SYNOPSIS

Name of Sponsor/Company: Astellas Pharma GmbH (Successor in interest to Fujisawa GmbH)		
Name of Finished Product: FK506 (Prograf)		
Name of Active Ingredient: Tacrolimus		

Title of Study: A Multicentre, Randomized, Open Clinical Study to Compare the Efficacy and Safety Of A Combination of Tacrolimus and Mycopenolate Mofetil Based Regimen With or Without Induction in Elderly Recipients Undergoing Kidney Transplantation

Responsible Medical Officer/Coordinating Investigator:
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Investigator(s): [redacted]

Study Center(s): [redacted], Spain; [redacted], Germany; [redacted] France; [redacted], Switzerland; [redacted] Netherlands; [redacted], Belgium; [redacted], UK

Publication (reference): None available to date.

Study Period: **Date of First Enrollment:** 10 October 2004 **Date of Last Evaluation:** 1 August 2006	**Phase of Development:** Phase III

Objectives: The primary objective was to compare the renal function as well as the incidence of renal dysfunction, the incidence of death, graft loss and the incidence of acute rejection for the two treatment groups. The secondary study objective was to compare the efficacy and safety profiles of the two regimens in elderly renal transplanted patients.

Study Design: This was a multicenter, randomized, open, two-arm, parallel group, comparative phase III study. Patients were randomized to one of the following treatment groups:

- Group 1: Mycophenolate mofetil + Basiliximab + delayed Tacrolimus + Corticosteroids (1 week) [TAC-d/MMF/MAB]
- Group 2: Mycophenolate mofetil + Tacrolimus + Corticosteroids (3 months) [TAC/MMF]

Randomization was performed 1:1 and stratified by center.

Diagnosis and Main Criteria for Inclusion: Male or female patients with minimum 60 years of age and end stage kidney disease and were suitable candidates for primary renal transplantation or retransplantation were eligible for the study. Patients who received a kidney transplant from a cadaveric or living donor (not HLA identical) with compatible ABO blood type and who provided informed consent were included.

Number of Subjects (planned and analyzed): Based on a two-sided t-test and assuming a standard deviation of 23 ml/min in creatinine clearance, 115 patients per treatment group (230 in total) were

needed to detect a difference of 10 ml/min with a power of at least 90%. 267 patients were randomized to treatment. The Full Analysis Set (FAS) consisted of 254 patients: 132 patients in the TAC-d/MMF/MAB group and 122 in the TAC/MMF group.

Test Product, Dose And Mode of Administration: All patients in the TAC-d/MMF/MAB group began with an initial daily dose of tacrolimus on Day 7 which was 0.15 mg/kg p.o. given in two doses (equals 0.075 mg/kg twice daily). Subsequent oral tacrolimus doses were adjusted on the basis of clinical evidence of efficacy and occurrence of adverse events and targeted to obtain the following recommended whole blood trough level ranges:

Day 7 - 14: 10 - 15 ng/ml
Day 15 - 42: 5 -12 ng/ml
Day 43 - 183: 5 -10 ng/ml

The initial daily dose of tacrolimus in the TAC/MMF group was 0.15 mg/kg p.o. given in two doses (equals 0.075 mg/kg twice daily) post-operatively. Subsequent oral tacrolimus doses were adjusted on the basis of clinical evidence of efficacy and occurrence of adverse events and targeted to obtain the following recommended whole blood trough level ranges:

Day 0 - 14: 10 - 15 ng/ml
Day 15 - 42: 8 - 12 ng/ml
Day 43 - 183: 5 - 10 ng/ml

Lot Numbers: FK506: 0.5 mg tacrolimus immediate-release capsules, [redacted], [redacted]; 1.0 mg tacrolimus immediate-release capsules, [redacted], [redacted], [redacted]; 5.0 mg tacrolimus immediate-release capsules, [redacted], [redacted], [redacted], [redacted], [redacted].

Duration of Study and Treatment: Patients were followed for 6 months with 8 scheduled assessment visits.

Criteria for Evaluation: The first primary endpoint was renal function, as measured by creatinine clearance at Month 6 calculated using the Cockcroft formula. The second primary endpoint was a composite endpoint consisting of the overall incidence of renal dysfunction, patient death, graft loss, and first biopsy proven acute rejection (BPAR).
Secondary efficacy and safety endpoints were: acute rejection (incidence of and time to, incidence and time to first corticosteroid-resistant rejection, overall frequency of acute rejection episodes); biopsy proven acute rejection (incidence of and time to first BPAR, incidence of and time to first corticosteroid-resistant BPAR, overall frequency of BPAR episodes); severity of BPAR; patient and graft survival; incidence of adverse events; absolute change in serum lipids (cholesterol, LDL, triglycerides); incidence and duration of delayed graft function; renal dysfunction; incidence of diabetes mellitus.

Statistical Methods:
Primary endpoint analysis: A two-step sequential testing strategy was applied for the two primary endpoints.
Step 1: The first primary endpoint was tested by analysis of variance including the factors treatment, pooled center, and treatment by pooled center interaction.
Step 2: In case the results from Step 1 were statistically significant, differences in the proportion of failures for the composite endpoint were to be tested by the Cochran-Mantel-Haenszel test controlling for center. The Breslow-Day test was used for testing homogeneity of the results across centers.
For both analyses, centers were pooled with regard to country/geographic region to form pooled centers with at least 8 patients. Both tests were performed at significance level α=5% (two-sided). No adjustment for multiplicity was done since the sequential testing procedure controls the multiple α

level.

Secondary efficacy and safety analyses: In general, descriptive statistics were used and included number, mean, standard deviation, median, minimum and maximum for continuous variables. For categorical variables frequencies and, where appropriate, percentages were determined.
Treatments were compared with Chi-square or Fisher's exact test. Time to event was analyzed using Kaplan-Meier cumulative survival probability estimates and comparisons of treatments were analyzed using the Wilcoxon-Gehan test.

Analysis sets:
The full analysis set (FAS) consists of all randomized and transplanted patients with results attributed to the treatment group they were randomized to and who received at least one dose of study medication. The per-protocol set (PPS) consists of all FAS patients except for those with major protocol violations.
All analyses were based on the FAS. Analyses of the per-protocol data set (PPS) were not performed, as this set did not differ significantly from the FAS in either treatment group (difference < 20%).

RESULTS:
Analysis Sets and Subject Disposition:

Table 1: Populations for Analysis – Number of Patients

	TAC-d/MMF/MAB (N= 139)	TAC/MMF (N=128)	Total (N=267)
Excluded from FAS	7	6	13
Not transplanted, no study medication received	2	4	6
Not transplanted, study medication received	5	2	7
Full Analysis Set*	132	122	254
Excluded from PPS	10	4	14
Per Protocol Set†	122	118	240

* All randomized and transplanted patients who received at least one dose of study medication (tacrolimus [TAC], mycophenolate mofetil [MMF], basiliximab [MAB], steroids)

† All FAS patients without major protocol deviations

Table 2: Patient Disposition – Number of Patients (%)

	TAC-d/MMF/MAB (N=132)	TAC/MMF (N=122)	Total (N=254)
Completed	94 (71.2)	88 (72.1)	182 (71.7)
Total Deaths	6 (4.5)	1 (0.8)	7 (2.8)
During study	2 (1.5)	1 (0.8)	3 (1.2)
After withdrawal/EOS	4 (3.0)	0 (0.0)	4 (1.6)
Withdrawn ~	36 (27.3)	33 (27.0)	69 (27.2)
Graft loss	5 (3.8)	9 (7.4)	14 (5.5)
Adverse event	15 (11.4)	13 (10.7)	28 (11.0)
Withdrawal of informed consent	4 (3.0)	3 (2.5)	7 (2.8)
Lost to follow-up	2 (1.5)	1 (0.8)	3 (1.2)
Protocol violation	9 (6.8)	5 (4.1)	14 (5.5)
Other	1 (0.8)	2 (1.6)	3 (1.2)

FAS
~ For reasons other than death

Approximately 70% of the enrolled patients completed the study, with the most common reason for withdrawal being due to an adverse event for both treatment arms. Three patients died during the study and 4 patients died following discontinuation. Causes of death of the two patients in the TAC-d/MMF/MAB group who died during the study were respiratory failure and multiple organ failure and the cause of death of the patient in the TAC/MMF group was hemorrhagic cerebral infarction.

Demographics:
Characteristics of patients in the two groups were well-matched with the exception of age: there were slightly more patients in the TAC-d/MMF/MAB group who were ≥ 65 years: 96 patients (72.7%) vs. 82 patients (67.2%).
Differences in donor characteristics and transplantation risk factors were unremarkable between the two groups with the exception of the number of female donors. There were significantly more female donors in the TAC/MMF group (67/54.9%) compared with the TAC-d/MMF/MAB group (53/40.2%)

(p=0.019; Chi-square test).

Study Drug Exposure:
The protocol schedule to initiate tacrolimus administration on Day 7 was well followed by patients in the TAC-d/MMF/MAB group. For patients who completed the study, the mean daily dose of tacrolimus at Month 6 was the same in both treatment groups at 0.06mg/kg (SD ±0.03in the TAC-d/MMF/MAB group and SD ±0.04 in the TAC/MMF group). Mean trough levels at Month 6 for patients who completed the study were comparable between the groups and well within the targeted range: TAC-d/MMF/MAB 8.53 (SD ±2.65) and TAC/MMF 8.75 (SD ±2.75).

Primary Endpoint and Efficacy Results:
Step 1 of the primary endpoint analysis was performed on the set of FAS patients who had Month 6 creatinine clearance estimates based on serum creatinine measurements either from Month 6 (completers) or from the follow-up visit (withdrawn patients). The mean creatinine clearance at Month 6 was 45.7mL/min (SD ±16.01mL/min) in the TAC-d/MMF/MAB group and 45.0mL/min (SD 18.2mL/min) for the TAC/MMF group. The difference in mean creatinine clearance between both treatment groups was not statistically significant. Since the results of Step 1 were not significant, testing as per Step 2 were not necessary. The incidence of composite endpoint events was similar in the two treatment groups:

Table 3: Composite Endpoint Event Incidence – Number of Patients (%)

	TAC-d/MMF/MAB N=132	TAC/MMF N=122
Composite endpoint incidences*	68 (51.5)	70 (57.4)
Renal dysfunction	35 (26.5)	36 (29.5)
Biopsy proven acute rejection	22 (16.7)	21 (17.2)
Graft loss	11 (8.3)	13 (10.7)
Death	0	0

FAS
* Only the first event per patient was used. In case more than one event occurred on the same day, the worst event was used for analysis.

Table 4: Overall Frequency of Graft Rejection – Number of Patients (%)

	TAC-d/MMF/MAB N= 132	TAC/MMF N=122
Acute rejection (based on signs & symptoms)	51 (38.6%)	38 (31.1%)
Biopsy confirmed acute rejection	25 (18.9%)	22 (18.0%)
Steroid-resistant	8 (6.1%)	7 (5.7%)
Resolved with treatment	7 (5.3%)	6 (4.9%)
Histological grade:		
Mild	12 (9.1%)	10 (8.2%)
Moderate	10 (7.6%)	12 (9.8%)
Severe	3 (2.3%)	0 (0.0%)
Chronic rejection	1 (0.8%)	0 (0.0%)

FAS

The rate of estimated 6 month graft survival was comparable: 90.0% in the TAC-d/MMF/MAB group and 87.6% in the TAC/MMF group (difference not statistically significant).
During the study, 12 (9.1%) patients in the TAC-d/MMF/MAB group lost their renal allograft which was comparable to the 15 (12.3%) graft losses in the TAC/MMF group.

Safety Results:

There was no statistically significant difference between treatment groups in the estimated patient survival rate over six months: 96.1% in the TAC-d/MMF/MAB group compared with 99.2% in the TAC/MMF group.

The overall incidence of adverse events and serious adverse events, both regardless of relationship to study drug and those assessed by the investigator as being causally-related to study medication, were comparable for the two treatment groups. 15 (11.4%) patients in the TAC-d/MMF/MAB group and 13 (10.7%) patients in the TAC/MMF group withdrew from the study due to an adverse event.

Table 5: Incidence of the Most Frequently Reported Adverse Events Regardless of Relationship to Study Medication – Number of Patients (%), Events

MedDRA SOC MedDRA High Level Term MedDRA Preferred Term	TAC-d/MMF/MAB N= 132		TAC/MMF N=122	
Infections and infestations	86 (65.2)	154	75 (61.5)	145
Metabolism and nutrition disorders	70 (53.0)	128	67 (54.9)	97
Hypokalaemia †	**11 (8.3)**	**12**	**1 (0.8)**	**1**
Hyponatraemia †	**11 (8.3)**	**11**	**2 (1.6)**	**3**
Renal and urinary disorders	57 (43.2)	77	58 (47.5)	79
Gastrointestinal disorders	51 (38.6)	92	51 (41.8)	85
Injury, poisoning and procedural complications	43 (32.6)	55	47 (38.5)	60
Blood and lymphatic system disorders	48 (36.4)	65	36 (29.5)	46
General disorders and administration site conditions	40 (30.3)	53	35 (28.7)	52
Investigations	43 (32.6)	56	30 (24.6)	39
Vascular disorders	29 (22.0)	31	28 (23.0)	32
Cardiac disorders	22 (16.7)	24	17 (13.9)	21
Rate and rhythm disorders NEC †	**11 (8.3)**	**12**	**2 (1.6)**	**2**
Musculoskeletal and connective tissue disorders	20 (15.2)	20	16 (13.1)	17
Respiratory, thoracic and mediastinal disorders	18 (13.6)	23	16 (13.1)	18
Nervous system disorders	13 (9.8)	16	18 (14.8)	22
Skin and subcutaneous tissue disorders	13 (9.8)	13	11 (9.0)	12
Reproductive system and breast disorders	7 (5.3)	10	9 (7.4)	10
Psychiatric disorders	8 (6.1)	9	6 (4.9)	7

Full Analysis Set

Adverse events coded using MedDRA 8.0; Most frequently reported defined as incidence rate of at least 5% in either treatment group. Only SOC classification presented except for high level terms and preferred terms which differed significantly between the groups.

† p-value < 0.05 (Fisher's exact test)

NEC = Not elsewhere classified

The number of reported serious adverse events was comparable between groups at 74 (56.1%) in the TAC-d/MMF/MAB group and 76 (62.3%) in the TAC/MMF group. Infections were the most commonly reported serious adverse event in both groups indicated by the investigator as being causally related to study drug and occurred in 15 (11.4%) of patients in the TAC-d/MMF/MAB group and in 16 (13.1%) of patients in the TAC/MMF group.

Differences between the treatment groups were found in the mean change in serum lipids between Baseline and Month 6 however none of the differences reached statistical significance as shown in the table below:

Table 6: Mean Change in Serum Lipids from Baseline to Month 6 – Mean (SD)

	TAC-d/MMF/MAB N=94*	TAC/MMF N=88*
Total cholesterol mmol/L	0.29 (±1.36)	0.34 (±1.16)
LDL mmol/L	0.01 (±1.03)	0.64 (±0.99)
Triglycerides mmol/L	0.17 (±1.5)	-0.11 (±1.16)

* Patients who completed the study.

Delayed graft function (DGF), defined as post operative dialysis for >1 day between Day 0 and Day 7 occurred in 40 (30.3%) of patients in the delayed TAC/MAB/MMF group and in 29 (23.8%) of patients in the TAC/MMF group. Six patients in each group (4.5%, delayed TAC/MAB/MMF group and 4.9%, TAC/MMF group) had a never functioning graft.

De novo renal dysfunction (creatinine clearance <40mL/min at Month 6) was reported in 37 (39.4%) of patients in the TAC-d/MMF/MAB group compared with 35 (39.8%) of patients in the TAC/MMF group.

In patients without a pre-existing condition, hyperglycemia was reported in 21 (20.2%) patients in the TAC-d/MMF/MAB group and in 28 patients (28.6%) patients in the TAC/MMF group. Similarly, diabetes mellitus (based on the WHO definition and defined as elevated fasting glucose levels of ≥7mmol/L confirmed by a second measurement, or antidiabetic treatment for > 30 consecutive days) was newly diagnosed in 45 (44.1%) patients in the TAC-d/MMF/MAB group and in 50 (54.3%) patients in the TAC/MMF group. Mean corticosteroid maintenance dose at Month 6 was low in both groups at 0.0mg/kg (SD±0.1) in the TAC-d/MMF/MAB group and 0.1mg/kg (SD±0.1) in the TAC/MMF group.

CONCLUSIONS:

These study results showed that tacrolimus can safely be used as a primary immunosuppressant in elderly patients. The delay of tacrolimus administration and the addition of induction with basiliximab to the regimen did not convincingly provide an advantage in preventing acute rejection or preserving renal function in this population of elderly renal transplant patients; however, this regimen enabled early steroid-free maintenance therapy in the majority of patients.

Date of Report: August 2007