Sponsor

Novartis

Generic Drug Name

Fingolimod

Therapeutic Area of Trial

Organ transplantation

Approved Indication

Investigational

Study Number

CFTY720A2218\CFTY720A2218E1

Title

A 24-month extension to a one-year, multicenter, double blinded, double dummy, randomized study to evaluate the safety and the efficacy of fingolimod combined with full-dose cyclosporin (CsA) steroids versus mycophenolate mofetil (MMF) combined with full-dose CsA and steroids, in de novo adult renal transplant recipients.

Phase of Development

Phase II

Study Start/End Dates

04 Nov 2004 to 08 Jun 2006

Study Design/Methodology

A two-year extension to a one year, multicenter, double blinded, double-dummy, randomized study to evaluate the safety and efficacy of two doses of fingolimod (5.0 or 2.5 mg) combined with full-dose CsA and steroids in comparison to MMF combined with full dose CsA and steroids in de novo adult renal transplant recipients. All patients who completed the core study either on or off study medication would be followed for two additional years, regardless of whether they would be on or off study medication during the extension. Patients who were eligible to receive study medication in this extension continued to receive the same study medication (fingolimod or MMF) to which they were randomized in the core study. Once database lock occurred, the investigators and patients were unblinded to the patient's treatment group in the core study and the patients continued taking study medication from an open-label supply.

Centres

31 centers in 10 countries: Australia (2), Canada (2), Czech Republic (2), France (4), Germany (3), Hungary (1), Italy (1), Japan (13), New Zealand (1), United States (2)

Objectives

The objective of this extension is to assess long term safety and efficacy data of two doses of fingolimod (2.5 or 5.0 mg) combined with full dose CsA and steroids versus MMF combined with full dose CsA and steroids 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 and 5 mg/day once a day in combination with CsA and corticosteroids,

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

Oral MMF 2 g/day divided in two doses, in combination with CsA and corticosteroids

Criteria for Evaluation

Primary variables:

- Biopsy-proven acute rejection over 36 months post transplantation
- graft loss over 36 months post transplantation
- death over 36 months post transplantation
- premature discontinuation from study over 36 months post-transplantation

Secondary variables:

Overall safety and individual efficacy parameters at Month 24 and Month 36 post-transplantation

Statistical Methods

Two analyses were to be done using the extension data, the first when all patients reach the Month 24 visit and the second when all patients reach the Month 36 visit. The key efficacy parameter was the incidence over the 36 months of the composite end-point of biopsy proven acute rejection, graft loss, death, or discontinuation from study. The key safety parameters include renal, cardiac and pulmonary function, infections and malignancies.

Both primary and secondary efficacy analyses would be based on the intent-to-treat population (ITT), comprising all patients who are randomized, receive at least one dose of randomized study medication and are transplanted. The efficacy analyses would consider all data from the ITT population collected during the entire study (from randomization day) through 36 months post-transplantation regardless of whether patients discontinue study medication at any time point.
The safety population would consist of all patients who are randomized, receive at least one dose of

randomized study medication, and have at least one safety/tolerability assessment after the first dose of randomized study medication. All safety analyses were to be performed on the safety population on data collected during the entire study (from first administration of first dose of study medication) through 36 months post-transplantation regardless of whether patients discontinue study medication at any time point. Some safety analyses would be performed on the subset of patients who received study medication during the extension.

Inclusion/Exclusion Criteria

The main inclusion and exclusion criteria for the core study CFTY720A2218 were:

Inclusion: Patients aged 18 to 65 years old scheduled to undergo primary or secondary, cadaver (including non-heart beating donor category 4), or non-HLA identical living donor renal allograft transplant.

Exclusion: Recipients of a multi-organ transplantation, of dual kidneys, of donor category 1-3 non-heart beating donor kidneys, or with a renal cold ischemia time > 40 hours. Also patients with a pulse rate < 50 bpm or new clinically significant cardiological abnormalities including cardiac failure, QTc >500 ms, a history of symptomatic bradycardia, cardiac arrest or myocardial infarction, second or third degree AV block or arrhythmias requiring treatment with Class III antiarrhythmics. Patients with an absolute neutrophil count of < 1,500/mm_3, leukopenia (< 2,500/mm_3), or severe liver disease, history of malignancy, coagulopathy or severe systemic infections. Breast feeding women, patients with severe digestive disorders, patients who are HIV or hepatitis B surface antigen positive, whose highest panel reactive antibody was > 50% or who are recipients of A-B-O incompatible transplants or T-cell cross-match positive transplants, or who received induction therapy with monoclonal or polyclonal antilymphocyte agents, or ketamine during transplant surgery, were also excluded.

The inclusion and exclusion criteria for this extension study were:

a) The patient has given written informed consent to participate in the extension study.

b) The patient has completed the Month 12 visit of the core study either on or off study medication.

c) 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		
	5 mg + FDN n (%)	2.5 mg + FDN n (%)	MMF + FDN n (%)
Number of patients randomized	87	90	94
Completed core study	67 (77.0)	65 (72.2)	67 (71.3)
Completed extension	1 (1.1)	1 (1.1)	1 (1.1)
Completed core on study medication	47 (54.0)	41 (45.6)	48 (51.1)
Entered extension on study medication	32 (36.8)	27 (30.0)	35 (37.2)
Entered extension off study medication	10 (11.5)	10 (11.1)	7 (7.4)
Completed extension on study medication	1 (1.1)	1 (1.1)	0

The results of the core study CFTY720A2218 and its extension study CFTY720A2218E1 were analyzed in aggregate due to the insufficient efficacy data collected in the extension trial FTY720A2218E1following the discontinuation of the clinical development program of fingolimod in renal transplantation.

Demographic and Background Characteristics

	Fingolimod		
	5 mg + FDN (N=87)	2.5 mg + FDN (N=89)	MMF + FDN (N=94)
Age [years]:			
Mean	43.4	44.6	44.1
(SD)	(12.95)	(11.80)	(12.82)
Median	45	46	46
Range (Min-Max)	(18 - 66)	(18 - 65)	(18 - 65)
Gender [n (%) of patients]			
Male	50 (57.5%)	52 (58.4%)	69 (73.4%)
Female	37 (42.5%)	37 (41.6%)	25 (26.6%)
Race [n (%) of patients]			
Caucasian	63 (72.4%)	65 (73.0%)	66 (70.2%)
Japanese	18 (20.7%)	18 (20.2%)	21 (22.3%)
Black	0	2 (2.2%)	3 (3.2%)
Oriental	0	2 (2.2%)	0
Hispanic	1 (1.1%)	0	0
Other	5 (5.7%)	2 (2.2%)	4 (4.3%)
BMI [kg/m^2)			
n	84	84	90
Mean	23.8	23.6	24.7
(SD)	(3.70)	(4.14)	(4.73)
Median	23.7	23.3	24.1
Range (Min-Max)	(17.7 – 34.6)	(16.2 – 33.0)	(13.4 - 40.6)

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Primary Objective Result(s)

The fingolimod clinical development program in renal transplantation was discontinued following the analysis of the data from the pivotal trials CFTY720A124 and CFTY720A125, which demonstrated that fingolimod was associated with decreased graft function as estimated by creatinine clearance, increased rates of macular edema and respiratory adverse events in comparison to MMF with standard doses of cyclosporin. Due to the results of these pivotal trials, the company decided to discontinue all ongoing trials in the fingolimod program in renal transplantation. There was not sufficient efficacy data collected in the extension trials at the time of discontinuation from which to draw any conclusions therefore, no efficacy data analysis was performed.

Secondary Objective Result(s)

See above

Safety Results

Adverse Events by System Organ Class

System organ class (MedDRA)	FTY720 5 mg + FDN (N=87) n (%)	FTY720 2.5 mg + FDN (N=90) n (%)	MMF + FDN (N=94) n (%)
Injury, poisoning and procedural complications	63 (72.4)	66 (73.3)	65 (69.1)
Gastrointestinal disorders	60 (69.0)	59 (65.6)	73 (77.7)
Metabolism and nutrition disorders	52 (59.8)	59 (65.6)	56 (59.6)
Infections and infestations	65 (74.7)	55 (61.1)	65 (69.1)
General disorders & administrative site conditions	50 (57.5)	52 (57.8)	59 (62.8)
Vascular disorders	42 (48.3)	50 (55.6)	48 (51.1)
Blood and lymphatic system disorders	40 (46.0)	46 (51.1)	31 (33.0)
Renal and urinary disorders	42 (48.3)	39 (43.3)	48 (51.1)
Skin and subcutaneous tissue disorders	30 (34.5)	37 (41.1)	37 (39.4)
Nervous system disorders	33 (37.9)	36 (40.0)	34 (36.2)
Respiratory, thoracic and mediastinal disorders	38 (43.7)	33 (36.7)	33 (35.1)
Investigations	38 (43.7)	31 (34.4)	32 (34.0)
Psychiatric disorders	20 (23.0)	29 (32.2)	27 (28.7)
Musculoskeletal & connective tissue disorders	30 (34.5)	29 (32.2)	41 (43.6)
Cardiac disorders	37 (42.5)	23 (25.6)	27 (28.7)

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

System organ class (MedDRA)	Fingolimod 5 mg + FDN (N=87) n (%)	Fingolimod 2.5 mg + FDN (N=90) n (%)	MMF + FDN (N=94) n (%)
Nausea	26 (29.9)	31 (34.4)	24 (25.5)
Constipation	31 (35.6)	27 (30.0)	34 (36.2)
Urinary tract infection	21 (24.1)	27 (30.0)	31 (33.0)
Hypertension	20 (23.0)	26 (28.9)	28 (29.8)
Anaemia	18 (20.7)	26 (28.9)	13 (13.8)
Graft dysfunction	19 (21.8)	24 (26.7)	12 (12.8)
Leukopenia	20 (23.0)	23 (25.6)	7 (7.4)
Hyperkalaemia	19 (21.8)	22 (24.4)	19 (20.2)
Diarrhea	19 (21.8)	21 (23.3)	20 (21.3)
Peripheral oedema	20 (23.0)	19 (21.1)	25 (26.6)

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Serious Adverse Events and Deaths

	Fingolimod 5 mg +FDN (N=87) n (%)	Fingolimod 2.5 mg +FDN (N=90) n (%)	MMF +FDN (N=94) n (%)
Number of patients who died during the study	1 (1.1)	0	5 (5.3)
General disorders and administration site conditions	0	0	2
Renal and urinary disorders	0	0	1
Respiratory, thoracic and mediastinal disorders	0	0	1
Vascular disorders	1	0	1
Number of patients with SAEs in any body system	55 (63.2)	45 (50.0)	53 (56.4)
Blood and lymphatic system	5 (5.7)	4 (4.4)	5 (5.3)
Cardiac disorders	5 (5.7)	6 (6.7)	5 (5.3)
Congenital familial and genetic disorders	1 (1.1)	0 (0.0)	1 (1.1)

Endocrine disorders	1 (1.1)	0 (0.0)	1 (1.1)
Eye disorders	0 (0.0)	4 (4.4)	0 (0.0)
Gastrointestinal disorders	9 (10.3)	5 (5.6)	11 (11.7)
General disorders and administrative site conditions	4 (4.6)	3 (3.3)	3 (3.2)
Hepatobiliary disorders	1 (1.1)	2 (2.2)	1 (1.1)
Immune system disorders	2 (2.3)	2 (2.2)	4 (4.3)
Infections and infestations	29 (33.3)	12 (13.3)	27 (28.7)
Injury, poisoning and procedural complications	18 (20.7)	12 (13.3)	8 (8.5)
Investigations	10 (11.5)	3 (3.3)	2 (2.1)
Metabolism and nutritional disorders	5 (5.7)	2 (2.2)	5 (5.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4 (4.6)	2 (2.2)	1 (1.1)
Nervous sys tem disorders	2 (2.3)	1 (1.1)	3 (3.2)
Psychiatric disorders	1 (1.1)	1 (1.1)	0 (0.0)
Renal and urinary disorders	10 (11.5)	6 (6.7)	8 (8.5)
Reproductive system and breast disorders	2 (2.3)	1 (1.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (3.4)	2 (2.2)	3 (3.2)
Skin and subcutaneous tissue disorders	2 (2.3)	0 (0.0)	1 (1.1)
Vascular disorders	6 (6.9)	2 (2.2)	9 (9.6)

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Other Relevant Findings

Date of Clinical Trial Report

August 18, 2009 (Includes Core and Extension)

Date Inclusion on Novartis Clinical Trial Results Database

August 28, 2007

Date of Latest Update