Sponsor

Novartis

Generic Drug Name

Fingolimod

Therapeutic Area of Trial

Organ transplantation

Approved Indication

Investigational

Study Number

FTY720A2302/ FTY720A2302E1

Title

A two-year extension to a one-year, multicenter, open-label, randomized study to evaluate the safety and the efficacy of fingolimod combined with tacrolimus and steroids versus mycophenolate mofetil (MMF) combined with tacrolimus and steroids, in de novo adult renal transplant recipients.

Phase of Development

Phase III

Study Start/End Dates

06 May 2005 to 13 Apr 2006

Study Design/Methodology

This was a two-year extension to a one-year, multicenter, open-label, randomized study to evaluate the safety and the efficacy of fingolimod combined with tacrolimus and steroids versus MMF combined with tacrolimus and steroids, in de novo adult renal transplant recipients. Patients who have completed the Month 12 visit of the 12-month core study FTY720A2302 were offered the opportunity to participate in this two-year extension protocol. This included both patients on study medication and patients off study medication at month 12 of the core study. Patients who were still on study medication at the Month 12 visit of the core study continued to receive the study medication to which they were originally randomized.

- Group 1: Fingolimod 2.5 mg once daily + tacrolimus + corticosteroids
- Group 2: MMF 2.0 g daily dose in two divided doses + tacrolimus + corticosteroids

Centres

15 centers in 6 countries: Belgium (2), Germany (1), Netherlands (1), Poland (2), United Kingdom (4), United States (5)

Publication

Objectives

The objective of this extension is to assess long term efficacy and safety of fingolimod combined with corticosteroids and tacrolimus versus MMF combined with corticosteroids and tacrolimus in de novo adult renal transplant recipients beyond 12 months post-transplantation and to provide continued treatment for patients who have completed the 12-month core study on study medication.

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

Oral fingolimod 2.5 mg/day once daily with tacrolimus and corticosteroids

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

Oral MMF MMF 2.0 g/day in two divided doses with tacrolimus and corticosteroids

Criteria for Evaluation

Efficacy

The primary efficacy variable was the first occurrence of treated BPAR, graft loss, death or premature discontinuation from study.

Safety/tolerability

Safety assessments for patients who receive study medication during the extension will consist of monitoring and recording adverse events and serious adverse event, the regular monitoring of hematology, blood chemistry and urine values, BK polyoma virology, measurements of vital signs and performance of physical examinations, electrocardiogram, pulmonary function tests and chest X-rays.

Statistical Methods

The primary efficacy analysis would be performed to compare the FTY720 group to the MMF group using the confidence interval approach of testing first for non-inferiority and then for superiority. For the test of non-inferiority, a non-inferiority margin of 10% would be used. The null hypothesis of the primary efficacy analysis is that fingolimod 2.5 mg combined with tacrolimus and steroids regimen is inferior to the MMF combined with tacrolimus and steroids regimen, while the alternative hypothesis is that fingolimod combined with tacrolimus and steroids regimen is not inferior to the MMF combined with tacrolimus and steroids regimen. Alpha error 0.025 will be used for the non-inferiority test using the confidence interval approach.

Study Population: Inclusion/Exclusion Criteria and Demographics

The main inclusion and exclusion criteria for the core study FTY720A2302 were:

Inclusion: Male and female patients aged 18 to 65 years scheduled to undergo a primary renal allograft transplant from a cadaver or non-HLA identical living donor renal allograft transplant

Exclusion: Recipients of multi-organ transplantation or of dual kidneys; Highest (past or current) panel reactive antibody (PRA) > 50%; Recipients of A-B-O incompatible transplants; Patients who received T-cell crossmatch positive transplants; Renal cold ischemia time greater than 40 hours; Pulse

rate < 50 beats per minute (bpm) at baseline after 3 minutes resting in a supine position; Permanent or transient arrhythmia requiring current treatment with Class III antiarrhythmic drugs (e.g. amiodarone, bretylium, sotalol, ibulitide, azimilide, dofelitide); History of symptomatic bradycardia or syncope, or of cardiac arrest; Increased QTc interval > 500 ms at baseline; History of myocardial infarction within the last 6 months prior to enrollment or with current unstable coronary disease; Cardiac failure or any severe cardiac disease as determined by the investigator; History or presence of a second-degree AV block or a third degree AV block; Absolute neutrophil count of < 1,500/mm^3, or absolute leukocyte count <2,500/$mm^{3;}$ Evidence of severe liver disease; Severe digestive system disorder; Human Immunodeficiency Virus (HIV) positive or hepatitis B surface antigen positive; Any past or present malignancy, except excised squamous or basal cell carcinoma of the skin successfully excised at least 2 years prior to randomization; Severe systemic infections currently or within the 2 weeks prior to randomization; Any history of coagulopathy or medical condition requiring long-term anticoagulation after transplantation; Use of ketamine for sedation or anesthesia for the transplant surgery; Use of any investigational drug within 4 weeks prior to randomization; Use of induction therapy; Any patient with known diabetic retinopathy, macular edema or other retinal vascular diseases known to be associated with macular edema.

The inclusion and exclusion criteria for this extension study were:

- The patient has given written informed consent to participate in the extension study.
- The patient has completed the Month 12 visit of the core study either on or off study medication.
- Females capable of becoming pregnant are required to practice a medically approved method of birth control as long as they are on study medication and for a period of 3 months following discontinuation of study medication.

Number of Subjects

	Fingolimod 2.5 mg N=48	MMF 2 g N=54
Completed core study[1]	16 (33.3)	27 (50.0)
Completed core on study medication[1]	12 (25.0)	27 (50.0)
Entered extension	2 (4.2)	2 (3.7)
Premature discontinuation	37 (77.1)	29 (53.7)
Main reason for discontinuation		
Adverse event(s)	11 (22.9)	2 (3.7)
Abnormal laboratory value(s)	1 (2.1)	0
Unsatisfactory therapeutic effect	3 (6.3)	0
Protocol violation(s)	0	2 (3.7)
Subject withdrew consent	5 (10.4)	1 (1.9)
Lost to follow-up	0	1 (1.9)
Administrative reasons[1]	16 (33.3)	21 (38.9)
Graft loss	1 (2.1)	2 (3.7)

The results of the core study FTY720A2302 and its extension study FTY720A2302E1 were analyzed in aggregate due to the insufficient efficacy data collected in the extension trial FTY720A2302 following the discontinuation of the clinical development program of fingolimod in renal transplantation.

Demographic and Background Characteristics

		Fingolimod 2.5 g N = 48	MMF 2g N=54
Age (years)	Mean	47.1	44.2
	SD	9.64	11.74
	Median	48.0	44.0
	Range	24-64	20-69
Age group – n (%)	18 to 29	2 (4.2)	8 (14.8)
	30-39	7 (14.6)	9 (16.7)
	40-49	18 (37.5)	17 (31.5)
	50-59	16 (33.3)	16 (29.6)
	60 or older	5 (10.4)	4 (7.4)
Gender – n(%)	Male	36 (75.0)	37 (68.5)
	Female	12 (25.0)	17 (31.5)
Race – n(%)	Caucasian	42 (87.5)	48 (1.9)
	Black	4 (8.3)	1 (1.9)

	Hispanic	2 (4.2)	4 (7.4)
	Other	0	1 (1.9)
Height (cm)	Mean	172.6	171.3
	SD	9.88	9.39
	Median	172.5	171.0
	Range	145-189	151-188
Weight (kg)	Mean	77.8	75.2
	SD	14.44	14.28
	Median	75.9	74.7
	Range	52.0-115.8	45.7-104.5
Body Mass Index	Mean	26.1	25.6
	SD	4.04	4.48
	Median	25.3	24.8
	Range	19.6-40.1	19.1-36.0

Primary Objective Result(s)

Incidence within 12 months	Fingolimod 2.5 mg N=48	MMF 2 g N=54
Graft loss or death	3 (6.3)	3 (5.6)
Graft loss	1 (2.1)	3 (5.6)
Death	2 (4.2)	0
Biopsy proven acute rejection	12 (25.0)	10 (18.5)
Any biopsy proven acute rejection	13 (27.1)	10 (18.5)

Incidence refers to the number of patients having the event at least once

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Secondary Objective Result(s)

Incidence within 12 months	Fingolimod 2.5 mg N=48	MMF 2g N=54
Treated BPAR or treated borderline rejection	12 (25.0)	10 (18.5)
Antibody treated BPAR	4 (8.3)	1 (1.9)
Treated BPAR	11 (22.9)	10 (18.5)
Treated ABPAR	12 (25.0)	10 (18.5)
Treated BPAR of grade 2A or higher	6 (12.5)	6 (11.1)
Treated acute rejection	14 (29.2)	15 (27.8)
Biopsy proven chronic rejection	1 (2.1)	1 (1.9)
Treated CCAR where AR was suspected	10 (20.8)	10 (18.5)
Treated clinically-confirmed Acute Rejection (CCAR)	10 (20.8)	10 (18.5)
Glomerular lesions	2 (4.2)	3 (5.6)

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Safety Results

Adverse Events by System Organ Class

	Fingolimod 2.5 mg	MMF 2 g
No. (%) of patients studied	49	54
No. (%) of patients with AE(s)	40 (100)	53 (98.1)
System organ class affected	n (%)	n (%)
Blood and lymphatic system disorders	13 (26.5)	18 (33.3)
Cardiac disorders	8 (16.3)	11 (20.4)
Ear and labyrinth disorders	1 (2.0)	1 (1.9)
Endocrine disorders	2 (4.1)	3 (5.6)
Eye disorders	16 (32.7)	9 (16.7)
Gastrointestinal disorders	30 (61.2)	39 (72.2)
General disorders and administration site disorders	18 (36.7)	23 (42.6)
Hepatobiliary disorder	3 (6.1)	2 (3.7)
Immune system disorders	4 (8.2)	7 (13.0)
Infections and infestations	28 (57.1)	38 (70.4)
Injury, poisoning and procedural complications	33 (67.3)	30 (55.6)
Investigations	23 (46.9)	23 (42.6)
Metabolism and nutrition disorders	27 (55.1)	30 (55.6)
Musculoskeletal and connective tissue disorders	13 (26.5)	18 (33.3)
Neoplasms benign, malignant and unspecified	1 (2.0)	1 (1.9)
Nervous system disorders	17 (34.7)	17 (31.5)
Psychiatric disorders	13 (26.5)	16 (29.6)
Renal and urinary disorders	22 (44.9)	26 (48.1)
Reproductive system and breast disorders	6 (12.2)	4 (7.4)
Respiratory, thoracic and mediastinal disorders	17 (34.7)	14 (25.9)
Skin and subcutaneous tissue disorders	8 (16.3)	10 (18.5)
Surgical and medical procedures	1 (2.0)	1 (1.9)
Vascular disorders	19 (38.8)	20 (37.0)

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

	Fingolimod 2.5 mg N=49	MMF 2g N=54
Nausea	15 (30.6)	17 (31.5)
Blood creatinine increased	11 (22.4)	12 (22.2)
Diarrhea	10 (20.4)	26 (48.1)
Urinary tract infection	10 (20.4)	24 (44.4)
Constipation	10 (20.4)	12 (22.2)
Hyperkalaemia	10 (20.4)	12 (22.2)
Hypertension	10 (20.4)	11 (20.4)
Procedural pain	9 (18.4)	12 (22.2)
Graft dysfunction	9 (18.4)	9 (16.7)
Anaemia	9 (18.4)	8 (14.8)

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Serious Adverse Events and Deaths

	Fingolimod 2.5 mg N=48	MMF 2 g N=54
Deaths	2 (4.2)	0
Patients with at least one SAE	32 (65.3)	36 (66.7)
Discontinuation due to AEs	11 (22.9)	2 (3.7)

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Body System Preferred term (MedDRA)	Fingolimod 2.5 mg N=49 n (%)	MMF 2 g N=54 n (%)
Patients with at least one SAE	32 (65.3)	36 (66.7)
Blood and lymphatic system disorders	2 (4.1)	3 (5.6)
Leukopenia	0	2 (3.7)
Cardiac disorders	2 (4.1)	3 (5.6)
Endocrine disorders	1 (2.0)	3 (5.6)

Eye disorders	6 (12.2)	5 (9.3)
Macular oedema	6 (12.2)	5 (9.3)
Gastrointestinal disorders	5 (10.2)	5 (9.3)
Abdominal pain	1 (2.0)	2 (3.7)
Diarrhoea	1 (2.0)	2 (3.7)
Nausea	0	2 (3.7)
Vomiting	0	2 (3.7)
General disorders and administration site conditions	2 (4.1)	5 (9.3)
Pyrexia	1 (2.0)	3 (5.6)
Immune system disorders	3 (6.1)	5 (9.3)
Transplant rejection	3 (6.1)	5 (9.3)
Infections and infestations	7 (14.3)	19 (35.2)
Urinary tract infection	1 (2.0)	7 (13.0)
Cytomegalovirus infection	1 (2.0)	4 (7.4)
Urosepsis	0	2 (3.7)
Cellulitis	2 (4.1)	0
Injury, poisoning and procedural complications	6 (12.2)	12 (22.2)
Complications of transplanted kidney	2 (4.1)	2 (3.7)
Drug toxicity	0	2 (3.7)
Graft dysfunction	1 (2.0)	2 (3.7)
Investigations	9 (18.4)	9 (16.7)
Blood creatinine increased	6 (12.2)	8 (14.8)
Alanine aminotransferase increased	2 (4.1)	0
Metabolism and nutrition disorders	5 (10.2)	4 (7.4)
Dehydration	0	2 (3.7)
Musculoskeletal and connective tissue disorders	0	1 (1.9)
Neoplasms benign, malignant and unspecified	1 (2.0)	0
Nervous system disorders	4 (8.2)	2 (3.7)
Psychiatric disorders	0	1 (1.9)
Renal and urinary disorders	6 (12.2)	6 (11.1)
Hydronephrosis	0	2 (3.7)
Renal impairment	0	2 (3.7)
Urinary incontinence	1 (2.0)	2 (3.7)
Reproductive system and breast disorders	1 (2.0)	0
Respiratory, thoracic and mediastinal disorders	1 (2.0)	4 (7.4)
Pulmonary oedema	0	2 (3.7)
Surgical and medical procedures	0	1 (1.9)
Vascular disorders	3 (6.1)	5 (9.3)

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Other Relevant Findings	
Date of Clinical Trial Report May 7, 2009 (Includes Core and Extension)	
	Date Inclusion on Novartis Clinical Trial Results Database
	Date of Latest Update