre-defined Holter-ECG findings, by visit (Safety Set)

Visit Finding	FTY720 0.5 mg N=2415 n (%)
Screening - N'	2399
Frequent VPCs	187 (7.8)
Nonsustained Ventricular Tachycardia 3-10 beats	41 (1.7)
Nonsustained Ventricular Tachycardia > 10 beats	3 (0.1)
Sustained Ventricular Tachycardia	0 (0.0)
Torsade de Pointes	0 (0.0)
Ventricular Fibrillation or Ventricular Flutter	0 (0.0)
Frequent short episodes of Nonsustained Supraventricular Tachycardia	11 (0.5)

Atrial Fibrillation	1 (0.0)
Atrial Flutter	1 (0.0)
Mobitz I (Wenckebach) 2nd Degree AV Block	54 (2.3)
2:1 AV Block	6 (0.3)
High Grade AV Block	1 (0.0)
Mobitz II AV Block	0 (0.0)
Complete Heart Block	0 (0.0)
Pause > 3.0 seconds	1 (0.0)
Average heart Rate < or equal 40 for any one hour	0 (0.0)
Marked Sinus Bradycardia (HR < 30)	0 (0.0)
Intermittitent Ectopic Atrial Rhythm	45 (1.9)
Intermittitent Junctional Rhythm	2 (0.1)
VPCs > 30 in one hour	130 (5.4)
Other	24 (1.0)
Day 1 - N'	2375
Frequent VPCs	107 (4.5)
Nonsustained Ventricular Tachycardia 3-10 beats	14 (0.6)
Nonsustained Ventricular Tachycardia > 10 beats	1 (0.0)
Sustained Ventricular Tachycardia	0 (0.0)
Torsade de Pointes	0 (0.0)
Ventricular Fibrillation or Ventricular Flutter	0 (0.0)
Frequent short episodes of Nonsustained Supraventricular Tachycardia	2 (0.1)
Atrial Fibrillation	1 (0.0)
Atrial Flutter	0 (0.0)
Mobitz I (Wenckebach) 2nd Degree AV Block	35 (1.5)
2:1 AV Block	14 (0.6)
High Grade AV Block	0 (0.0)
Mobitz II AV Block	0 (0.0)
Complete Heart Block	0 (0.0)
Pause > 3.0 seconds	1 (0.0)
Average heart Rate < or equal 40 for any one hour	2 (0.1)
Marked Sinus Bradycardia (HR < 30)	0 (0.0)
Intermittitent Ectopic Atrial Rhythm	24 (1.0)
Intermittitent Junctional Rhythm	2 (0.1)
VPCs > 30 in one hour	104 (4.4)
Other	16 (0.7)

N'= number of patients with non-missing HOLTER data at each visit.
N' is used as the denominator in the percentage calculation.

Other Relevant Findings None.
Date of Clinical Trial Report 20-Jun-2012 (content final)
Date Inclusion on Novartis Clinical Trial Results Database 21-Sep-2012
Date of Latest Update