Full Novartis Clinical Trials Result Template

Sponsor

Novartis Pharma S.A.S

Generic Drug Name

fingolimod

Trial Indication(s)

Relapsing-Remitting Multiple Sclerosis [RRMS]

Protocol Number

CFTY720DFR03

Protocol Title

A 4-month, Prospective, Open-label, Multi-centre Phase IV Study to Assess Response to Fingolimod Initiation According to Coping Profile in Adult Patients With Highly Active Relapsing Remitting Multiple Sclerosis in France**.** GRACE study

Clinical Trial Phase

Phase IV

Phase of Drug Development

Phase IV

Study Start/End Dates

Study initiation date: 10-Aug-2011 (first patient first visit)

Study completion date: 29-Jun-2013 (last patient last visit)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a 4-month multicentre phase IV prospective open-label study, to assess fingolimod in 250 patients with active relapsing-remitting multiple sclerosis (patients with a very active form of the disease despite immunomodulators therapy or a rapidly progressing severe RRMS) included by approximately 50 neurologists.

Centers

56 centers in one country France

Publication

Not applicable

Objectives:

Primary objective

To assess the mean change in the HADS (Hospital Anxiety and Depression Scale) anxiety sub-score between inclusion and Month 4 (M4) in the entire population of patients with RRMS treated with fingolimod, and according to the coping profile of the patient (oriented towards tasks, emotions or avoidance) assessed by a self-administered questionnaire

Secondary objectives

- To assess the patient CGI-I (Clinical Global Impression-Improvement) and clinician CGI-Improvement at M4 in the entire population and according to the coping profile of the patient.
- To assess the satisfaction with fingolimod treatment in patients with RRMS, either treatment-naive (severe and rapidly progressing RRMS) or those who are transitioning from a prior disease-modifying drug, using the TSQM 9 scale (Treatment Satisfaction Questionnaire for Medication-9 items), and according to the coping profile of the patient.
- To assess of the safety and tolerability of fingolimod 0.5 mg/day (in particular cardiac effects at initiation, liver function and the occurrence of macular oedema).

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

fingolimod 0.5 mg capsule qd

Statistical Methods

Patient data were described in terms of demographic parameters and baseline characteristics, efficacy parameters, parameters of safety and tolerability, and other assessments. Data from all centres participating in the study were combined.

Descriptive statistics including mean, standard deviation, min, max, and median for quantitative variables and frequency tables for qualitative variables were presented at each visit and for differences between visits.

The suspension of inclusions and initiation of treatment from 20 January to 11 June 2012 and the resumption thereof, taking into account changes added to the exclusion criteria, as well as procedures for monitoring the administration of the first dose of fingolimod, has led to distinguishing between the two cohorts; "pre-Amendment No. 1" and "post-Amendment No. 1".

The data were described globally for all patients included, and in two subgroups defined by the date of inclusion, before or after the Amendment No. 1.

Statistical tests were carried out in bilateral situation at a significance level of 0.05. They can only have an indicative value however, given the descriptive nature of this open, non-comparative study.

Study Population: Key Inclusion/Exclusion Criteria

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

- Men and women aged 18-65 years having given their written informed consent before any assessment is conducted.
- Patients with relapsing-remitting multiple sclerosis [RRMS] (McDonald criteria revised in 2005) and corresponding to the indication for fingolimod:
  a- Patients with highly active disease despite a full and adequate course with interferon beta (lasting at least one year). Patients shall have had at least one relapse in the previous year while on therapy, and have at least 9 T2 hyperintense lesions on cranial MRI or at least one lesion enhanced after gadolinium injection. A "non-responder" can also be defined as a patient whose relapse rate has not changed or has increased compared to the previous year, or continues to have severe relapses.

  or

  b- Patients with severe and rapidly progressing RRMS, defined as 2 or more disabling relapses over one year combined with 1 or more enhanced lesion(s) after gadolinium injection on cerebral MRI, or a significant increase in T2 lesion load compared with a previous recent MRI.

- Patients with an EDSS score from 0 to 5.5 inclusive.
- Patients who benefit from social security.
- Patients capable of understanding and completing self-administered questionnaires in French (however, in case of difficulties filling in the questionnaire, the patient may be assisted by a third party/trusted person).

Exclusion criteria:

Patients meeting the following criteria were not eligible for inclusion in this study:

1. Patients with secondary progressive multiple sclerosis (SPMS) or primary progressive (PPMS).
2. Patients with a history of chronic immune system disease other than MS.
3. Patients with a known immunodeficiency syndrome.
4. Patients at increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive treatments or those immunocompromised by prior treatments).
5. Patients with severe active infection or chronic active infection (such as hepatitis or tuberculosis).
6. Patients diagnosed with an evolving cancer, except basal cell skin carcinoma.
7. Patients with a diagnosis of macular oedema at inclusion (patients with a history of macular oedema or at risk for macular oedema, [diabetes or history of uveitis] will be allowed to enter the study on condition that they do not have macular oedema during an ophthalmological control visit).
8. Patients with negative antibodies (IgG) against the varicella-zoster virus.
9. Patients who have received live or live-attenuated vaccines (including varicella-zoster virus or measles) within 2 months prior to the first dose of fingolimod.
10. Patients with any unstable medical condition, as assessed by the investigator at each centre.
11. Patients:
    - receiving drugs that may induce bradycardia, such as Class Ia antiarrhythmics (e.g., quinidine, disopyramide) or Class III (e.g., amiodarone, sotalol), according to the New York Heart Association classification, beta-blockers, bradycardic calcium blockers (such as verapamil, diltiazem or ivabradine), digoxin, anticholinesterases or pilocarpine;

- with atrioventricular block (AVB) second degree or higher, sick sinus syndrome, sinoatrial block, history of symptomatic bradycardia or recurrent syncope, a significant prolongation of the QT interval (QTc > 470 msec in women or > 450 msec for men), ischaemic heart disease (including angina), cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension or severe sleep apnoea.

12. Patients receiving drugs that may prolong the QTc interval.
13. Patients with severe hepatic impairment (Child-Pugh Class C) or abnormal liver function test results (i.e. > 3N).
14. Patients with WBC count < 3,500/mm^3 or lymphocytes < 800/mm^3.
15. Patients with any other factor (i.e. severe psychiatric or progressive neurological disorders, disorders other than MS) that could interfere with the patient's ability to cooperate and comply with study procedures.
16. Pregnant or breastfeeding women.
17. Women of childbearing age unless they have a negative pregnancy test at inclusion and they use an effective method of contraception.
18. Patients with a history of hypersensitivity to the study drug or drugs from similar chemical classes.
19. Patients having participated in any clinical research study evaluating another drug or experimental treatment within 6 months before inclusion.
20. Patients having previously participated in clinical trials of fingolimod.

Participant Flow Table

		Total n (%)
Screenings		226
Patients		
Untreated patients		28
Primary reason of discontinuation		
	Patient health does not justify to continue study drug	1 (3.6 %)
	Patient does not respond to protocol criteria	4 (14.3 %)
	Consent withdrawal	2 (7.1 %)
	Administrative problems	21 (75.0 %
Treated patients		198
Completed		186 (93.9 %)
Discontinued		12 (6.1 %)
Primary reason for premature discontinuation		
	Adverse event(s)	6 (3.0 %)
	Abnormal laboratory value(s)	4 (2.0 %)
	Abnormal test procedure result(s)	0 (0.0 %)
	Unsatisfactory therapeutic effect	0 (0.0 %)
	Patient health does not justify to continue study drug	0 (0.0 %)
	Patient does not respond to protocol criteria	0 (0.0 %)
	Consent withdrawal	0 (0.0 %)
	Lost to follow-up	0 (0.0 %)
	Administrative problems	1 (0.5 %)
	Death	0 (0.0 %)
	Investigator decision	1 (0.5 %)

Treated patients: having at least one dose of study medication

Baseline Characteristics

Demographics - ITT population

		Total (N = 198)
Sex	N	198
	Male	53 (26.8 %)
	Female	145 (73.2 %)
Age (years)	N	198

		Total (N = 198)
	Mean	37.9
	SD	9.47
	Minimum	18.5
	Median	37.5
	Maximum	66.9
Age (n(%))	N	198
	<40 years	120 (60.6 %)
	>= 40 years	78 (39.4 %)
Height (cm)	N	196
	Mean	168.5
	SD	8.74
	Minimum	147.0
	Median	168.0
	Maximum	195.0

Summary of Efficacy

Primary Outcome Result(s)

Change in HADS Anxiety sub- score from baseline to Month 4– Intent to treat (ITT) population

		Before amendment (N = 139)	After amendment (N = 59)	Total (N = 198)	Comparability test
Baseline	N	137	55	192	
	Mean	8.7	9.1	8.8	
	SD	4.49	4.02	4.35	
	Minimum	0.0	0.0	0.0	
	Median	8.0	9.0	8.0	
	Maximum	20.0	19.0	20.0	
Baseline	N	137	55	192	
	<=7	59 (42.4 %)	19 (32.2 %)	78 (39.4 %)	
	8-10	32 (23.0 %)	17 (28.8 %)	49 (24.7 %)	
	>10	46 (33.1 %)	19 (32.2 %)	65 (32.8 %)	
	Missing	2	4	6	
Follow-up visit	N	130	54	184	
	Mean	8.1	8.1	8.1	
	SD	4.14	3.87	4.05	
	Minimum	0.0	1.0	0.0	
	Median	7.0	8.0	8.0	
	Maximum	18.0	18.0	18.0	
Follow-up visit	N	130	54	184	
	<=7	67 (48.2 %)	24 (40.7 %)	91 (46.0 %)	
	8-10	25 (18.0 %)	14 (23.7 %)	39 (19.7 %)	
	>10	38 (27.3 %)	16 (27.1 %)	54 (27.3 %)	
	Missing	9	5	14	
Change from baseline	N	129	51	180	
	Mean	-0.6	-1.0	-0.7	Wilcoxon test : p=0.664
	SD	3.49	2.68	3.27	
	Minimum	-10.0	-7.0	-10.0	
	Median	-1.0	-1.0	-1.0	
	Maximum	9.0	3.0	9.0	
	[IC95 mean]	[-1.2;-0.0]	[-1.7;-0.2]	[-1.2;-0.2]	
	p-value (#)	0.018	0.019	0.001	

		Before amendment (N = 139)	After amendment (N = 59)	Total (N = 198)	Comparability test
Change from baseline (*)	N	129	51	180	
	> 0	44 (31.7 %)	17 (28.8 %)	61 (30.8 %)	
	0	20 (14.4 %)	6 (10.2 %)	26 (13.1 %)	
	< 0	65 (46.8 %)	28 (47.5 %)	93 (47.0 %)	
	Missing	10	8	18	

(*) change from baseline : worsening if score increased by at least 1
(#) p-value associated to Wilcoxon's rank sum test
Comparability test : comparison between Before/After amendment groups using Student's t test or Wilcoxon
Percentages are based on column sample size (N=)

HADS Anxiety sub-score according to CISS coping style at baseline / ITT population

		CISS coping style at baseline			
		Task oriented (N = 29)	Emotion oriented (N = 73)	Avoidance oriented (N = 87)	Comparability test
Baseline	N	29	73	86	
	Mean	6.4	11.2	7.5	
	SD	3.28	3.84	4.15	
	Minimum	2.0	3.0	0.0	
	Median	6.0	11.0	7.0	
	Maximum	15.0	20.0	17.0	
Baseline	N	29	73	86	
	<=7	22 (75.9 %)	10 (13.7 %)	45 (51.7 %)	
	8-10	4 (13.8 %)	23 (31.5 %)	20 (23.0 %)	
	>10	3 (10.3 %)	40 (54.8 %)	21 (24.1 %)	
	Missing	0	0	1	
Follow-up visit	N	26	69	83	
	Mean	6.2	9.9	7.1	
	SD	3.62	4.02	3.61	
	Minimum	2.0	2.0	0.0	
	Median	5.0	9.0	7.0	
	Maximum	14.0	18.0	16.0	
Follow-up visit	N	26	69	83	

		CISS coping style at baseline			
		Task oriented (N = 29)	Emotion oriented (N = 73)	Avoidance oriented (N = 87)	Comparability test
	<=7	19 (65.5 %)	22 (30.1 %)	48 (55.2 %)	
	8-10	2 (6.9 %)	16 (21.9 %)	20 (23.0 %)	
	>10	5 (17.2 %)	31 (42.5 %)	15 (17.2 %)	
	Missing	3	4	4	
Change from baseline	N	26	69	82	
	Mean	-0.3	-1.2	-0.5	Kruskal-Wallis : p=0.093
	SD	2.15	3.79	3.12	
	Minimum	-4.0	-10.0	-10.0	
	Median	0.0	-2.0	0.0	
	Maximum	3.0	9.0	9.0	
	[IC95 mean]	[-1.1;0.6]	[-2.1;-0.3]	[-1.2;0.2]	
	p-value (#)	0.520	0.002	0.157	
Change from baseline (*)	N	26	69	82	
	> 0	8 (27.6 %)	20 (27.4 %)	32 (36.8 %)	
	0	8 (27.6 %)	6 (8.2 %)	12 (13.8 %)	
	< 0	10 (34.5 %)	43 (58.9 %)	38 (43.7 %)	
	Missing	3	4	5	

(*) change from baseline : worsening if score increased by at least 1
(#) p-value associated to Wilcoxon's rank sum test
Comparability test : comparison between CISS coping style groups (Kruskal-Wallis)
Percentages are based on column sample size (N=)

Secondary Outcome Result(s)

CGI according to CISS coping style at baseline - ITT population

		CISS coping at baseline		
		Task oriented (N = 29)	Emotion oriented (N = 73)	Avoidance oriented (N = 87)
CGI clinician's assessment	N	28	73	86
	Improvement	6 (20.7 %)	28 (38.4 %)	38 (43.7 %)
	No change	20 (69.0 %)	35 (47.9 %)	42 (48.3 %)
	Worsening	2 (6.9 %)	10 (13.7 %)	6 (6.9 %)
	Missing	1	0	1
CGI patient's assessment	N	26	69	81
	Improvement	9 (31.0 %)	37 (50.7 %)	44 (50.6 %)

		CISS coping at baseline		
		Task oriented (N = 29)	Emotion oriented (N = 73)	Avoidance oriented (N = 87)
	No change	15 (51.7 %)	24 (32.9 %)	32 (36.8 %)
	Worsening	2 (6.9 %)	8 (11.0 %)	5 (5.7 %)
	Missing	3	4	6
CGI clinician's and patient's assessment (*)	N	26	69	81
	Improvement (concordant)	4 (13.8 %)	20 (27.4 %)	28 (32.2 %)
	No change (concordant)	14 (48.3 %)	18 (24.7 %)	21 (24.1 %)
	Worsening (concordant)	1 (3.4 %)	6 (8.2 %)	2 (2.3 %)
	Discordant	7 (24.1 %)	25 (34.2 %)	30 (34.5 %)
	Missing	3	4	6

(*) : CGI clinician's and patient's assessment : either concordant if both patient and clinician reported the same trend in change (improvement or worsening, or no change)
independently of the intensity of change, either discordant in other cases (improvement/no change, improvement/worsening, no change/worsening : [Clinician / Patient])
Percentages are based on column sample size (N=)

Treatment Satisfaction Questionnaire for Medication-9 items (TSQM 9) - ITT population

		Total (N = 198)
EFFECTIVENESS	N	183
	Mean	67.4
	SD	18.85
	Minimum	0.0
	Median	66.7
	Maximum	100.0
CONVENIENCE	N	182
	Mean	88.3
	SD	15.74
	Minimum	33.3
	Median	100.0
	Maximum	100.0
GLOBAL SATISFACTION	N	186
	Mean	66.3
	SD	21.19
	Minimum	7.1
	Median	64.3
	Maximum	100.0

Summary of Safety

Safety Results

Adverse events (*), according to organ system (sorted by descending frequency)
Safety population

	Total (N = 198)
NERVOUS SYSTEM DISORDERS	49 (24.7%)
INFECTIONS AND INFESTATIONS	32 (16.2%)
GASTROINTESTINAL DISORDERS	28 (14.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	28 (14.1%)
INVESTIGATIONS	21 (10.6%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	17 (8.6%)
CARDIAC DISORDERS	14 (7.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	14 (7.1%)
PSYCHIATRIC DISORDERS	10 (5.1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	9 (4.5%)

EYE DISORDERS	9 (4.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	9 (4.5%)
VASCULAR DISORDERS	6 (3.0%)
HEPATOBILIARY DISORDERS	2 (1.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (1.0%)
RENAL AND URINARY DISORDERS	2 (1.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (1.0%)
ENDOCRINE DISORDERS	1 (0.5%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (0.5%)

(*) : Treatment emergent adverse events only
Rows are sorted by descending frequency of 'Total' column
A patient contributing to one of the categories defined by table rows is taken into account only once in this category, whatever the number of events reported.
Percentages are based on column sample size (N=)

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

Adverse events (*), according to preferred term (sorted by descending frequency)
Safety population

	Total (N = 198)
HEADACHE	28 (14.1%)
NASOPHARYNGITIS	12 (6.1%)
HEART RATE DECREASED	11 (5.6%)
MULTIPLE SCLEROSIS RELAPSE	11 (5.6%)
ASTHENIA	9 (4.5%)
NAUSEA	9 (4.5%)
BRADYCARDIA	8 (4.0%)
FATIGUE	7 (3.5%)
ARTHRALGIA	6 (3.0%)
DIARRHOEA	6 (3.0%)

Rows are sorted by descending frequency of 'Total' column
A patient contributing to one of the categories defined by table rows is taken into account only once in this categorye, whatever the number of events reported.
Percentages are based on column sample size (N=)

Serious Adverse Events and Deaths – Safety population

No. (%) of subjects studied	198
No. (%) of subjects with AE(s)	129 (65.2 %)
Number (%) of subjects with serious or other significant events	24 (12.1 %)
Death	0 (0.0)
SAE(s)	24 (12.1 %)
Discontinued due to AE(s)	10 (5.1 %)

Other Relevant Findings

Not applicable

Conclusion:

Coping has received growing interest in multiple sclerosis these last years and represents crucial adjustment to disease-related challenges. In GRACE study, the CISS (Coping Inventory for Stressful Situations) coping strategy preferably adopted by the patients was predominantly the avoidance, even though the other profiles were fairly adopted. The relapsing-remitting multiple sclerosis population recruited in GRACE study was less anxious and depressive than the one reported by other authors.

The anxiety and depression scores decreased after 4 months of fingolimod treatment, particularly in emotion-oriented patients, whereas these scores did not change for task and avoidance oriented patients. Interestingly, the impact on fatigue scores was also meaningful in emotion and avoidance oriented patients.

The study also confirmed the safety profile of fingolimod and its efficacy.

Understanding and determining coping profiles seems of utmost interest when initiating new Multiple Sclerosis related therapy, to identify prematurely adherence levels and the patients who may benefit from further psychological support.

The duration of our study was relatively short, and it would be interesting to design longitudinal studies that describe the evolution of coping strategies as a function of disease's evolution.

Date of Clinical Trial Report

25 April 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

25 June 2014

Date of Latest Update

Reason for Update