SYNOPSIS

Name of Sponsor/Company: Astellas Pharma GmbH (Successor in interest to Yamanouchi Europe/Fujisawa GmbH)

Name of Finished Product: Prograf™

Name of Active Ingredient: Tacrolimus (FK506)

Title of Study: A multicenter, randomized, open clinical study to compare the efficacy and safety of a combination therapy of tacrolimus with sirolimus versus tacrolimus with mycophenolate mofetil in kidney transplantation.

Responsible Medical Officer: [redacted], MD

Investigator(s): [redacted] and [redacted] (Austria); [redacted], and [redacted] (Australia); [redacted], [redacted], and [redacted] (Belgium); [redacted], and [redacted] (Czech Republic); [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] (Germany); [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] (Spain); [redacted], [redacted], and [redacted] (France); Mr. [redacted], and Mr. [redacted] (UK); [redacted] (Hungary); [redacted], and [redacted] (Italy); [redacted] (Netherlands); [redacted], [redacted], and [redacted] (Poland); [redacted], (Romania), and [redacted], (Sweden).

Study Centers: 51 centers in the following countries, Austria, Australia, Belgium, Czech Republic, France, Germany, Hungary. Italy, Netherlands, Poland, Romania, Spain, Sweden, and UK

Publication (reference): None

Study Period:
Date of First Enrollment: 11 October 2004
Date of Last Evaluation: 31 July 2006 (last patient last visit)

Phase of Development: III

Objectives: The primary objective of this study was to compare the efficacy and safety of two tacrolimus-based therapy regimens in patients undergoing primary renal transplantation.

Study Design: This was an open-label, multicenter, randomized, phase III, parallel-group study. Patients received either tacrolimus with sirolimus (arm 1), or tacrolimus with mycophenolate mofetil (MMF) (arm 2), for 6 months. For the first three months of the study all patients received corticosteroid therapy in addition to their randomized treatment.

Diagnosis and Main Criteria for Inclusion: Patients aged between 18 and 60 years undergoing a primary renal transplantation or re-transplantation (unless a previous graft had been lost due to immunological reasons within 12 months) were eligible for enrollment into the study. Patients receiving a kidney transplant from a cadaveric or living donor (not HLA identical) with compatible ABO type were included. Key exclusion criteria were high immunological risk (defined as panel reactivity antibody [PRA] grade >50), cold ischemia time of greater than 30 hours for the donor kidney, malignancy, or a history of malignancy.

Number of Subjects (planned and analyzed): The planned sample size was 300 patients per treatment arm (600 patients in all). Randomization to treatment arm was 1:1, and was stratified by center. Of the patients recruited to the study, 607 patients had no major protocol violations and were eligible for the Per-Protocol Population (304 from arm 1 and 303 from arm 2). The Full Analysis Set, which included patients who received a transplant and at least one dose of study medication, comprised 634 patients: 318 from arm 1 and 316 from arm 2.

Test Product, Dose And Mode of Administration:
Tacrolimus: tacrolimus was administered orally or, if necessary, via nasogastric tube, or intravenously. The first dose (0.1 mg/kg) was administered no more than 12 hours before reperfusion.

A further 0.1 mg/kg was administered between four and 12 hours after reperfusion. Patients receiving a transplant from a living donor could receive the initial dose of tacrolimus (no more than 0.2 mg/kg/day) within 72 hours of reperfusion. Subsequent doses of tacrolimus were given orally with water, twice daily for the next six months. Dosage was adjusted according to clinical evidence of efficacy and occurrence of AEs, using blood trough tacrolimus levels as a guide.

Sirolimus: the first dose of sirolimus (6 mg loading dose) was administered orally on the day of surgery at the same time as the first pre-operative dose of tacrolimus. Subsequent doses of sirolimus were given orally at the same time as the morning dose of tacrolimus. For the first 28 days of the study, the daily dose of sirolimus was 2 mg (once daily), followed by a reduced daily dose of 1 mg (once daily) for the remainder of the study.

MMF: the first dose of MMF (loading dose of 1 g) was given orally before surgery. For the first two weeks of the study the daily dose of MMF was 2 g (2 x 1 g), followed by a reduced daily dose of 1 g (2 x 0.5 g) for the remainder of the study.

Corticosteroids: all patients received corticosteroids in addition to their randomized treatment, for the first three months of the study. The first dose of methylprednisolone (500 mg) or equivalent, was administered intravenously (i.v.) on the day of surgery. A further corticosteroid i.v bolus was administered the following day. Subsequent doses of corticosteroids were given orally, beginning with 20 mg once daily until Day 14, reducing to 5 mg once daily by Day 43. Planned corticosteroid therapy ended on Day 90 of the study.

Lot Numbers: Patients received tacrolimus from batch numbers [redacted], [redacted] (0.5 mg), [redacted] (1 mg), [redacted], and [redacted] (5 mg). Batch numbers of MMF capsules (250 mg) were: [redacted], and [redacted]. Sirolimus (1 mg) batch numbers were as follows: [redacted] and [redacted]. All of the batches of study medication for this trial were used within their expiry date.

Duration of Study and Treatment: The duration of the study was six months. The day of reperfusion was designated as Day 0. All patients received a daily dose of tacrolimus for the entire six-month study period. Likewise, sirolimus (arm 1 only) and MMF (arm 2 only) were administered daily for the entire six-month study period. In addition, corticosteroid therapy (all patients) was given for the first three months of the study.

Criteria for Evaluation: The primary efficacy endpoint was renal function at Month 6 – assessed using calculated creatinine clearance (Cockcroft and Gault formula).

Secondary efficacy endpoints included occurrence and frequency of acute rejection, biopsy-proven acute rejection, and patient and graft survival.

Important safety endpoints included incidence of Adverse Events (AEs), absolute change in serum lipids, renal dysfunction, incidence of diabetes mellitus, and incidence of hypertension.

AEs of particular interest were infections, cardiac AEs, neurological disorders, nephrological disorders, glucose metabolism disorders, gastrointestinal disorders, malignancies, and AEs leading to dose modification, patient discontinuation, or death.

Statistical Methods: Calculated creatinine clearance at Month 6 (the primary efficacy measure) was compared between the treatment arms using a linear model adjusted for factors of treatment and pooled center. Non-inferiority of arm 1 compared to arm 2 was to be shown based on a non-inferiority limit of 7.5 ml/min. If non inferiority could be concluded then a test for superiority of arm 1 compared with arm 2 was to be performed. Secondary efficacy endpoints at Month 6 were analyzed using the Kaplan-Meier method. These included the incidence of, and time to, acute rejection (AR), corticosteroid-resistant acute rejection (CRAR), biopsy-proven acute rejection (BPAR), and corticosteroid-resistant biopsy-proven acute rejection (BCAR), graft survival, and patient survival. Differences between treatment arms, over the six-month study period, were assessed using a two-sided Wilcoxon-Gehan test. Two-sided 95% confidence limits for the difference in survival at Month 6 were calculated using normal approximation with variance calculated according to the Greenwood formula.

For safety endpoints, differences between treatment arms were assessed using descriptive p-values of Fisher's exact test. Tests were based on the number of patients who experienced events, not the number of episodes. All other safety variables (e.g. laboratory data, and vital signs) were summarized using descriptive statistics.

Primary and secondary endpoint analysis was based on the full analysis set (FAS) and the per-protocol set (PPS).

RESULTS:

Analysis Sets and Subject Disposition: A total of 659 patients from 51 centers were randomized to receive treatment. Three analysis sets were defined:

Full Analysis Set (FAS): all randomized patients who received a transplant, with results attributed to their randomized treatment arm, and who received at least one dose of study medication (tacrolimus, sirolimus, MMF).

Per Protocol Set (PPS): all randomized patients who were eligible for the FAS, excluding those who had major protocol violations.

Of the 659 patients randomized to receive treatment, 634 underwent transplantation and received at least one dose of study medication (tacrolimus, sirolimus, or MMF), and thus were eligible for the FAS. A total of 27 FAS patients were excluded from PPS: 14 patients from arm 1 (4.4%) and 13 patients from arm 2 (4.1%). Details of the analysis sets and subject disposition are summarized in the table below:

	Number of patients		
	Tacrolimus/ Sirolimus/ Steroids(3mo)	**Tacrolimus/ MMF/ Steroids(3mo)**	**Total**
Recruited	**333**	**326**	**659**
Full Analysis Set (FAS)	**318**	**316**	**634**
Excluded from FAS	15	10	25
Not transplanted	14	10	24
No study medication received	1	0	1
Per Protocol Set (PP)	**304**	**303**	**607**
Excluded from PPS	14	13	27
MMF taken	11	0	11
Antibody induction	2	5	7
History of malignancy	1	4	5
Non-compliance	0	3	3
No tacrolimus records	0	1	1
Completed	**251 (78.9)**	**270 (85.4)**	**521 (82.2)**
Withdrawn ~	66 (20.8)	43 (13.6)	109 (17.2)
Died during study	1 (0.3)	3 (0.9)	4 (0.6)
Graft loss	8 (2.5)	14 (4.4)	22 (3.5)
Adverse event	48 (15.1)	20 (6.3)	68 (10.7)
Withdrawal of informed consent	2 (0.6)	0 (0.0)	2 (0.3)
Lost to follow-up	1 (0.3)	3 (0.9)	4 (0.6)
Protocol violation	3 (0.9)	4 (1.3)	7 (1.1)
Other	4 (1.3)	2 (0.6)	6 (0.9)

Demographics: A summary of patient demographics and viral status at baseline is provided below**.** The two treatment arms were well matched with respect to demographic details and viral status at baseline.

Donor/recipient mismatch, donor type, and cold ischemia time were comparable for both treatment arms. A slight trend toward a lower mismatch rate was observed in patients receiving tacrolimus with sirolimus in terms of HLA type B matching.

	Number of Patients (%)		
	Tacrolimus/ Sirolimus/ Steroids(3mo)	**Tacrolimus/ MMF/ Steroids(3mo)**	**p-value**
Male	204 (64.2)	204 (64.6)	
Female	114 (35.8)	112 (35.4)	0.915
Age (years) Median (range)	46.0 (18–66)	46.0 (18–72)	0.471
Weight (kg) Median (range)	70.00 (35.0–111.0)	73.0 (27.0–121.0)	0.477
Height (cm) Median (range)	170.0 (140–196)	170 (130–195)	0.896
Caucasian	299 (94.0)	303 (95.9)	
Viral status at baseline ~:			
CMV negative	92 (29.1)	95 (30.3)	0.754
HBV positive	6 (1.9)	4 (1.3)	0.752
HCV positive	7 (2.2)	10 (3.2)	0.445

Study Drug Exposure: Based on target whole blood trough levels of tacrolimus, compliance to tacrolimus was good in both treatment arms throughout the study. Patients receiving tacrolimus with MMF received slightly higher doses of tacrolimus and had slightly higher whole blood trough levels of tacrolimus than those who received tacrolimus with sirolimus. Sirolimus and MMF administration closely followed that described in the protocol. Maintenance doses of corticosteroids were generally administered according to the regimen described in the protocol. Scheduled withdrawal of corticosteroids was well followed; at Month 6, 77.7% of patients in arm 1 and 69.1% of patients in arm 2 were no longer receiving corticosteroid therapy. There was no statistically significant difference between the two treatment arms with respect to the mean cumulative maintenance dose of corticosteroids at Month 3 or Month 6.

Efficacy Results :

Primary Efficacy Measure: Based on the primary efficacy variable (creatinine clearance) tacrolimus administered with sirolimus and steroids is non-inferior in efficacy to the current standard combination of tacrolimus, MMF and steroids. Non-inferiority was predefined as a maximum difference in creatinine clearance of 7.5 ml/min at Month 6. Non-inferiority of tacrolimus and sirolimus (arm 1) compared with tacrolimus and MMF (arm 2), was demonstrated for the set of completers in both the FAS and PPS. The lower boundaries of the two-sided 95% CI for the difference in mean adjusted creatinine clearance were -2.58 ml/min (FAS), and -2.28 ml/min (PPS). Both values were considerably higher than the pre-defined non-inferiority margin (7.5 ml/min) thus proving non-inferiority of tacrolimus and sirolimus against tacrolimus and MMF.

The results of the sensitivity analysis (including all patients with creatinine clearance values at Month 6 or the Month 6 follow-up visit) supported the non-inferiority of tacrolimus with sirolimus compared with tacrolimus and MMF.

Secondary Efficacy Measures: None of the secondary efficacy variables showed significant differences between the two regimens. Acute rejection (diagnosed by clinical signs and symptoms) was reported by 25.8% of patients receiving tacrolimus with sirolimus and by 24.4% receiving tacrolimus with MMF. Only three biopsy samples showed evidence of rejection classified as severe by the Banff criteria (one from patients treated with tacrolimus with sirolimus and two from patients treated with tacrolimus with MMF). In total, a numerically greater number of biopsies were performed in arm 1 compared with arm 2. At Month 6, 83.8% of patients in arm 1 and 87.1% in arm 2 were free from BPAR and 95.3% and 97.4% of patients respectively, were free from corticosteroid-resistant BPAR. Patient survival at Month 6 was 99% for both groups, and graft survival at Month 6 was equivalent for both regimens: 92.7% in arm 1 and 93.3% in arm 2.

Safety Results:
As expected in a predominantly *de novo* transplantation study, the number of AEs reported was high (approximately 93%) in both treatment arms. The most frequently reported AEs (irrespective of causality) were metabolism and nutrition disorders, infections and infestations, blood and lymphatic and gastrointestinal disorders. Hypercholesterolemia, hyperlipidaemia, and peripheral oedema were more common in patients receiving tacrolimus with sirolimus, than in patients receiving tacrolimus with MMF ($p<0.05$, Fisher's exact test). Conversely, the incidence of hyperkalemia, cytomegalovirus infection (CMV), nasopharyngitis, leukopenia, and diarrhea, was higher in patients receiving tacrolimus with MMF than in patients receiving tacrolimus with sirolimus ($p<0.05$, Fisher's exact test; $p<0.001$ for CMV infection and leukopenia). Hypercholesterolemia was identified as being a causally-related to tacrolimus/sirolimus combination therapy. This finding is consistent with the known AE profile of sirolimus. CMV infections, diarrhea, and leukopenia were identified as being causally-related to tacrolimus/MMF combination therapy.

Four patients died during the six-month study period: one patient from arm 1 and three patients from arm 2. In addition, two patients (both of whom received tacrolimus with sirolimus) died after withdrawal. None of the deaths reported during the study were considered to be related to study drug.

The incidence of certain serious adverse events (SAEs) differed significantly between treatment arms. Fewer patients receiving tacrolimus with sirolimus experienced SAEs of renal vascular and ischemic conditions, CMV infections, and cardiac disorders (including ischemic coronary artery disease) compared with patients receiving tacrolimus with MMF ($p<0.05$ Fisher's exact test). Conversely, the number of patients who experienced SAEs due to procedural complications and urinary and procedural complications was lower in arm 1 than arm 2 ($p<0.05$, Fisher's exact test). However, there were no significant differences between treatment arms with respect to related SAEs.

In total, 68 patients withdrew from the study as a result of AEs: 48 (15.1%) from arm 1 and 20 (6.3%) from arm 2. The incidence of new onset diabetes mellitus between Months 2 and 6 in patients without pre-existing diabetes was comparable in the two treatment groups: 46 patients (17.2% of 268 patients) in arm 1 and 44 patients (16.4% of 268 patients) in arm 2. A requirement for long-term antidiabetic medication (more than 30 consecutive days) was reported for 16 patients receiving tacrolimus with sirolimus (n=287 remaining at Month 6), and for 25 patients receiving tacrolimus with MMF (n= of 278 remaining at Month 6).
The two treatment arms were comparable with respect to the overall incidence of cardiac AEs and in terms of the requirement for antihypertensive agents. Peripheral oedema was reported by more patients receiving tacrolimus with sirolimus (6.9%) than receiving tacrolimus with MMF (3.2%) but concomitant use of diuretics was similar in both groups.
Post baseline increases in serum lipids that occurred up to Month 3 were significantly greater for patients in arm 1 than for patients in arm 2 ($p<0.05$ for all comparisons). However, between baseline and Month 6, there were no significant differences between treatment groups with respect to post-baseline changes in serum lipids (analyzed using completers). At Month 6, the mean total-, LDL-, HDL- cholesterol and triglyceride levels were numerically higher in patients treated with tacrolimus and sirolimus than in those receiving tacrolimus with MMF. Furthermore, the proportion of patients requiring lipid lowering therapy during the study was lower for arm 2 (33.5%) than for arm 1 (42.1%).

There were no clinically significant differences between the two regimens with respect to changes in hematology, or vital signs. At Month 6, mean post-baseline increases in liver enzyme ratios were statistically greater for patients in arm 1 than for patients in arm 2: SGOT/AST increased by 9.9 U/l in arm 1 and 5.9 U/l in arm 2 ($p=0.0235$), and SGPT/ALT increased by 12.6 U/l in arm 1 and 5.6 U/l in arm 2 ($p=0.0274$).

CONCLUSIONS:

- Tacrolimus administered with sirolimus and steroids is equivalent in efficacy to tacrolimus with MMF and steroids in patients with end-stage renal disease undergoing primary renal transplantation.
- Both regimens could be administered safely to the population treated. The incidence and type of adverse events reported during the study reflected the known safety profile of both adjunctive therapies (sirolimus and MMF).
- CMV infections, diarrhea, and leukopenia were identified as causally-related events associated with tacrolimus/MMF combination therapy whereas hypercholesterolemia was identified as being a causally-related to tacrolimus/sirolimus combination therapy.
- Tacrolimus can safely be combined with sirolimus and with MMF.
- Using sirolimus in combination with tacrolimus in the schema prescribed in this study achieved efficacy and safety results which were at least as good as results obtained with the widely used immunosuppressive regimen based on tacrolimus, MMF, and steroids.

Date of Report: September 2007