Full Novartis CTRD Template

Sponsor

Novartis Pharma

Generic Drug Name

Fingolimod

Therapeutic Area of Trial

Relapsing-remitting Multiple Sclerosis

Approved Indication

Indicated for the treatment of relapsing-remitting Multiple Sclerosis (RRMS).

It has been approved for the treatment of relapsing MS in the US (on 21-Sep-2010), Europe (on 17-03-2011), and other countries.

Protocol Number

CFTY720DDE01

Title

A 6-month multicenter, single-arm, open-label study to investigate changes in biomarkers after initiation of treatment with 0.5 mg fingolimod (FTY720) in patients with relapsing-remitting multiple sclerosis

Study Phase

Phase IIIb

Study Start/End Dates

10-Feb-2011 to 11-Jul-2012

Study Design/Methodology

This study used a 6-month open-label, multi-center, single treatment arm design, including approximately 445 patients with relapsing remitting MS (RRMS) to collect data on biomarkers after initiation of fingolimod (FTY720) treatment.
After signing the informed consent, patients entered a Screening Phase (up to 4 weeks) to determine eligibility for the study. At the baseline visit, eligible patients were dispensed study medication and entered the 6-month open-label treatment phase. As fingolimod is registered and commercially available, neither an extension of the study nor a second follow-up visit was to take place. Visit 5 was the follow-up visit for patients discontinuing treatment.

Centers

65 centers in Germany

Publication

Dehmel T, Diaz-Lorente M, Opgenoorth B, Hartung HP, Kieseier BC: ”The effect of fingolimod on peripheral blood mono-nuclear cell phenotypes: a prospective study”; AAN (2012)

T. Dehmel, Wolffram K, Warnke C, Hermsen D, Boege F, Bergstroem T, Hartung HP, Diaz-Lorente M, Kieseier BC: “Phenotypes of Peripheral Blood Mononuclear Cells and Immunoglobulin Analysis under Treatment with Fingolimod: A Prospective Study”; AAN (2013)

Dehmel T, Diaz-Lorente M, Opgenoorth B, Hartung HP, Kieseier BC: “Die Wirkung von Fingolimod auf mononukleäre Zellen des peripheren Blutes: Eine prospektive Studie“; DGN (2012)

Dehmel T, Wolffram K, Warnke C, Hermsen D, Boege F, Bergstroem T, Pawlita M, Hartung HP, Diaz-Lorente M, Kieseier BC: “A prospective study of a german cohort of patients with relapsing-remitting multiple sclerosis under treatment with fingolimod: Peripheral blood mononuclear cell phenotypes and analysis of immunglobulins”; DGN (2013, accepted)

Dehmel T, Diaz-Lorente M, Wolffram K, Hermsen D, Boege F, Hartung HP, Kieseier BC: “Peripheral blood mononuclear cell phenotypes under treatment with fingolimod: a prospective study of a German cohort of patients with relapsing-remitting multiple sclerosis”; ECTRIMS (2013)

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

Test Product: fingolimod (FTY720) capsules

Dose: 0.5mg daily

Administration: orally

Statistical Methods

All statistical analyses were performed by Novartis Pharma, Nuremberg, Germany. The change from baseline to month 6 with respect to the primary outcome variables, the reduction of CD4+ and CD8+ naive T cells (CCR7+CD45RA+) and central memory T cells (CCR7+CD45RA-), as well as the elevation of effector memory T cells (CCR7-CD45RA-) and (CCR7-CD45RA+) and finally the reduction of central memory Th17 cells (CD4+ CCR4+ and CCR6+) at month 6 compared to baseline was planned to be performed by an analysis of covariance model (ANCOVA) with the factors center, sex, duration of disease and the covariate baseline CD4+ and CD8+ naive T cells (CCR7+CD45RA+) +), central memory T cells (CCR7+CD45RA-), and effector memory T cells (CCR7-CD45RA-) and (CCR7-CD45RA+) and Th17 cells, respectively. However, due to the fact that these analyses are rather exploratory by nature and no clear indication exists as to an association between sex and change in biomarkers or between disease duration and change in biomarkers the percent change from baseline to month 6 with respect to the primary outcome variables is presented along with a 95% confidence interval. Percent changes in the biomarkers were also reported for Day 28, month 4, and end of study. In the end of study analysis all patients were considered irrespective as to the time of their last visit. In the month 6 analysis only completers were included. Additionally, the course of the biomarkers over time was displayed descriptively as well as graphically for the ITT population. All variables were measured as % of parent population, in this case CD4+ and CD8+ cells.

Confirmatory analysis of primary outcomes was performed for the Intent-to-Treat Population. In addition, analysis of the primary outcomes was performed using the Per-Protocol Population for sensitivity.

The secondary parameters, results of the FACS analyses for B lymphocytes, monocytes and NK cells were displayed by visit, as well as percent changes from baseline to day 28, month 4, and month 6. Again, these parameters were measured as % of parent population, in these cases lymphocytes. Results for BDNF in pg/ml, assessed by ELISA, were also displayed by visit as well as percent changes from baseline to day 28, month 4, month 6, and end of study. Other secondary parameters, like EDSS were again presented by visit as well as change from baseline to month 6. OCT and ECG results were displayed by visit.

To explore potential relationships between biomarkers and gender, as well as whether or not the patient had an infection, and disease duration an analysis of covariance, adjusted for the respective baseline biomarker and covariates gender, infection, and disease duration, respectively were performed. Additionally, percent change is presented with 95% confidence intervals stratified by gender, disease duration and infection, where disease duration was stratified by less than 7 years versus greater or equal to 7 years.

Data are summarized with respect to demographic and baseline characteristics (including disease characteristics), outcome variables and measurements and safety observations. Frequency distributions are provided for categorical variables. Descriptive statistics of mean, standard deviation, minimum, median and maximum are presented for continuous variables.

Patients with notable laboratory abnormalities, as specified in the protocol, were presented in a listing for laboratory parameters like SGOT, SGPT, total bilirubin, glucose, creatinine, amylase, cholesterol, sodium, potassium, calcium, hemoglobin, platelets, leukocytes, granulocytes, and lymphocytes. Other laboratory parameters were presented by visit. Vital signs were also presented by visit. Furthermore, ECG measurements pre- and post-dose were presented.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

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

1. Written informed consent from patients capable of giving or withholding full informed consent must be obtained before any assessment is performed.
2. Male or female subjects aged 18-65 years.
3. Subjects with relapsing remitting forms of MS defined by 2010 revised McDonald criteria.
4. Patients with high disease activity despite treatment with a disease modifying therapy (≥ 1 relapse in the previous year, ≥ 9 hyperintense T2 lesions or ≥1 Gd-enhancing lesion *or* "non-responding" which could be defined as unchanged or increased relapse rate or ongoing severe relapses compared to previous year) ***or*** patients with rapidly evolving severe RRMS (e.g. ≥ 2 relapses with disease progression in one year and ≥ 1 Gd-enhancing lesion or with a significant increase in T2 lesions compared to a recent MRI).
5. Patients with Expanded Disability Status Scale (EDSS) score of 0-6.5.

Sufficient ability to read, write, communicate and understand.

Exclusion criteria

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

1. Patients with a manifestation of MS other than relapsing remitting MS.
2. Patients with a history of chronic disease of the immune system other than MS, which requires systemic immunosuppressive treatment, or a known immunodeficiency syndrome.
3. History or presence of malignancy (other than localized basal cell carcinoma of the skin and carcinoma in situ of the cervix) in the last 5 years

4. Diabetic patients with moderate or severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy and uncontrolled diabetic patients with HbA1c > 7%.
5. Diagnosis of macular edema during Screening Phase (patients with a history of macular edema will be allowed to enter the study provided that they do not have macular edema at the ophthalmic screening visit).
6. Patients with 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.
7. Negative for varicella-zoster virus IgG antibodies at Screening.
8. Have received any live or live attenuated vaccines (including for varicella-zoster virus or measles) within 1 month prior to baseline.
9. Patients who have received total lymphoid irradiation or bone marrow transplantation.
10. Patients who expect to be treated with any disease modifying drugs (DMD) during the study (i.e. IFN-β, glatiramer acetate); however no washout is needed for DMDs prior to baseline.
11. Patients who have been treated with:
    - Systemically applied 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 at any time.
    - Cyclophosphamide and mitoxantrone within 6 months prior to start of fingolimod
12. Patients with any medically unstable condition, as assessed by the primary treating physician at each site.
13. Patients with any of the following cardiovascular conditions:
    - Patients receiving antiarrythmics class Ia (e.g. quinidine, disopyramide, chinidin, ajmaline, procainamide) or class III (e.g. amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide) or beta blockers
    - Patients receiving heart rate lowering calcium channel blockers (e.g. verapamil, diltiazem or ivabradine) or other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine).
    - Significant QT prolongation (QTc>470 msec (female) or >450 msec (males))
    - 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 of second degree AV block or a third degree AV block, sick-sinus syndrome or sinoatrial block.
- History of symptomatic bradycardia or recurrent syncope, known ischaemic heart disease, cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnea
- resting pulse rate <45 bpm

14. Patients with any of the following pulmonary conditions
    - Pulmonary fibrosis
    - Active tuberculosis
15. Patients with severe hepatic dysfunction (Child-Pugh-Class C)
16. Patients with any of the abnormal laboratory values:
    - white blood cell (WBC) count <3,500/mm^3 or lymphocyte count <800/mm^3
17. Patients with any of the following neurologic/psychiatric disorders:
    - history of substance abuse (drug or alcohol) in the past five years or any other factor (i.e. serious psychiatric condition) that may interfere with the subject's ability to cooperate and comply with the study procedures;
    - progressive neurological disorder, other than MS, which may affect participation in the study
18. Participation in any clinical research study evaluating another investigational drug or therapy within 6 months prior to baseline
19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5mIU/ml)
20. Women of child-bearing potential defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods, at least 1 of which must be a primary form.

    Primary forms:

    - hormonal contraception [combination of oral contraceptives (PI=0.1-0.9), hormonal transdermal patch (PI= 0.72 uncorr.; 0.9 corr.), combined injected hormones, injected single hormone (PI=0.3-1.4; 0.88 corr.), implanted hormones (PI=0-0.08), or hormonal vaginal ring (PI=0.65 uncorr.; 0.4 corr.)]
    - tubal sterilization
    - partner's vasectomy
    - intrauterine device (synthetic progestin containing IUDs, IUD copper T380, PI=0.16)

Secondary forms: Barrier forms (always used with spermicide)

- male latex condom
- diaphragm
- cervical cap

Others:

- vaginal sponge (contains spermicide)
- Oral contraceptives without estrogen (e.g. "mini-pills"), nonsynthetic pregesterone only IUDs, female condoms, cervical shield, periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Reliable contraception should be maintained throughout the study and for 12 weeks after study drug discontinuation.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks prior to baseline. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

21. History of hypersensitivity to the active substance or to any other of the excipients of the study drug.
22. Prior enrolment in a trial with fingolimod. Patients who failed to be enrolled in another clinical trial with fingolimod, i.e. screening failures, may be enrolled.

Participant Flow

Patient dispositions:

		Total (N=446) N (%)
Study completion	treated	446 (100.0)
	discontinued	26 (5.8)
	completed	420 (94.2)

Reason for discontinuation	Adverse event(s)	13 (2.9)
	Abnormal laboratory value(s)	4 (0.9)
	Subject withdrew consent	6 (1.3)
	Lost to follow-up	2 (0.4)
	Administrative problems	1 (0.2)

Baseline Characteristics

Demographic data

Population: Safety population

Variable		Statistic	(N = 446)
Age [yrs]		N	446
		N miss.	0
		Mean	39.2
		SD	9.47
		Min	18
		Q25	32.0
		Median	40.0
		Q75	46.0
		Max	68
Sex	Male	n (%)	144 (32.3)
	Female	n (%)	302 (67.7)
Race	Caucasian	n (%)	441 (98.9)
	Asian	n (%)	1 (0.2)
	Other	n (%)	4 (0.9)

Outcome Measures

Primary Outcome Result(s)

Percent change from baseline in primary outcome parameters at month 6 (ITT population)

Biomarker	N	Mean	Std. Dev.	Lower 95% confidence limit	Upper 95% confidence limit
CD4+ naïve T cells	378	-82.7	9.5	-83.7	-81.8
CD4+ central memory T cells	376	-46.7	146.5	-61.6	-31.9
CD4+ effector memory T cells	378	66.7	40.5	62.6	70.8
CD8+ naïve T cells	379	-66.5	73.6	-73.9	-59.0
CD8+ central memory T cells	379	-41.3	196.9	-61.2	-21.4
CD8+ effector memory T cells	377	26.5	95.9	16.8	36.2
CD4+CCR6+ Th17	129	17.7	82.7	3.3	32.1

Percent change from baseline in primary outcome parameters at end of study (ITT population)

Biomarker	N	Mean	Std. Dev.	Lower 95% confidence limit	Upper 95% confidence limit
CD4+ naïve T cells	402	-82.6	9.7	-83.6	-81.7
CD4+ central memory T cells	400	-48.3	142.2	-62.3	-34.3
CD4+ effector memory T cells	402	67.1	40.6	63.1	71.1
CD8+ naïve T cells	404	-66.9	71.4	-73.9	-59.9
CD8+ central memory T cells	404	-42.7	190.8	-61.4	-24.0

CD8+ effector memory T cells	402	25.5	93.4	16.4	34.7
CD4+CCR6+ Th17	137	18.3	82.1	4.4	32.1

Secondary Outcome Result(s)

Percent change from baseline in secondary outcome parameters at month 6 (ITT population):

Biomarker	N	Mean	Std. Dev.	Lower 95% confidence limit	Upper 95% confidence limit
CD19+ B cells	281	-62.9	25.5	-65.9	-59.9
CD14+ monocytes	279	300.6	217.3	275.0	326.3
CD56+ NK cells	254	317.9	199.95	293.2	342.6
BDNF	308	18.5	89.6	8.5	28.6

Percent change from baseline in secondary outcome parameters at end of study (ITT population):

Biomarker	N	Mean	Std. Dev.	Lower 95% confidence limit	Upper 95% confidence limit
CD19+ B cells	298	-61.5	29.98	-64.9	-58.1
CD14+ monocytes	297	299.5	213.6	275.1	323.9
CD56+ NK cells	270	314.9	198.3	291.2	338.7
BDNF	312	18.98	89.6	9.0	28.96

Safety Results

Adverse Events by System Organ Class

Incidence of AEs by primary system organ class (Safety set):

No. (%) of patients studied	446 (100)	
No. (%) of patients with AE(s)	372 (83.4)	
System organ class affected	n	(%)
Blood and lymphatic system disorders	60	(13.5)
Cardiac disorders	19	(4.3)
Ear and labyrinth disorders	19	(4.3)
Endocrine disorders	1	(0.2)
Eye disorders	32	(7.2)
Gastrointestinal disorders	73	(16.4)
General disorders and administration site conditions	51	(11.4)
Hepatobiliary disorders	3	(0.7)
Immune system disorders	2	(0.4)
Infections and infestations	164	(36.8)
Injury, poisoning and procedural complications	14	(3.1)
Investigations	59	(13.2)
Metabolism and nutrition disorders	21	(4.7)
Musculoskeletal and connective tissue disorders	52	(11.7)
Neoplasms benign, malignant and unspecified	18	(4.0)
Nervous system disorders	178	(39.9)
Psychiatric disorders	40	(9.0)
Renal and urinary disorders	6	(1.3)
Reproductive system and breast disorders	6	(1.3)
Respiratory, thoracic and mediastinal disorders	24	(5.4)
Skin and subcutaneous tissue disorders	29	(6.5)
Social circumstances	1	(0.2)
Surgical and medical procedures	3	(0.7)
Vascular disorders	17	(3.8)

Incidence of AEs by preferred term (at least 3% incidence in any group; Safety group):

No. (%) of patients studied	446		
	n	% of patients	% of all AEs
AE preferred term			
LYMPHOPENIA	46	(10.3)	(4.2)
VERTIGO	14	(3.1)	(1.3)
DIARRHOEA	26	(5.8)	(2.4)
NAUSEA	16	(3.6)	(1.5)
NASOPHARYNGITIS	79	(17.7)	(7.2)

BRONCHITIS	15	(3.4)	(1.4)
CYSTITIS	15	(3.4)	(1.4)
SINUSITIS	14	(3.1)	(1.3)
FATIGUE	18	(4.0)	(1.6)
BACK PAIN	15	(3.4)	(1.4)
HEADACHE	48	(10.8)	(4.4)
MULTIPLE SCLEROSIS RELAPSE	115	(25.8)	(10.5)
DEPRESSION	17	(3.8)	(1.6)

Number of patients who died or experienced other serious or clinically significant adverse events (Safety set):

	No. (%) of AEs	No. (%) of patients (n=446)
All AEs	1093 (100.0)	372 (83.4)
with suspected drug relation	302 (27.6)	183 (41.0)
leading to dose adjustment or temp. interruption	41 (3.8)	29 (6.5)
leading to permanent discontinuation	49 (4.5)	33 (7.4)
requiring concomitant medication/non-drug therapy	528 (48.3)	279 (62.6)
Serious AEs	54 (4.9)	30 (6.7)
Deaths		0 (0.0)
SAEs with suspected drug relation	13 (1.2)	10 (2.2)
SAEs leading to permanent discontinuation	12 (1.1)	8 (1.8)

Other Relevant Findings

Number (%) of patients discontinued study drug for AEs by system organ class

No. (%) of patients studied 446 (100%)
No. (%) discontinued due to AE(s) 33 (7.4%)

System organ class affected	n	% of patients	% of all AEs
Blood and lymphatic system disorders	8	(1.8)	(16.3)
Cardiac disorders	3	(0.7)	(6.1)
Ear and labyrinth disorders	2	(0.4)	(4.1)
Eye disorders	4	(0.9)	(10.2)
Gastrointestinal disorders	3	(0.7)	(8.2)
General disorders and administration site disorders	3	(0.7)	(6.1)
Infections and infestations	1	(0.2)	(2.0)
Injury, poisoning and procedural complications	1	(0.2)	(2.0)
Investigations	6	(1.3)	(16.3)
Metabolism and nutrition disorders	1	(0.2)	(2.0)

Neoplasms benign, malignant and unspecified	2	(0.4)	(4.1)
Nervous system disorders	7	(1.6)	(20.4)
Reproductive system and breast disorders	1	(0.2)	(2.0)

Date of Clinical Trial Report

21 June 2013

Date Inclusion on Novartis Clinical Trial Results Database

09 July 2013

Date of Latest Update