SUMMARY OF REPORT NUMBER FG02-506-03

NAME OF COMPANY: Fujisawa GmbH **NAME OF FINISHED PRODUCT:** Prograf™ **NAME OF ACTIVE INGREDIENT:** Tacrolimus (FK506)	**INDIVIDUAL STUDY TABLE REFERRING TO PART IVB OF DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**

Title of the study: A multicentre, randomised, open clinical study to compare the efficacy and safety of a combination of tacrolimus with sirolimus versus a tacrolimus / mycophenolate mofetil based regimen in kidney transplantation

Investigators: [redacted]

Study centres: In total, 75 centres, in 16 countries, participated in the study.

Study period: First patient enrolled: 19 May 2002 Last patient visit: 26 September 2003	**Clinical phase:** IIIb

Objectives: The objectives of the study were to compare, in an adult kidney transplanted population, the efficacy and safety of three tacrolimus based treatment regimens, tacrolimus in combination with steroids and two different doses of sirolimus versus tacrolimus in combination with steroids and MMF, and to gain further information about an effective sirolimus trough level range in combination with tacrolimus. In particular, to determine whether there were any differences in the rate of patients with biopsy-proven acute rejections within the first six months following transplantation.

Methodology: The criteria for evaluation are listed below. Incidence of rejection episodes, adverse events, serum creatinine concentrations, tacrolimus dose and trough levels, sirolimus dose and trough levels, MMF dose, steroids dose, concomitant medication. Days hospitalised and days on dialysis were assessed on a continuous basis. Vital signs measurements and laboratory assessments were performed at Day 0 and all planned visits.

Number of patients (planned and analysed): Approximately 855 patients (285 per treatment group) were to be enrolled in the study.
Randomised to receive treatment: 995 patients (333 in the low dose sirolimus triple therapy group, 331 in the high dose sirolimus triple therapy group and 331 in the MMF triple therapy group).
Analysed: 977 patients were in the full analysis set (325 in the low dose sirolimus triple therapy group, 325 in the high dose sirolimus triple therapy group and 327 in the MMF triple therapy group).

Diagnosis and main criteria for inclusion: Patients, at least 18 years of age, with end stage kidney disease who were suitable candidates for primary renal transplantation or re-transplantation and who provided informed consent.

Test product, dose and mode of administration: Tacrolimus, as part of a triple immunosuppressive treatment regimen. The dose of oral tacrolimus was adjusted on the basis of clinical evidence of efficacy and occurrence of adverse events and according to whole blood trough levels; the initial oral dose was 0.1mg/kg twice a day (or 0.04mg/kg/day i.v.).

The treatment regimen also included: methylprednisolone (or equivalent), 500mg/day or less i.v. bolus (Day 0) , 125mg/day i.v. bolus (Day 1), and once daily doses of prednisone (or equivalent), 20mg/day p.o. (Days 2-14), 15mg/day p.o. (Days 15-28), 10mg/day p.o. (Days 29-42), and

5mg/day p.o. (Days 43-183).

Only patients randomised to one of the two sirolimus triple therapy groups received sirolimus: in the low dose sirolimus triple therapy group, the loading dose was 1.5mg sirolimus p.o. followed by a daily maintenance dose of 0.5mg sirolimus p.o. In the high dose sirolimus triple therapy group, the loading dose was 6.0mg sirolimus p.o. followed by a daily maintenance dose of 2.0mg sirolimus p.o.

Only patients randomised to the MMF triple therapy group were to receive MMF at a dose of 500mg twice a day.

Duration of treatment: 6 months

Criteria for evaluation: The efficacy endpoints of the study were the rate of patients with biopsy-proven acute rejections within the first six months following transplantation, the incidence of and time to first biopsy-proven acute rejection, overall frequency of biopsy-proven acute rejections, incidence of and time to first corticosteroid-resistant acute rejection, severity of biopsy-proven rejections, graft survival rate, renal function as assessed by calculated creatinine clearance (Cockroft's formula), treatment failure and delayed graft function. The safety endpoints were patient survival, the overall incidence of adverse events, safety laboratory data and vital signs.

Statistical methods: The population used for the analyses of both efficacy and safety was the full analysis set, which included all randomised and transplanted patients, with results attributed to the treatment group that they were randomised to, and who received at least one dose of study medication (tacrolimus, or sirolimus or MMF). Baseline and demographic data were analysed using Fisher's exact test and the Kruskal Wallis test. The main efficacy data were analysed using confidence intervals derived from Kaplan-Meier estimates and standard errors according to Greenwood's formula and the normal approximation, the Wilcoxon Gehan test and Fisher's exact test. The incidences of adverse events were compared using Fisher's exact test.

SUMMARY – CONCLUSIONS

Disposition. Of the 325 patients in the low dose sirolimus group, seven (7/325, 2.2%) died, five of them (5/325, 1.5%) during the study, 49 (49/325, 15.1%) were withdrawn due to reasons other than death, and 271 (271/325, 83.4%) completed the treatment phase. The most common reason for withdrawal from the study was adverse events (19/325, 5.8%). Of the 325 patients in the high dose sirolimus group, seven (7/325, 2.2%) died, four of them (4/325, 1.2%) during the study, 70 (70/325, 21.5%) were withdrawn due to reasons other than death, and 251 (251/325, 77.2%) completed the treatment phase. The most common reason for withdrawal from the study was adverse events (34/325, 10.5%). Of the 327 patients in the MMF group, seven (7/327, 2.1%) died, five of them (5/327, 1.5%) during the study, 48 (48/327, 14.7%) were withdrawn due to reasons other than death, and 274 (274/327, 83.8%) completed the treatment phase. The most common reason for withdrawal from the study was adverse events (16/327, 4.9%).

Demographics. Overall the treatment groups were well balanced in terms of patient demographics and baseline characteristics. Statistically significant differences between treatment groups in terms of median age of patients, which ranged between 46.0 (min: 18; max: 73) years in the low dose sirolimus group and 49.0 (min: 18; max: 73) years in the high dose sirolimus group (p=0.022: Kruskal Wallis test) and median weight of patients, which ranged between 68.0 (min: 42; max: 107) kg in the low dose sirolimus group and 72.0 (min: 42; max: 100) kg in the MMF group (p=0.022: Kruskal Wallis test), are apparently due to the relatively large sample size rather than related to clinically relevant differences. There were more males than females in the study. The treatment groups were well balanced in terms of viral status at baseline, primary diagnosis, number of previous transplants, AB0 mismatch, HLA mismatch, PRA-grade and CMV status of the recipient and donor. The treatment groups were balanced in terms of donor demographics and viral status, and in addition the demographic characteristics of donors and recipients were in general similar in all treatment groups, however on average, donors for the high dose sirolimus group were slightly younger (43.7±14.5 years) than recipients in this group (47.3±12.4 years), and the percentage of male donors was lower than the percentage of male recipients in all treatment groups.

Efficacy, primary endpoint. The estimated rates of patients with biopsy-proven acute rejections at six months were 0.261 on low dose sirolimus, 0.163 on high dose sirolimus and 0.234 on MMF. According to the sequential Bonferroni-Holm approach based on confidence intervals, non-inferiority of the high dose sirolimus regimen versus the MMF regimen in terms of these rates was

demonstrated. The corresponding point estimate and 98.3% confidence interval for the difference MMF minus high dose sirolimus were 0.071 and (-0.004, 0.147), and the lower bound of -0.004 being below zero indicates that the subsequent assessment of superiority failed slightly. The unadjusted p-value of the Wilcoxon Gehan test, comparing the time to first biopsy-proven acute rejection, was 0.026 for the comparison of the high dose sirolimus regimen versus the MMF regimen. Non-inferiority of the low dose sirolimus regimen compared to the high dose sirolimus regimen based on the corresponding 97.5% confidence, which was (-0.175, -0.21), could not be demonstrated. The point estimate for this difference was -0.098 and the unadjusted p-value of the Wilcoxon Gehan test was 0.003, indicating on a non-confirmatory level that the high dose regimen was in fact superior to the low dose regimen in terms of time to first biopsy-proven acute rejection. Non-inferiority of the low dose sirolimus regimen compared to the MMF regimen could also not be demonstrated: the estimated difference MMF minus low dose sirolimus was -0.027 with a 97.5% confidence interval of (-0.109, 0.055). The unadjusted p-value of the Wilcoxon Gehan test for this comparison was 0.454.

Efficacy, secondary endpoints. No statistically significant differences were observed between treatment groups with respect to estimated rates of patients with biopsy-proven corticosteroid-resistant acute rejections within the first six months following transplantation. These rates were 0.083 on low dose sirolimus, 0.075 on high dose sirolimus and 0.070 on MMF, 95% confidence intervals for treatment comparison were (-0.055, 0.029) for MMF minus low dose sirolimus, (-0.045, 0.036) for MMF minus high dose sirolimus and (-0.051, 0.034) for high dose minus low dose sirolimus. The p-values of the Wilcoxon Gehan test for treatment comparisons in terms of time to first biopsy-proven corticosteroid-resistant acute rejections were 0.605 for low dose sirolimus versus MMF, 0.947 for high dose sirolimus versus MMF and 0.659 for low dose versus high dose sirolimus.

The estimated rate of patients with acute rejections based on signs and symptoms at six months was 0.317 on low dose sirolimus, 0.227 on high dose sirolimus and 0.285 on MMF. Following the same sequential confidence interval based approach as specified for the confirmatory analysis, but without a confirmatory level of evidence, the 98.3% confidence interval for the difference MMF minus high dose sirolimus being (-0.025, 0.141) and thus having a lower bound above -0.1 provides further support for non-inferiority of the high dose sirolimus regimen compared to the MMF regimen. All other lower bounds of confidence intervals violated the non-inferiority margin. Furthermore, on a descriptive level the estimated rate of patients with acute rejections based on signs and symptoms at six months was significantly lower (p=0.011: Wilcoxon Gehan test) on high dose sirolimus (0.227) compared to low dose sirolimus (0.317), and the corresponding 95% confidence interval for high minus low dose was (-0.160, -0.020). This rate was 0.285 in the MMF treatment regimen, which, giving 95% confidence intervals of (-0.105, 0.040) for MMF minus low dose sirolimus and (-0.011, 0.126) for MMF minus high dose sirolimus, was not statistically significantly different from the rates observed for the two other treatment groups. The Wilcoxon Gehan p-value was 0.466 for MMF versus low dose sirolimus and 0.072 for MMF versus high dose sirolimus.

There were no statistically significant differences between the treatments in terms of the rates of patients with corticosteroid-resistant acute rejections based on signs and symptoms at six months. These rates were 0.100 on low dose sirolimus, 0.085 on high dose sirolimus and 0.083 on MMF, 95% confidence intervals for treatment comparison were (-0.063, 0.030) for MMF minus low dose sirolimus, (-0.046, 0.042) for MMF minus high dose sirolimus and (-0.062, 0.032) for high dose minus low dose sirolimus. The p-values for treatment comparisons in terms of time to first corticosteroid-resistant acute rejections based on signs and symptoms were 0.696 for low dose sirolimus versus MMF, 0.908 for high dose sirolimus versus MMF and 0.624 for low dose versus high dose sirolimus.

The treatment groups were similar in terms of the number of patients receiving dialysis and the total number of days of dialysis.

The treatment groups were similar in terms of the percentage of patients with primary non-functioning graft (low dose sirolimus: 83/325, 25.5%; high dose sirolimus: 75/325, 23.1%; MMF: 68/327, 20.8%) and graft loss (low dose sirolimus: 24/325, 7.4%, including 4 after withdrawal; high dose sirolimus: 29/325, 8.9%, including 2 after withdrawal; MMF: 25/327, 7.6%, including 3 after withdrawal). There was no statistically significant difference between the treatment groups in terms of time to graft loss: the estimated proportion of patients free from graft loss at six months was

0.926 (95% confidence interval: 0.898 to 0.955) on low dose sirolimus, 0.910 (95% confidence interval: 0.879 to 0.942) on high dose sirolimus and 0.924 (95% confidence interval: 0.895 to 0.924) on MMF.

The estimated rate of patients free from treatment failure during the six months post-transplantation was significantly lower in the high dose sirolimus group compared to the other treatment groups: At Month 6, the estimated proportion of patients free from treatment failure was 0.887 (95% confidence interval: 0.853 to 0.922) on low dose sirolimus, 0.824 (95% confidence interval: 0.783 to 0.866) on high dose sirolimus and 0.894 (95% confidence interval: 0.861 to 0.928) on MMF, and the 95% confidence intervals for treatment comparison were (-0.055, 0.041) for low dose sirolimus minus MMF, (-0.124, -0.017) for high dose sirolimus minus MMF and (0.009, 0.117) for low dose minus high dose sirolimus. P-values of the Wilcoxon Gehan test were 0.022 for high dose sirolimus versus the MMF, 0.045 for high dose versus low dose sirolimus and 0.808 for low dose sirolimus versus MMF.

Median serum creatinine levels for all patients tended to decrease over the course of the study in all treatment groups in a similar way. There was no statistically significant difference between the treatment groups in terms of serum creatinine level at Visit Month 6 (p=0.676: Kruskal Wallis test), with median values of 130.0µmol/L on low dose sirolimus, 132.6µmol/L on high dose sirolimus and 131.0µmol/L on MMF. There was a statistically significant difference between the treatment groups with respect to creatinine clearance at Visit Month 6 (p=0.019: Kruskal Wallis test). Median (min – max) creatinine clearance at this visit was 52.8 (10.1-112.7) mL/min on low dose sirolimus, 50.2 (11.7-112.7) mL/min on high dose sirolimus and 53.0 (15.4-132.2) mL/min on MMF.

Safety. A total of 21 patients died, seven in each of the treatment groups. Of these, two in the low dose sirolimus group, three in the high dose sirolimus group and two in the MMF group died after withdrawal.

There were no statistically significant differences between the treatment groups in terms of patient survival; p-values of the Wilcoxon Gehan test for pair-wise treatment comparisons ranged between 0.772 for low dose versus high dose sirolimus and 0.977 for low dose sirolimus versus MMF.

Overall, the percentage of patients reporting adverse events during the study was slightly higher in the high dose sirolimus group compared to the two other treatment groups. Differences were less pronounced with regards to the incidence of any adverse event (90.8% of patients on low dose sirolimus, 94.8% of patients on high dose sirolimus and 91.7% of patients on MMF) but larger with regards to causally related adverse events (67.7% of patients on low dose sirolimus, 78.2% of patients on high dose sirolimus and 70.3% of patients on MMF).

Hyperlipemia, anaemia, urinary tract infection, diarrhoea, abnormal kidney function, hypertension and increased creatinine were the most commonly reported adverse events. For adverse events with an incidence rate of at least 4.5% in either treatment group, statistically significant differences (Fisher's exact test) between treatment groups were observed in terms of the incidence of hyperlipemia (19.4% on low dose sirolimus, 24.0% on high dose sirolimus and 11.0% on MMF, resulting in p<0.001), diarrhoea (11.4% on low dose sirolimus, 10.5% on high dose sirolimus and 18.0% on MMF, resulting in p=0.010), abnormal kidney function (13.2% on low dose sirolimus, 17.2% on high dose sirolimus and 9.8% on MMF, resulting in p=0.021), hypertension (14.8% on low dose sirolimus, 15.4% on high dose sirolimus and 9.2% on MMF, resulting in p=0.030), diabetes mellitus (7.1% on low dose sirolimus, 14.2% on high dose sirolimus and 10.4% on MMF, resulting in p=0.013), hypercholesteremia (5.8% on low dose sirolimus, 13.2% on high dose sirolimus and 5.5% on MMF, resulting in p<0.001), leucopenia (4.6% on low dose sirolimus, 5.5% on high dose sirolimus and 9.8% on MMF, resulting in p=0.023), cyst (4.3% on low dose sirolimus, 8.6% on high dose sirolimus and 4.0% on MMF, resulting in p=0.022) and pneumonia (1.8% on low dose sirolimus, 6.5% on high dose sirolimus and 1.8% on MMF, resulting in p=0.002).

The incidence of serious adverse events was higher in the high dose sirolimus group compared to low dose sirolimus and MMF. On high dose sirolimus, a total of 55.4% of patients reported any serious adverse event during the study compared to 41.2% on low dose sirolimus and 41.9% on MMF. The incidence of serious adverse events, which were considered to be related to study medication, was also higher in the high dose sirolimus group compared to low dose sirolimus and MMF: 33.2% in the high dose sirolimus group, 23.4% in the low dose sirolimus group and 21.1% in the MMF group.

The most commonly reported serious adverse events were abnormal kidney function, creatinine

increased, CMV infection, pneumonia, urinary tract disorder and kidney tubular necrosis. Among serious adverse events with an incidence rate of at least 0.8% in either treatment group, a significantly (Fisher's exact test) higher incidence rate on high dose sirolimus compared to low dose sirolimus and MMF was observed for abnormal kidney function (4.9% on low dose sirolimus, 8.3% on high dose sirolimus and 2.8% on MMF, resulting in p=0.006), pneumonia (1.2% on low dose sirolimus, 4.3% on high dose sirolimus and 0.9% on MMF, resulting in p=0.008), cyst (1.8% on low dose sirolimus, 2.8% on high dose sirolimus and 0.3% on MMF, resulting in p=0.025) and anaemia (0.3% on low dose sirolimus, 1.8% on high dose sirolimus and 0.3% on MMF, resulting in p=0.049).

No malignancies were reported for the low dose sirolimus and for the MMF group; in the high dose sirolimus group one lymphoma and one lymphoma like reaction were reported (2/325, 0.6%).

Conclusions. The confirmatory analysis of the primary endpoint demonstrated non-inferiority of the high dose sirolimus triple treatment regimen compared to the MMF triple treatment regimen and failed demonstrating superiority of the high dose sirolimus regimen versus the MMF regimen only slightly. Non-inferiority of the low dose sirolimus treatment regimen compared to high dose sirolimus of MMF could not be established. On a descriptive level, efficacy in terms of preventing acute rejections was similar between the low dose sirolimus regimen and the MMF regimen, and was slightly better for the high dose sirolimus regimen. However, this needs to be weighed against the dislipidemia in both sirolimus groups and an increased rate of premature withdrawal due to adverse events with higher sirolimus doses.

Date of report: August 2004