SUMMARY OF REPORT NUMBER FG04-506-01

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: An open, multicentre, randomised, parallel group study to compare the safety and efficacy of a tacrolimus/azathioprine/steroid triple regimen with and without the induction of the monoclonal antibody basiliximab in children after kidney transplantation		
Investigators: [redacted]		
Study centres: In total, 15 centres in six European countries participated in this study		
Study period: First patient enrolled: 03 March 2001 Last patient visit: 15 March 2004		**Clinical phase:** III
Objectives: The objective of the study was to compare the efficacy and safety of a tacrolimus-based triple regimen (tacrolimus/azathioprine/steroids) with and without the induction of a monoclonal antibody (basiliximab) at 6 months after transplantation in a paediatric kidney transplant population. In particular, to determine whether there were differences in the incidence of acute rejection, especially of corticosteroid-resistant acute rejection and with regard to patient and graft survival.		
Methodology: Each patient was randomly assigned to the standard treatment regimen with or without basiliximab before transplantation. Patients were treated with the study immunosuppressive regimen for six months. Doses of immunosuppressive medication, tacrolimus blood levels, rejection episodes, dialysis data, adverse events, serum creatinine levels, and hospitalisation were assessed on a continuous basis. Vital signs were assessed at each study visit. Clinical laboratory was evaluated at baseline (Day 0), Month 3 and Month 6 / end of study visits. Viral status was assessed at baseline and end of study visit.		
Number of patients (planned and analysed): Approximately 170 patients were to be enrolled into the study (Protocol amendment 2, 2 December 2002) and randomised in a 1:1 ratio to the treatment groups. A total of 197 patients were randomised to receive treatment (95 in the treatment group without basiliximab, 102 in the basiliximab group). The Full Analysis Set comprised 192 patients (93 in the treatment group without basiliximab and 99 patients in the basiliximab group). Analyses of key efficacy variables were additionally stratified by age groups children (patients with age < 12 years) and adolescents (patients with age ≥ 12 years).		
Diagnosis and main criteria for inclusion: Patients of age 18 or younger with end-stage kidney disease receiving a kidney transplant from a cadaveric or living donor with compatible AB0 blood type were eligible for to enter the study. Informed written consent had to be given by the patient's representatives (if the patient was minor) and/or the patient.		
Test product, dose and mode of administration: Tacrolimus, as part of a triple or quadruple immunosuppressive regimen. The initial dose was 0.3mg/kg, subsequent doses were adjusted according to blood through levels. In the basiliximab arm, two doses of basiliximab, 10mg in patients <40kg or 20mg in patients ≥40kg, were administered as an		

intravenous infusion. The first dose of basiliximab was administered prior to reperfusion. The second dose was administered at Day 4 after transplantation.
The treatment regimen comprised also azathioprine, daily dose 1 – 2 mg/kg p.o. or i.v. during the first week, 1- 2 mg/kg p.o. from Day 8 onwards and methylprednisolone or equivalent on Day 0 (300 – 600mg/m^2 i.v., bolus) followed by prednisone therapy or equivalent administered orally with daily doses of 60mg/m^2 at Day 1, 40mg/m^2 from Day 2 to Day 7, 30mg/m^2 from Day 8 to Day 14, 20mg/m^2 from Day 15 to Day 28, 10mg/m^2 from Day 29 to Day 42 and ≤ 10mg/m^2 from Day 43 on.

Duration of treatment: 6 months

Criteria for evaluation:

Primary efficacy endpoint. The primary efficacy endpoint of the study was the incidence of and time to first biopsy-proven acute rejection over the first six months after transplantation.

Secondary efficacy endpoints. The secondary efficacy endpoints were the frequency of acute rejection at six months after transplantation including suspected rejection without biopsy, incidence of and time to first corticosteroid-resistant acute rejections at six months after transplantation, the severity of biopsy-proven acute rejections, renal function as measured by serum creatinine concentrations at six months after transplantation and graft survival.

Secondary safety endpoints.

The secondary safety endpoints were patient survival and the incidence of adverse events at six months after transplantation.

Statistical methods: The full analysis set was used for analysis of all efficacy and safety endpoints. The incidence of acute rejections was assessed using Chi-square test or Fisher's exact test, if any expected cell frequency was less than five. Time to event data were analysed using the Kaplan-Meier method and comparisons between treatment groups were made using the Wilcoxon Gehan test. Baseline and demographic data were compared using Chi-square test or Fisher's exact test for categorical data and Student's t-test or Wilcoxon rank-sum test for continuous measurements. Adverse event data were compared using Fisher's exact test.

SUMMARY – CONCLUSIONS

Disposition. Of the 93 patients in the treatment group without basiliximab, 17 (17/93, 18.3%) were withdrawn from the study, eight of them (8/93, 8.6%) due to nonfatal adverse events. 76 patients (76/93, 81.7%) completed the study.
Of the 99 patients in the basiliximab group, 11 (11/99, 11.1%) were withdrawn from the study, four of them (4/99, 4.0%) due to nonfatal adverse events. 88 patients (88/99, 88.9%) completed the study. No deaths occurred during the study.

Demographics. The treatment groups were reasonably balanced in terms of patient demographics and baseline characteristics. There were more male patients than female patients enrolled. No relevant differences were observed with respect to primary diagnosis, number of previous transplants, ABO mismatch, HLA mismatch and PRA-grade of the recipient and donor. Slight imbalances were seen in donor demographics and viral status.

Efficacy, primary endpoint. There was no statistically significant difference between the two treatment groups in terms of the incidence of biopsy-proven acute rejection (p-value=0.8296: Chi-square test). The incidence of biopsy-proven acute rejection episodes was 20.4% in the treatment group without basiliximab and 19.2% in the basiliximab group. There was no statistically significant difference between the treatment groups in terms of estimated rate of patients free from biopsy-proven acute rejection during the 6 months after transplantation (p-value=0.603: Wilcoxon Gehan test). The estimated proportion of patients free from biopsy-proven acute rejection at Month 6 was 0.764 in the treatment group

without basiliximab compared to 0.788 in the basiliximab group.

Efficacy, secondary endpoints. There were no statistically significant differences in the incidence of corticosteroid-resistant acute rejections (p-value=1.0000: Fisher's exact test) or time to corticosteroid-resistant acute rejection (p-value=0.891: Wilcoxon Gehan test). The incidence of corticosteroid-resistant acute rejection was low in both groups. In the full analysis set, 3.2% of the patients without basiliximab treatment and 3.0% of the patients with basiliximab treatment had such rejections. All corticosteroid-resistant acute rejections were confirmed by biopsy.
There were also no statistically significant differences between the two treatment groups in terms of the incidence of acute rejection (including suspected acute rejections) (p-value=0.5891: Chi-square test) or time to first acute rejection (p-value=0.879: Wilcoxon Gehan test).
A slight tendency towards a lower histological severity of rejections was observed in the basiliximab group compared to the group without basiliximab.
The course of serum creatinine levels and glomerular filtration rate over time was similar in both treatment groups. No statistically significant difference was found between treatment groups at Visit Month 6, neither for serum creatinine (p-value=0.3461: Wilcoxon rank sum test) nor for glomerular filtration rate (p-value=0.3495: Wilcoxon rank sum test). Median serum creatinine levels at Month 6 were 86μmol/L in the treatment group without basiliximab treatment and 91μmol/L with basiliximab treatment. Median glomerular filtration rates were 79.4mL/min/1.73m² in the treatment group without basiliximab and 77.6 mL/min/1.73m² in the basiliximab group.
No statistically significant difference between treatment groups was observed with respect to graft survival during the 6 months after transplantation (p-value=0.901: Wilcoxon Gehan test). Five patients in each group experienced graft loss during the study.

Efficacy, other endpoints. There was also no statistically significant difference between treatment groups in terms of treatment failure during 6 months after transplantation (p-value=0.377 Wilcoxon Gehan test). The estimated proportion of patients free from treatment failure at Month 6 was 0.866 in the treatment group without basiliximab compared to 0.908 in the basiliximab group.

Safety, secondary endpoints. No patient died during the study. The overall incidence of adverse events was similar in both treatment groups. In the treatment group without basiliximab, 84 patients (84/93, 90.3%) reported 504 adverse events during the study. This includes 57 patients (57/93 61.3%) with at least one adverse event which was considered to be causally related to study drug administration. Sixty-one patients (61/93 65.5%) reported serious adverse events, including 32 patients (32/93, 34.4%) with at least one serious adverse event considered to be causally related to study medication. In the basiliximab group, 91 patients (91/99, 91.9%) reported 600 adverse events. This includes 64 patients (64/99 64.6%) with at least one adverse event which was considered to be causally related to study medication. Sixty-three patients (63/99 63.6%) experienced serious adverse events were reported, including 45 patients (45/99, 45.5%) with at least one serious adverse event which was considered to be causally related.
Most commonly reported (incidence ≥ 15%). adverse events were hypertension (36/93, 38.7% without and 34/99, 34.3% with basiliximab), creatinine increased (27/93, 29.0% without and 30/99, 30.3% with basiliximab), urinary tract infection (26/93, 28.0% without and 19/99, 19.2% with basiliximab), diarrhea (20/93, 21.5% without and 19/99, 19.2% with basiliximab), hypophosphatemia (17/93, 18.3% without and 18/99, 18.2% with basiliximab), hypomagnesemia (15/93, 16.1% without and 13/99, 13.1% with basiliximab) and anemia (12/93, 12.9% without and 15/99, 15.2% with basiliximab). Adverse events with a significantly higher incidence rate in the basiliximab group than in the treatment group without basiliximab were toxic nephropathy (4/93, 4.3% versus 14/99, 14.1%, p-

value = 0.0248: Fisher's exact test), and abdominal pain (2/93, 2.2% versus 11/99, 11.1%, p-value = 0.0190: Fisher's exact test). Most commonly reported serious adverse events were creatinine increased (16/93, 17.2% without and 19/99 19.2% with basiliximab), urinary tract infection (10/93, 10.8% without and 5/99, 5.1% with basiliximab), kidney tubular necrosis (6/93, 6.5% without and 8/99, 8.1% with basiliximab) and toxic nephropathy (3/93, 3.2% without and 11/99, 11.1% with basiliximab). No serious adverse event had a statistically significant higher incidence in either treatment group compared to the other treatment group. The most frequent serious adverse events which were assessed by the investigator as causally related were creatinine increased (4/93, 4.3% without and 13/99, 13.1% with basiliximab; p-value=0.0412, Fisher's exact test) and toxic nephropathy (2/93, 2.2% without and 11/99, 11.1% with basiliximab; p-value=0.0190, Fisher's exact test).

Safety, other endpoints No significant differences or tendencies were seen between the treatment groups in laboratory data, vital signs and echocardiography.

Conclusions

Administration of basiliximab in combination with tacrolimus, azathioprine, and corticosteroids in children was safe, but did not show an increase of efficacy compared to the triple regimen without basiliximab.

Patient and graft survival were high in both groups. The incidence of corticosteroid-resistant acute rejection was similarly low in both groups. Although toxic nephropathy was more often reported in the basiliximab arm, renal function assessed by mean creatinine level and glomerular filtration rate was good in both groups. The incidence of infection was also similar in both treatment groups and there were no cases of PTLD in the basiliximab arm.

Date of report: January 2005