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| **Sponsor**<br>Novartis |
| **Generic Drug Name**<br>Fingolimod |
| **Therapeutic Area of Trial**<br>Organ transplantation |
| **Approved Indication**<br>Investigational |
| **Study Number**<br>CFTY7200A125E1 |
| **Title**<br>A two-year extension to a one-year, multicenter, partially blinded, double-dummy, randomized study to evaluate the efficacy and safety of fingolimod combined with reduced-dose or full-dose cyclosporin (CsA) and corticosteroids versus mycophenolate mofetil (MMF) combined with full-dose CsA and corticosteroids, in *de novo* adult renal transplant recipients |
| **Phase of Development**<br>Phase III |
| **Study Start/End Dates**<br>24-May-2004 to 16-May-2006 |
| **Study Design/Methodology**<br>A two-year extension to a one year, multicenter, partially blinded,, randomized study to evaluate the safety and efficacy of fingolimod 5 mg + reduced-dose CsA (RDC) + corticosteroids and fingolimod 2.5 mg + full-dose CsA (FDC) + corticosteroids, in comparison to MMF 2.0 mg + FDC 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. |
| **Centres**<br>72 centers in 10 countries: United Stated (42), Canada (9), Italy (5), Argentina (4) and Brazil (4), Colombia (2), Germany (2), Switzerland (2), France (1) and Mexico (1) |

## Publication

This extension study was terminated early due to the discontinuation of the fingolimod clinical program in transplantation. There will be no publication reporting the results.

## Objectives

Primary objective(s)

The objective of this extension study was to provide continued treatment beyond 12 months post-transplantation and to assess long term efficacy and safety of fingolimod (5.0 or 2.5 mg) in combination with CsA in de novo adult renal transplant recipients.

Secondary objective(s)

None

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

Oral fingolimod 2.5 mg/day and 5 mg/day divided in two doses, 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

The primary efficacy variable was the first occurrence of biopsy-proven acute rejection, graft loss, death or premature discontinuation from core study.

### Secondary variables

The secondary objectives are to provide long-term information under continued study medication beyond 12 months post transplantation on all other efficacy and safety parameters.

### Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events, serious adverse events (with their severity and relationship to study drug), and pregnancies, the regular monitoring of hematology, blood chemistry and urine values, measurements of vital signs and performance of physical examinations, electrocardiogram, pulmonary function tests, chest X-rays, and ophthalmic evaluations.

### Pharmacology

Pharmacokinetic evaluation blood sampling were to be performed in all patients on study medication at Months 18, 24, 30, and 36.

### Other

Not applicable

## Statistical Methods

Two analyses were to be performed 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 would be 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 included renal, cardiac and pulmonary function, infections and malignancies.

As in the core study, both primary and secondary efficacy analyses were to be based on the intent-to-treat population (ITT), comprising all patients who were 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 timepoint.

The safety population consisted of all patients who were randomized, received at least one dose of randomized study medication, and had at least one safety/tolerability assessment after the first dose of randomized study medication. All safety analyses were performed on the safety population on data collected during the entire study through 36 months post-transplantation, regardless

of whether patients discontinued study medication at any timepoint.

## Study Population: Inclusion/Exclusion Criteria and Demographics

The main inclusion and exclusion criteria for the core study CFTY720A125 were:

**Inclusion:** Male and female patients aged between 18 and 65 years who were scheduled to undergo primary cadaver donor or primary non-HLA identical living donor renal transplantation; and negative pregnancy test within 7 days prior to randomization and the practice of a medically approved method of contraception while receiving study medication and for a period of 3 months following discontinuation of study medication for females capable of pregnancy.

**Exclusion:** recipients of multi-organ transplantation; renal cold ischemia time greater than 40 hours; highest panel reactive antibody (PRA)>50%, recipients of A-B-O incompatible transplants or T-cell cross match positive transplants; a pulse rate < 50 beats per minute at baseline, history of symptomatic bradycardia (syncope) arrhythmia requiring current treatment with Class III antiarrhythmic drugs; history of cardiac arrest; history or presence of a second degree AV block or a third degree AV block, myocardial infarction within the last 6 months prior to enrollment or with current unstable coronary disease; cardiac failure (resting dyspnea, with Grade ≥ 3 according to Old New York Heart Association Classification) or any severe cardiac disease considered unsafe for the patient; increased QTc interval > 500 ms on Baseline ECG; absolute neutrophil count of <1,500/mm3 or leucopenia.

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 CFTY720124 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 drug(s).

## Number of Subjects

| | Fingolimod | | |
|---|---|---|---|
| | **5 mg + RDC N=79 n (%)** | **2.5 mg + FDC N=143 n (%)** | **MMF + FDC N=151 n (%)** |
| Entered extension study without taking medication | 8 (10.1) | 23 (16.1) | 29 (19.2) |
| Entered extension study and took medication | 71 (89.9) | 120 (83.9) | 122 (80.8) |
| Completed study medication | 0 | 0 | 0 |

## Demographic and Background Characteristics*

| | Fingolimod | | |
|---|---|---|---|
| | **5 mg +RDC (N=231)** | **2.5 mg +FDC (N=224)** | **MMF +FDC (N=229)** |
| **Age** [years]: | | | |
| Mean | 44.2 | 42.9 | 43.3 |
| (SD) | (12.13) | (12.26) | (12.54) |
| Median | 46.0 | 43.5 | 46 |
| Range (Min-Max) | (18 - 69) | (18 - 68) | (18 - 65) |
| **Gender** [n (%) of patients] | | | |
| Male | 153 (66.2%) | 144 (64.3%) | 149 (65.1%) |
| Female | 78 (33.8%) | 80 (35.7%) | 80 (34.9%) |
| **Race** [n (%) of patients] | | | |
| Caucasian | 142 (61.5%) | 146 (65.2%) | 146 (63.8%) |
| Black | 37 (16.0%) | 34 (15.2%) | 29 (12.7%) |
| Oriental | 6 (2.6%) | 4 (1.8%) | 4 (1.7%) |
| Other | 14 (6.1%) | 17 (7.6%) | 15 (6.6%) |
| Hispanic | 32 (13.9%) | 23 (10.3%) | 35 (15.3%) |
| **BMI** [kg/m$^2$) | | | |
| n | 220 | 216 | 226 |
| Mean | 26.3 | 26.1 | 25.9 |
| (SD) | (5.19) | (5.33) | (4.57) |
| Median | 26.0 | 25.3 | 25.5 |
| Range (Min-Max) | (16.9 – 42.1) | (15.8 – 60.5) | (16.1 – 41.6) |

Baseline demographic and background information of the patients participating in the core study CFTY720A125 are presented here. The information was not summarized separately for the Extension Safety Population.

**Primary Objective Result(s)** The fingolimod clinical development program in renal transplantation was discontinued follow-ing the analysis of the data from the pivotal trials CFTY720A124 and CFTY720A125, which dem-onstrated 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.

The results of the core trial were published (see "Publication" section above).

## Secondary Objective Result(s)

See above.

## Safety Results

### Adverse Events by System Organ Class

| System organ class (MedDRA) | Fingolimod 5 mg + RDN N=71 n (%) | Fingolimod 2.5 mg + FDN N=120 n (%) | MMF + FDN N=122 n (%) |
|---|---|---|---|
| **Number (%) of patients with at least one AE in any body system** | 44 (62.0) | 95 (79.2) | 85 (69.7) |
| Blood and lymphatic system disorders | 6 (8.5) | 12 (10.0) | 6 (4.9) |
| Cardiac disorders | 8 (11.3) | 7 (5.8) | 6 (4.9) |
| Eye disorders | 8 (11.3) | 19 (15.8) | 14 (11.5) |
| Gastrointestinal disorders | 8 (11.3) | 16 (13.3) | 24 (19.7) |
| General disorders & administrative site conditions | 13 (18.3) | 26 (21.7) | 20 (16.4) |
| Infections & infestations | 17 (23.9) | 36 (30.0) | 28 (23.0) |
| Injury, poisoning & procedural complications | 3 (4.2) | 16 (13.3) | 9 (7.4) |
| Investigations | 6 (8.5) | 11 (9.2) | 10 (8.2) |
| Metabolism & nutrition disorders | 6 (8.5) | 20 (16.7) | 12 (9.8) |
| Musculoskeletal & connective tissue disorders | 5 (7.0) | 17 (14.2) | 12 (9.8) |
| Nervous system disorders | 9 (12.7) | 16 (13.3) | 10 (8.2) |
| Psychiatric disorders | 3 (4.2) | 9 (7.5) | 7 (5.7) |
| Renal and urinary disorders | 7 (9.9) | 12 (10.0) | 9 (7.4) |
| Reproduction system and breast disorders | 3 (4.2) | 7 (5.8) | 5 (4.1) |
| Respiratory, thoracic & mediastinal disorders | 8 (11.3) | 23 (19.2) | 10 (8.2) |
| Skin & subcutaneous tissue disorders | 4 (5.6) | 10 (8.3) | 8 (6.6) |
| Vascular disorders | 4 (5.6) | 12 (10.0) | 8 (6.6) |

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

| AE (MedDRA preferred term) | Fingolimod 5 mg + RDN N=71 n (%) | Fingolimod 2.5 mg + FDN N=120 n (%) | MMF + FDN N=122 n (%) |
|---|---|---|---|
| Urinary tract infection | 4 (5.6) | 13 (10.8) | 10 (8.2) |
| Oedema peripheral | 7 (9.9) | 12 (10.0) | 6 (4.9) |
| Cough | 1 (1.4) | 8 (6.7) | 4 (3.3) |
| Macular oedema | 5 (7.0) | 7 (5.8) | 4 (3.3) |
| Leukopenia | 4 (5.6) | 6 (5.0) | 0 |
| Headache | 3 (4.2) | 7 (5.8) | 4 (3.3) |
| Nasopharyngitis | 3 (4.2) | 5 (4.2) | 2 (1.6) |
| Upper respiratory tract infection | 3 (4.2) | 5 (4.2) | 1 (0.8) |
| Nausea | 2 (2.8) | 5 (4.2) | 6 (4.9) |
| Hypertension | 1 (1.4) | 5 (4.2) | 4 (3.3) |

## Serious Adverse Events and Deaths

| | Fingolimod 5 mg + RDN N=79 n (%) | Fingolimod 2.5 mg + FDN N=143 n (%) | MMF + FDN N=151 n (%) |
|---|---|---|---|
| Deaths | 1 (1.4) | 0 | 0 |
| SAEs | 10 (14.1) | 23 (19.2) | 18 (14.8) |
| Discontinued study medication due to Adverse events | 11 (13.9) | 21 (14.7) | 11 (7.3) |

| AE (MedDRA preferred term) | Fingolimod 5 mg + RDN N=71 n (%) | Fingolimod 2.5 mg + FDN N=120 n (%) | MMF + FDN N=122 n (%) |
|---|---|---|---|
| **Patients with at least one SAE** | 10 (14.1) | 23 (19.2) | 18 (14.8) |
| **Cardiac disorders** | 2 (2.8) | 2 (1.7) | 3 (2.5) |
| **Eye disorders** | 5 (7.0) | 7 (5.8) | 5 (4.1) |
| Macular oedema | 5 (7.0) | 7 (5.8) | 4 (3.3) |
| **General dis & adm site conditions** | 0 | 3 (2.5) | 3 (2.5) |
| Pyrexia | 0 | 1 (1.8) | 3 (2.5) |
| **Infections and infestations** | 2 (2.8) | 8 (6.7) | 7 (5.7) |
| **Injury, poison & proced complications** | 0 | 3 (2.5) | 1 (0.8) |
| **Metabolism & nutrition disorders** | 0 | 3 (2.5) | 0 |
| **Renal and urinary disorders** | 2 (2.8) | 4 (3.3) | 1 (0.8) |
| **Respiratory, thoracic & mediastinal disorders:** | 1 (1.4) | 3 (2.5) | 1 (0.8) |
| **Vascular disorders:** | 1 (1.4) | 4 (3.3) | 0 |
| **Deaths** | 1 (1.4) | 0 | 0 |

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| **Other Relevant Findings** |
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| **Date of Clinical Trial Report**<br>December 23, 2008 |