# SYNOPSIS

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| **Name of Sponsor/Company:** Astellas Pharma GmbH | | |
| **Name of Finished Product:** Advagraf® | | |
| **Name of Active Ingredient:** Tacrolimus | | |

**Title of Study:** A Multicenter, 1:1 Randomized, Double Blind, Two Arm Parallel Group Study to Evaluate and Compare the Efficacy and Safety of Modified Release Tacrolimus FK506E (MR4) Versus Tacrolimus FK506 in Combination with MMF (Cellcept®) and Steroids in Patients Undergoing Kidney Transplantation

**Coordinating Investigator:**
[redacted]
Germany

**Investigators:**
[redacted]

**Study Centers:** Argentina: [redacted] Austria: [redacted] Australia: [redacted] Belgium: [redacted] Brazil: [redacted] Canada: [redacted] ; Switzerland: [redacted] Czech Republic: [redacted] Germany: [redacted] Spain: [redacted] Finland: [redacted] France: [redacted] United Kingdom: [redacted] Greece [redacted] Hungary: [redacted] Ireland: [redacted] Italy: [redacted] Mexico: [redacted] Netherlands: [redacted] Poland: [redacted] Sweden: [redacted] South Africa: [redacted]

**Publication:** Not applicable.

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| **Study Period:** 18 August 2004 (first informed consent) to 28 December 2006 (last patient, last visit) | **Phase of Development:** Phase III |

**Objectives:** The objective of this study was to evaluate and to compare the efficacy and safety of a triple modified release tacrolimus (MR4)/mycophenolate mofetil (MMF)/steroid regimen with a triple standard tacrolimus (FK506)/MMF/steroid regimen in patients undergoing kidney transplantation. It was to be demonstrated that MR4 was non-inferior to FK506 with regards to the primary endpoint:

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| event rate of patients with biopsy-proven acute rejection within the first 24-weeks following transplantation. |
| **Study Design:** This was a multicenter, 1:1 randomized, double blind, double dummy, two arm parallel group Phase III study comparing a triple MR4/MMF/steroid regimen with a triple standard FK506/MMF/steroid regimen, over a period of at least 12 months. During the first 24 weeks of study duration a double blind, double dummy design was maintained and after the 24 weeks data were cleaned, the study was unblinded and continued in an open design extension phase until the last patient's 12 month visit. |
| **Diagnosis and Main Criteria for Inclusion:** Patients aged between 18 and 65 years with end-stage kidney disease who were suitable candidates for primary renal transplantation or re-transplantation receiving grafts from cadaveric or living donors and received tacrolimus-based immunosuppressive regimen after informed consent had been given. |
| **Number of Subjects (planned and analyzed):** It was planned to enroll 600 patients, 300 per treatment arm, in approximately 50 centers with a minimum of 8 patients and a maximum of 48 patients per site. In order to ensure a complete number of evaluable patients in the pharmacokinetic substudy, the planned number of patients was increased to approximately 680 patients (340 patients per treatment arm) in approximately 80 centers. |
| **Test Product, Dose and Mode of Administration:** MR4/MR4-Placebo was always administered together with FK506/FK506-Placebo every morning, whereas the evening dose of FK506/FK506-Placebo was given without the corresponding MR4/MR4-Placebo dose. Study drug was given in a blinded manner, according to the randomized treatment assignment for at least the first 24 weeks of treatment. The pre-operative dose of MR4/MR4-Placebo and FK506/FK506-Placebo was 0.1 mg/kg given orally in one dose, at any time of the day. The initial post-operative MR4/MR4 Placebo dose was 0.2 mg/kg/day given orally in one dose, preferably in the morning. The initial post-operative FK506/FK506-Placebo dose was 0.2 mg/kg/day given orally in two equal doses, starting in the morning or in the evening. All subsequent doses were taken twice daily, once in the morning and once in the evening. The investigator was able to adjust subsequent doses of MR4/MR4 Placebo and FK506/FK506 Placebo on the basis of clinical evidence of efficacy, occurrence of adverse events and according to whole blood tacrolimus trough level measurements.<br>MR4/MR4 Placebo and FK506/FK506 Placebo capsules were taken with fluid on an empty stomach or at least 1 hour before, or 2 to 3 hours after a meal.<br>An intravenous (i.v.) bolus of up to 1000 mg methylprednisolone (or equivalent) was given perioperatively (Day 0) with a second i.v. bolus of 125 mg being administered 1 day after reperfusion (Day 1). Thereafter oral prednisone (or equivalent) was administered on: Days 2 to 14, 20 mg/day; Days 15 to 28, 15 mg/day; Days 29 to 42, 10 mg/day; Days 43 to 84, 5 mg/day; thereafter, 0 to 5 mg/day.<br>The initial dose of mycophenolate mofetil (MMF, Cellcept®) was 2 g/day (split into two doses) starting pre-operatively and given for the first 14 days of the study. Thereafter the MMF dose was reduced to 1 g/day (split into two doses) to be maintained throughout the study. |
| **Lot Numbers:**<br>**MR4 Active:** 0.5 mg - [redacted] 1 mg – [redacted] 5 mg – [redacted]<br>**MR4 Placebo:** 0.5 mg – [redacted] 1 mg – [redacted] 5 mg – [redacted]<br>**FK506 Active:** 0.5 mg – [redacted] 1 mg – [redacted] 5 mg – [redacted]<br>**FK506 Placebo:** 0.5 mg – [redacted] 1 mg – [redacted] 5 mg – [redacted] |
| **Duration of Study and Treatment:** The study lasted at least 12 months per patient. After 12 months, |

extension visits were scheduled every 3 months until unblinding of the study. Depending on the time point of study unblinding, the total study duration was up to approximately 2 years for those patients who were included early on, and 12 months for the last patients included in the study.

**Criteria for Evaluation:** The primary efficacy variable was event rate of patients with biopsy-proven acute rejection within the first 24 weeks following transplantation. Secondary endpoints over the 12 months were: event rate of patients with biopsy-proven acute rejection within the first 12 months following transplantation, overall frequency, incidence and time to acute rejection and biopsy-proven acute rejection as well as corticosteroid resistant acute rejection and biopsy-proven corticosteroid resistant acute rejection within the first 24 weeks and 12 months following transplantation, severity of biopsy-proven acute rejection (Banff 97 criteria), patient and graft survival within the first 24 weeks and 12 months following transplantation and renal function assessed by calculated creatinine clearance (Cockcroft-Gault's formula) and serum creatinine within the first 24 weeks and 12 months following transplantation. Additional data driven analyses on the primary endpoint were carried out. Safety was assessed by adverse event monitoring, laboratory assessments and vital signs evaluations.

**Statistical Methods:** The primary endpoint, incidence of acute rejection proven by local biopsy within 24 weeks following transplantation was analyzed using Kaplan-Meier methods. The comparison of both treatment groups was done by testing for non-inferiority. Non-inferiority was shown if the two-sided 95% confidence interval for the difference was entirely below 10%. Efficacy analysis was based on two analysis sets. The primary analysis of efficacy data was based on the Per Protocol Set.

**RESULTS:**

**Analysis Sets and Subject Disposition:**

Of the 699 patients randomized to treatment, 667 (95.4%) were in the Full Analysis Set, 331 (95.7%) patients in the MR4 and 336 (95.2%) patients in the FK506 group. The Per Protocol Set included 571 (81.7%) patients, 280 (80.9%) patients in the MR4 and 291 (82.4%) patients in the FK506 group. In total, 135/667 (20.2%) patients prematurely discontinued the study medication. In the MR4 group, 74/331 (22.4%) patients in the MR4 group were withdrawn, 43 (13.0%) patients due to adverse events. In the FK506 group 61/336 (18.2%) patients in the FK506 group prematurely discontinued treatment, 39 (11.6%) patients due to adverse events.

**Demographics:**

The treatment groups were well balanced with regard to basic demographics and primary diagnoses with the exception of HLA DR mismatches that were significantly higher in the MR4 group.

**Study Drug Exposure:**

Although the mean whole blood tacrolimus trough levels were slightly lower for MR4 than FK506 by 2.4 ng/mL at Week 1, the whole blood tacrolimus trough levels for MR4 and FK506 were generally comparable.

Corticosteroid and MMF administration as maintenance therapy was comparable throughout the study for both MR4 and FK506 groups, with steroid withdrawal being performed in a similar manner for both formulations.

**Efficacy Results:**

At 24 weeks post transplant the difference [95% CI] in the primary endpoint, event rate of local biopsy confirmed acute rejection, between MR4 and FK506 in the Per Protocol Set was 4.5% [1.8% to 10.9%]. The upper limit of the CI was just outside the pre defined non-inferiority margin of 10%. Thus, the primary endpoint to demonstrate non-inferiority in the per-protocol set for prevention from biopsy proven acute rejection was not met. In the Full Analysis Set (intent to treat analysis), the difference [95% CI] was 3.8% [-2.1% to 9.6%] demonstrating that the criterion for non-inferiority was met in this analysis set.

At 12 months post transplant, the 95% CI of the difference between MR4 and FK506 in the event rate of local biopsy confirmed acute rejection was 3.9% [-2.6% to 10.4%]. The upper limit of the CI was just outside the pre defined non-inferiority margin of 10% (Per Protocol Set). In the Full Analysis Set, the difference [95% CI] was 3.2% [-2.9% to 9.3%], demonstrating that the criterion for non-inferiority was met in this analysis set.

The imbalance in HLA-DR mismatch between the MR4 and FK506 groups contributed to this finding. The HLA DR mismatch was reported statistically significantly more frequently in the MR4 group compared to the FK506 group. When adjusting for the imbalance in this prognostic factor, non-inferiority could be established for both analysis populations. In this case the treatment difference [95% CI] in the Per Protocol Set was 1.9% [-4.4% to 8.3%] and 2.4%, [-3.5% to 8.4%] in the Full Analysis Set.

The incidence of overall acute rejections diagnosed by signs and symptoms in the MR4 and FK506 groups was similar (32.1% and 26.5%) for the Per Protocol Set as well as for the Full Analysis Set (28.4% and 24.4%).

The incidence of local biopsy confirmed acute rejections in the MR4 and FK506 groups was also comparable (21.1% and 16.8%) for the Per Protocol Set as well as for the Full Analysis Set (17.8% and 14.9%).

The 12-month patient survival rates in the Full Analysis Set were comparable in the MR4 and FK506 groups (96.9% and 97.5%) as well as the graft survival rates (91.5% and 92.8%).

The 12-month difference [95% CI] between MR4 and FK506 in the efficacy failure rate was 3.3% [-3.4% to 10.0%] in the Per Protocol Set. In the Full Analysis Set, the difference [95% CI] between MR4 and FK506 in efficacy failure rate was 4.7% [-2.0% to 11.3%].

The incidence of initial renal dysfunction was comparable between MR4 and FK506 group. In both treatment groups comparatively good renal function was established at 12 months post-transplantation (66.76 mL/min for MR4 and 67.25 mL/min for FK506).

**Safety Results:**

The most frequently reported adverse events were consistent with the established safety profile for systemic tacrolimus. Metabolism and nutrition disorders, gastrointestinal disorders and infections and infestations being the most frequently affected system organ classes, with anemia, urinary tract infection and diarrhea being the most frequently reported MedDRA preferred terms. The incidence of patients with an adverse event of cytomegaloviral (CMV) infections was significantly higher in the FK506 group ($p = 0.038$; (Fisher's exact test) with MedDRA high level term of CMV infection being significantly higher in the MR4 group ($p = 0.038$; Fisher's exact test). The incidence of arthralgia in the MR4 and FK506 group of 8.8% and 3.9%, respectively was significantly higher in the FK506 group ($p = 0.010$; (Fisher's exact test).

The most frequently reported adverse events assessed by the investigator to be causally-related to study medication were also consistent with the established safety profile for systemic tacrolimus. Metabolism and nutrition disorders and infections and infestations were the most frequently affected system organ classes. The incidence of the most frequently reported serious adverse events regardless of relationship to study medication was generally comparable between MR4 and FK506 and was consistent with the established safety profile for systemic tacrolimus. There was a higher incidence of bacterial pyelonephritis and hemorrhages NEC in the MR4 group compared to the FK506 group ($p = 0.019$ and $p = 0.030$; Fisher's exact test, incidence <2%); however, incidence of the corresponding MedDRA high level term and MedDRA SOC term, bacterial infections and vascular disorders, respectively, was comparable between groups. In addition, the incidence of the MedDRA SOC of neoplasm benign, malignant and unspecified (incl. cysts and polyps) was significantly higher in the FK506 group compared to the MR4 group ($p=0.037$; Fisher's exact test). The incidence of adverse events in the MedDRA high level term of CMV infections being causally related to study drug was comparable between treatment groups; there was no statistically significant difference.

Six patients died during the 12 months post-transplant and twelve patients following discontinuation from the study. A total of four causes of deaths (for one patient, two causes of death were indicated) were considered to have a relationship to study drug; three in the MR4 group and one in the FK506 group. For nine patients, no assessment was done to establish relationship of causality between adverse event leading to death and study drug.

There were no differences in the incidence of the most frequently reported causally-related serious adverse events between MR4 and FK506 associated with a p-value < 0.05 (Fisher's exact test). The

incidence of serious adverse events was consistent with the known safety profile of systemic tacrolimus.
Withdrawal due to an adverse event occurred in 13.0% of MR4 patients and 11.6% of FK506 patients. There were no differences in the incidence of the most frequently reported adverse events leading to discontinuation from the study between MR4 and FK506 associated with a p-value < 0.05 (Fisher's exact test). The incidence of adverse events leading to discontinuation was consistent with the known safety profile of systemic tacrolimus.
There were no clinically relevant differences in any hematology or biochemistry parameters between MR4 and FK506 during the study. Incidence of hypertension, hyperlipidaemia and diabetes was similar in both arms. Renal function was comparable through out the 12 months of the study in both arms with creatinine values in the MR4 and FK506 group of 130.68 µmol/L and 130.02 µmol/L, respectively. Corresponding figures for creatinine clearance were 66.76 mL/min for MR4 and 67.25 mL/min for FK506. There were no clinically relevant differences between the MR4 and FK506 treatment groups in vital signs (body weight, diastolic and systolic blood pressure and pulse) and in ECG results. Other safety observations, including physical examination and hospitalization details, were comparable for both MR4 and FK506.

**CONCLUSIONS:** In this renal transplantation study the primary hypothesis to demonstrate non-inferiority for the primary efficacy variable, event rate of biopsy confirmed acute rejection, was not met in the Per Protocol Analysis. Nevertheless, the study demonstrated non-inferiority of MR4 in the Full Analysis Set. The imbalance in HLA-DR mismatch between the MR4 and FK506 groups contributed to this finding. When biopsy-confirmed acute rejection event rates were adjusted for the influence of imbalanced HLA DR mismatch rates, non-inferiority was demonstrated for both analyses sets. Although the primary endpoint, non-inferiority in the per protocol set, was slightly missed the study in fact supports the concept of therapeutic equivalence of the two formulations.
The safety profile of MR4 was generally comparable to that of FK506, with safety findings being consistent with the established safety profile for systemic tacrolimus.
This double blind study demonstrated that MR4 is safe and efficacious when used as primary immunosuppressant in *de novo* kidney transplantation.

**Date of Report:** 23 April 2008