SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Europe R&D		
Name of Finished Product: Prograf®/MR4		
Name of Active Ingredient: Tacrolimus		

Title of Study: Pharmacokinetics of tacrolimus in *de novo* liver transplant patients treated with modified release tacrolimus, FK506E (MR4) or Prograf® based immunosuppression regime.

Responsible Medical Officer/Coordinating Investigator: NA

Investigator(s): [redacted]

Study Center(s): [redacted]

Publication (reference): NA

Study Period: **Date of First Enrolment:** 30th September 2004 **Date of Last Evaluation:** 27th February 2006	**Phase of Development:** III

Objectives: This PK sub-study aimed to obtain information on the pharmacokinetics of tacrolimus for Prograf and MR4 during the first 2 weeks after transplantation in *de novo* liver transplant patients.

Study Design: A multicentre, 1:1 randomised, double blind, double dummy, two arm parallel group phase III study comparing a dual modified release MR4 / steroid regimen with a standard tacrolimus Prograf / steroid regimen.

Diagnosis and Main Criteria for Inclusion:
Primary liver allograft transplantation patients ≥ 18 years of age.

Number of Subjects (planned and analysed):
24 subjects were planned for PK analysis. 25 were actually evaluable for analysis (13 in the MR4 treatment arm and 12 in the Prograf® treated arm).

Test Product, Dose And Mode of Administration:
The initial dose of MR4 was 0.2 mg/kg/day given orally in one dose. The first dose of MR4 should have been given in the morning following LTx. All subsequent doses should have been given in the morning only. The capsules were taken once daily (UID) in the morning.
The initial dose of Prograf was 0.1 mg/kg/day given orally in two doses (equals 0.05 mg/kg twice daily). The first dose of Prograf should have been started in the morning following LTx.
The investigator could adjust the patient's dose and modify the tacrolimus dose regimen as deemed necessary to minimise adverse events and maintain effective immunosuppression.
Doses of the blinded study medication were individually adjusted based on whole blood trough level measurements and clinical signs. Whole blood trough levels were recommended to be maintained in the range 10-20 ng/mL during the PK section of this study.

In this study it was prohibited to adjust only MR4 / MR4-Placebo without adjusting Prograf / Prograf-Placebo or vice-versa (or stopping only one of them temporarily) due to the double blind, double dummy design.

Lot Numbers:
Refer to the clinical report FG-506E-11-03-R-CR1 for all matters relating to Lot numbers.

Duration of Study and Treatment:
17 months enrolment period. 14 day treatment period.

Criteria for Evaluation:
The primary endpoint was the systemic exposure AUC_{0-24} of tacrolimus on Day 1, Day 3, Day 7 and Day 14. Secondary endpoints were: Determination of C_{max}, T_{max}, C_{12} or C_{24} (C_{min}).

Statistical Methods:
For continuous variables, descriptive statistics (N, mean, standard deviation, geometric mean, median, minimum and maximum) are calculated. For categorical variables, frequency distribution and percentage are summarised. All tests were performed exploratively.
The primary endpoint AUC0-24 was analysed for a parallel comparison design in analogy to bioequivalence procedures, i.e. based on an assumed lognormal distribution, a two-sided 90% confidence interval (i.e. α=0.10 two-sided) for the ratio of means and an acceptance interval of 0.8 - 1.25. A patient number of 24 was considered sufficient.

RESULTS:

Analysis Sets and Subject Disposition:

The patients enrolled into the PK sub-study were divided into two sets. The Full PK Set (FPS) consisted of all patients enrolled into the PK sub-study who signed a PK informed consent form and for whom there were at least some PK assessments performed (i.e. blood samples taken in Profile 1). The PK Analysis Set (PKAS) consisted of all patients from the FPS for which there were 4 complete PK profiles available and for whom there was no major PK related protocol violation. Included in the PKAS were a total of 25 patients (MR4 n=13, Prograf n=12). Only patients in the PKAS were included in the analysis of pharmacokinetic parameters.

Demographics:

Mean ages (PKAS) were 55.7 and 53.4 years for the Prograf and the MR4 treatment arms respectively. In the Prograf arm there were 8 males and 4 females. In the MR4 arm there were 11 males and 2 females. All patients in the PKAS were of Caucasian ethnicity.

Study Drug Exposure:

The mean total daily doses of both MR4 and Prograf decreased during the early post-transplant period when the mg/kg dose of MR4 was approximately double that of Prograf (Day 1 and Day 3). By Day 7 the mg/kg mean doses were almost identical, the mean MR4 dose having decreased to 0.158 mg/kg and the mean Prograf dose having increased to 0.150 mg/kg. By Day 14 both MR4 and Prograf mean doses had increased to 0.223 mg/kg and 0.176 mg/kg respectively.

Pharmacokinetics Results:

The systemic exposure to tacrolimus [$\ln(AUC_{0-24})$] on Day 1 was 58% higher for MR4 than for Prograf, although the mean total daily dose (mg/kg) was approximately double. On Days 3, 7 and 14, the $\ln(AUC_{0-24})$ for MR4 was 57%, 41% and 25% higher than that for Prograf. However, the mean total daily doses (mg/kg) of MR4 were approximately 89%, 5% and 27% higher than the corresponding mean Prograf doses at the times of the Day 3, Day 7 and Day 14 profiles (Synopsis Table 1 below).

Synopsis Table 1: Equivalence Comparison of Pharmacokinetic Parameters of Tacrolimus Administered as MR4 and Prograf

Day 1	Mean				Ratio (90% CI)
PK Parameters	MR4	N	Prograf	N	MR4: Prograf
AUC_{0-24}	320.44	13	216.63	12	147.9% (96.24 to 199.60)
$\ln(AUC_{0-24})$	268.25	13	169.31	12	158.4% (95.59 to 262.62)
C_{max}	21.29	13	12.21	12	174.3% (119.82 to 228.76)
$\ln(C_{max})$	18.83	13	8.92	12	211.1% (124.90 to 356.95)
C_{24}	9.97	13	9.18	12	108.6% (56.52 to 160.71)
$\ln(C_{24})$	7.52	13	6.28	12	119.8% (63.97 to 224.49)

Mean total daily dose on Day 1: MR4 = 0.191 mg/kg; Prograf = 0.094 mg/kg

Day 3	Mean				Ratio (90% CI)
PK Parameters	MR4	N	Prograf	N	MR4: Prograf
AUC_{0-24}	452.06	13	317.90	12	142.2% (95.63 to 188.78)
$ln(AUC_{0-24})$	377.65	13	239.90	12	157.4% (90.34 to 274.31)
C_{max}	27.82	13	19.47	12	142.9% (101.68 to 184.21)
$ln(C_{max})$	24.04	13	15.88	12	151.3% (93.53 to 244.86)
C_{24}	14.06	13	10.41	12	135.1 (86.57 to 183.59)
$ln(C_{24})$	11.47	13	7.42	12	154.5% (84.43 to 282.80)

Mean total daily dose on Day 3: MR4 = 0.164 mg/kg; Prograf = 0.087 mg/kg

Day 7	Mean				Ratio (90% CI)
PK Parameters	MR4	N	Prograf	N	MR4: Prograf
AUC_{0-24}	358.60	13	249.12	12	143.9% (109.48 to 178.41)
$ln(AUC_{0-24})$	327.23	13	231.54	12	141.3% (104.17 to 191.74)
C_{max}	23.20	13	19.94	12	116.3% (78.43 to 154.25)
$ln(C_{max})$	20.96	13	17.18	12	122.0% (84.52 to 176.23)
C_{24}	11.06	13	7.43	12	148.9% (107.73 to 190.01)
$ln(C_{24})$	9.77	13	6.97	12	140.2% (101.66 to 193.27)

Mean total daily dose on Day 7: MR4 = 0.158 mg/kg; Prograf = 0.150 mg/kg

Day 14	Mean				Ratio (90% CI)
PK Parameters	MR4	N	Prograf	N	MR4: Prograf
AUC_{0-24}	353.42	13	283.19	12	124.8% (100.19 to 149.40)
$ln(AUC_{0-24})$	338.27	13	269.88	12	125.3% (100.72 to 155.99)
C_{max}	24.85	13	29.34	11	84.7% (46.35 to 123.04)
$ln(C_{max})$	23.91	13	24.60	11	97.2% (71.30 to 132.54)
C_{24}	10.47	13	8.89	12	117.8% (91.77 to 143.75)
$ln(C_{24})$	9.76	13	8.64	12	113.0% (90.30 to 141.31)

Mean total daily dose on Day 14: MR4 = 0.223 mg/kg; Prograf = 0.176 mg/kg

PK Analysis Set

Natural log values transformed back to linear scale for presentation

CI = Confidence interval

There was good correlation between AUC_{0-24} and C_{24} for MR4 and Prograf (r=0.96 and r=0.86, respectively).

The systemic exposure to tacrolimus was also evaluated using dose normalised AUC_{0-24} (dose normalised to dose of 0.1 mg/kg), and is presented in Synopsis Table 2.

Synopsis Table 2: Equivalence Comparison of Dose Normalised Systemic Exposure of Tacrolimus Administered as MR4 and Prograf®

	Mean		Ratio (90% CI)
	MR4	Prograf	MR4: Prograf
Day 1 PK Parameters			
AUC_{0-24}	171.12	241.58	70.8% (31.92 to 109.75)
$ln(AUC_{0-24})$	140.83	181.92	77.4% (45.35 to 132.15)
Day 3 PK Parameters			
AUC_{0-24}	330.97	432.79	76.5% (24.80 to 128.15)
$ln(AUC_{0-24})$	263.63	299.77	87.9% (50.74 to 152.42)
Day 7 PK Parameters			
AUC_{0-24}	237.31	238.10	99.7% (63.88 to 135.45)
$ln(AUC_{0-24})$	222.82	191.17	116.6% (79.10 to 171.76)
Day 14 PK Parameters			
AUC_{0-24}	170.66	225.59	75.7% (43.30 to 108.01)
$ln(AUC_{0-24})$	157.14	186.38	84.3% (57.44 to 123.77)

PK Analysis Set

Data dose normalised to dose of 0.1 mg/kg

Natural log values transformed back to linear scale for presentation

CI = Confidence interval

CONCLUSIONS:

Systemic exposure to tacrolimus over the 24-hour period following the first administration of MR4 was 58% higher than that for Prograf. The mean $ln(AUC_{0-24})$ for MR4 on Days 3, 7 and 14 was 57%, 41% and 25% higher than for Prograf. There was good correlation between trough levels of tacrolimus and AUC for both MR4 and Prograf.

Dose normalised systemic exposure [$ln(AUC_{0-24})$] to tacrolimus for MR4 on Day 1 was approximately 77% compared to Prograf. On Days 3, 7 and 14 AUC_{0-24} of tacrolimus for MR4 compared to Prograf was approximately 88%, 117% and 84% respectively.

Date of Report: 2nd February 2007

SYNOPSIS

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

Title of Study: 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 Steroids in Patients Undergoing Primary Liver Transplantation

Coordinating Investigator: [redacted] Czech Republic

Investigators: [redacted]

Study Centers: Australia: [redacted] Belgium: [redacted] Brazil: [redacted] Canada: [redacted] Czech Republic: [redacted] Finland: [redacted] France: [redacted] Germany: [redacted] Spain [redacted] Ireland: [redacted] Italy: [redacted] New Zealand: [redacted] Norway: [redacted] Sweden: [redacted] Switzerland: [redacted] United Kingdom: [redacted]

Publication: Not applicable.

Study Period: 7 August 2004 (first informed consent) to 19 December 2006 (last patient, last visit)	**Phase of Development:** Phase III

Objectives: The objective of this study was to evaluate and compare the efficacy and safety of a dual MR4/steroid regimen with a dual FK506/steroid regimen in patients who underwent primary liver transplantation. The aim was to demonstrate the non-inferiority of MR4 to FK506 with regards to the primary endpoint (event rate of biopsy-confirmed acute rejection [BCAR] within the first 24 weeks post-transplantation [based on local biopsy assessment]).

Study Design: This was a multicenter, 1:1 randomized, double blind, double dummy, two arm parallel group Phase III study comparing a dual MR4/steroid regimen with a dual standard FK506/steroid regimen. Tacrolimus was administered for at least 1 year as a dual regimen in combination with steroids in both treatment arms. 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 period until the last patient had completed their 12-month visit.

Diagnosis and Main Criteria for Inclusion: Patients at least 18 years of age receiving a primary, split liver or a whole liver graft from a cadaveric donor with compatible AB0 blood type and receiving a tacrolimus-based immunosuppressive regimen after informed consent had been given.

Number of Subjects (planned and analyzed): It was planned to enroll 450 patients, 225 per treatment arm, in approximately 50 centers with a minimum of 8 and a maximum of 36 patients per centre. In order to ensure a complete number of evaluable patients in the pharmacokinetic substudy, the planned number of patients was increased in Protocol Amendment 3 to approximately 480 (240 patients per treatment arm), with a maximum of 42 patients per center. Of the 475 patients randomized to treatment, 471 (99.2%) were in the Full Analysis Set, 237 (99.2%) patients in the MR4 and 234 (99.2%) patients in the FK506 group.

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 initial MR4/MR4-Placebo dose was 0.2 mg/kg/day given orally in one dose, preferably in the morning following transplantation. If immunosuppressive therapy was started in the evening of the day of transplantation, 0.1 mg/kg/day was to be administered. All subsequent doses were taken once daily in the morning only. The initial FK506/FK506-Placebo dose was 0.1 mg/kg/day given orally in two equal doses (0.05 mg/kg twice daily), starting in the morning or in the evening following transplantation. 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.

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.

An intravenous (i.v.) bolus of up to 500 to 1000 mg methylprednisolone (or equivalent) was given perioperatively. A post-operative steroid taper for ≤ 5 days according to local center practice was allowed. Oral prednisone (or equivalent) was administered up to Day 14, 15 to 20 mg/day; Days 15 to 42, 10 to 15 mg/day; thereafter, 0 to 10 mg/day.

Lot Numbers:
MR4 Active: 0.5 mg - [redacted]; 1 mg – [redacted] 5 mg – [redacted]
MR4 Placebo: 0.5 mg – [redacted] 1 mg – [redacted] 5 mg – [redacted]
FK506 Active: 0.5 mg – [redacted] 1 mg – [redacted]; 5 mg – [redacted]
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 (based on local biopsy assessment). Secondary endpoints were: event rate of patients with biopsy-proven acute rejection within the first 12 months following transplantation; incidence of 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; overall frequency of 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; and patient and graft survival within the first 24 weeks and 12 months following transplantation. 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 15%. 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 475 patients randomized to treatment, 471 (99.2%) were in the Full Analysis Set, 237 (99.2%) patients in the MR4 and 234 (99.2%) patients in the FK506 group. The Per Protocol Set included 360 (75.8%) patients, 182 (76.2%) patients in the MR4 and 178 (75.4%) patients in the FK506 group. In total, 165 (35.0%) patients prematurely discontinued the study medication. In the MR4 group, 87 (36.7%) patients were withdrawn, 59 (24.9%) patients due to adverse events. In the FK506 group 78 (33.3%) patients prematurely discontinued treatment, 58 (24.8%) patients due to adverse events.

Demographics:

The treatment groups were well balanced with regard to basic demographics and primary diagnoses.

Study Drug Exposure:

The initial dose of MR4 was double that of FK506 as defined in the protocol. The higher initial dose in the MR4 arm was maintained throughout the study, even though subsequent doses were adjusted based on the clinical situation in each patient and on pre-defined target whole blood tacrolimus trough level ranges. This difference between MR4 doses and FK506 doses became smaller over time. In the early period following initiation at two different doses, whole blood tacrolimus trough levels were generally higher in the MR4 arm; however, throughout the study, whole blood tacrolimus trough levels were generally comparable for the MR4 and FK506 treatment groups.

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:

Primary Endpoint: Event Rate of Patients with Local Biopsy-confirmed Acute Rejection within the First 24 Weeks

Per Protocol Set		
	FK506 (N=178)	**MR4 (N=182)**
Event rate for biopsy-confirmed acute rejection (primary endpoint)	33.7%	36.3%
Treatment difference† 95% confidence intervals p-value‡	2.6% -7.3%, 12.4% 0.512	
Full Analysis Set		
	FK506 (N=234)	**MR4 (N=237)**
Event rate for biopsy-confirmed acute rejection (primary endpoint)	29.3%	32.6%
Treatment difference† 95% confidence intervals p-value§	3.3% -5.7%, 12.3% 0.354	

† Rate of MR4 arm minus the rate of the FK506 arm

‡ Wilcoxon Gehan test for a difference between treatments over 24 weeks

Source: Tables 13.5.1.2.2.2 and 13.5.2.2.2.2

In the Per Protocol Set, the local biopsy-confirmed acute rejection event rates (Kaplan-Meier analysis) were 36.3% (MR4) and 33.7% (FK506). The difference in the event rates (MR4 minus FK506) was 2.6% with 95% confidence intervals for the difference of [-7.3%, 12.4%]. The confidence interval for the difference between the treatment arms was within the pre-defined non-inferiority margin of 15%, demonstrating non-inferiority of MR4 versus FK506. The results for the Full Analysis Set were similar to the results of the Per Protocol Set, supporting the finding of non-inferiority of MR4 versus FK506.

The 12-month incidence and event-rates of biopsy confirmed acute rejection episodes were similar to the 6-month results and were comparable for both treatment groups. This was the case for both analysis sets. The difference in the event rates (MR4 minus FK506) confirmed the findings of the 24-week analysis, with the 95% confidence intervals for both analysis sets being within the pre-defined non-inferiority margin of 15%, demonstrating non-inferiority of MR4 versus FK506.

The incidence of local biopsy confirmed acute rejections in the MR4 and FK506 groups was comparable (37.9% and 35.4%) for the Per Protocol Set as well as for the Full Analysis Set (29.5% and 26.9%).

The 12-month patient survival rates in the Full Analysis Set were comparable in the MR4 and FK506 groups (89.2% and 90.8%) as well as the graft survival rates (85.3% and 85.6%).

The 12-month difference [95% CI] between MR4 and FK506 in the efficacy failure rate was 0.8% [-9.2% to 10.8%] in the Per Protocol Set. In the Full Analysis Set, the difference [95% CI] between MR4 and FK506 in efficacy failure rate was 1.0% [-10.0% to 8.0%].

Safety Results:

The most frequently reported adverse events were consistent with the established safety profile for systemic tacrolimus. Metabolism and nutrition disorders, infections and infestations and gastrointestinal disorders were the most frequently affected system organ classes, with hypertension, anaemia, renal insufficiency, diarrhoea and hyperglycaemia being the most frequently reported MedDRA preferred terms. There were a number of adverse events with a difference in incidence between MR4 and FK506 associated with a p-value < 0.05 (Fisher's exact test). Therapeutic drug monitoring analyses and scar pain were reported more frequently following

administration of MR4; staphylococcal infections, intra-abdominal haemorrhage, hepatocellular damage and hepatitis NEC (MedDRA high level term), hepatitis, biloma were more frequently reported following administration of FK506. The incidence of all these events was relatively low, with 12 patients (5.1%) or less being affected with the exception of hepatocellular damage and hepatitis NEC (MedDRA high level term) which was reported by 37 (15.8%) patients in the FK506 arm and 20 (8.4%) patients in the MR4 arm.

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 renal and urinary disorders were the most frequently affected system organ classes. The incidence of adverse events was generally comparable between the MR4 and FK506 arms, with the exception of the MedDRA preferred term of hyperglycaemia and the MedDRA higher level term of confusion and disorientation which were significantly higher in the FK506 arm compared to the MR4 arm (p=0.031 and p=0.044; Fisher's exact test).

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 gastrointestinal disorders NEC in the FK506 group (2.1%) compared to the MR4 group (0%) (p = 0.030; Fisher's exact test) and a higher incidence of renal failure and impairment in the MR4 group (12.2%) compared to the FK506 group (6.0%) (p = 0.024; Fisher's exact test).

49 patients died during the first 12 months post-transplant, 21 patients during the study and 28 patients following discontinuation from the study. The number of deaths during the study was comparable for both MR4 and FK506 treatment groups, and there were no clinically relevant differences in the cause of death between the treatment groups. The most common cause of death during the study was multi-organ failure, and the most common cause of death following withdrawal from the study was sepsis.

A total of seven deaths were considered to have a possible or probable relationship to study drug; four deaths in the MR4 arm and three deaths in the FK506 arm.

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. 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: MR4 was non-inferior to FK506 for the event rate of biopsy-confirmed acute rejection at 24 weeks (primary endpoint) and 12 months post-transplant, based on the pre-defined non-inferiority margin of 15%. This was confirmed following central biopsy review.
The incidence of acute rejections, corticosteroid-resistant acute rejections and the histological grade of acute rejections were comparable for MR4 and FK506. Patient and graft survival were comparable for MR4 and FK506, and were consistent with previous experience. Efficacy failure rates were also comparable for MR4 and FK506.
MR4 had a similar safety profile to that established for FK506. In particular, the incidence of renal-related adverse events, diabetes mellitus and other glucose metabolism disorders, neurological adverse events, hypertension, vascular disorders and malignancies was comparable for MR4 and FK506.
There were no differences between treatment groups associated with a p-value of < 0.05 in the overall incidence of death, causally-related serious adverse events, or adverse events that led to discontinuation.
Differences between treatment groups associated with a p-value < 0.05 were observed for several events, some more frequently observed with FK506 (staphylococcal infections, intra-abdominal haemorrhage, hepatocellular damage and hepatitis NEC and biloma) and some more frequently observed with MR4 (therapeutic drug monitoring analyses and scar pain).
Clinical laboratory data supported the conclusion of similar safety profiles between MR4 and FK506, with renal function, blood glucose levels, hepatic function and serum lipids being comparable between the two formulations.
This double blind study demonstrated that MR4 is safe and efficacious when used as primary immunosuppressant in *de novo* liver transplantation.

Date of Report: 21 May 2008