Australian Government

Department of Health and Ageing

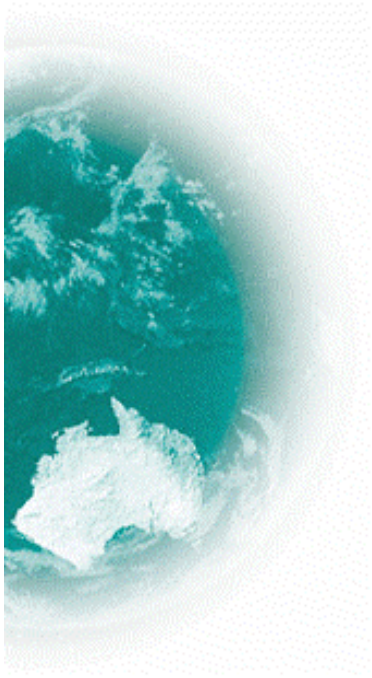
Therapeutic Goods Administration

Australian Public Assessment Report for Tacrolimus

Proprietary Product Name: Prograf-XL

Submission No: PM-2008-03783-3-2

Sponsor: Janssen-Cilag Pty Ltd



May 2010

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I. Introduction to Product Submission

Submission Details

Type of Submission	New Dosage Form
Decision:	Approved
Date of Decision:	19 March 2010
Active ingredient(s):	Tacrolimus
Product Name(s):	Prograf-XL
Sponsor's Name and Address:	Janssen-Cilag Pty Ltd Locked Bag 2070 North Ryde NSW 167
Dose form(s):	Modified release capsules
Strength(s):	0.5, 1 and 5 mg
Container(s):	Blister packs
Pack size(s):	0.5 and 5 mg: 30, 50 1 mg: 30, 50, 60 & 100
Approved Therapeutic use:	as an adjunct to liver, kidney, lung or heart allograft transplantation in adults and children.
Route(s) of administration:	Oral
Dosage:	Starting dose 0.075-0.30 mg/kg/day as a single morning dose

Product Background

Janssen-Cilag currently has registered tacrolimus (Prograf) immediate release (IR) capsules 0.5, 1 and 5 mg and concentrated injection 5 mg/1 mL. The present application seeks to register prolonged release (XL) capsules in the same dosage strengths as the IR capsules, for the same indications (adjunct to liver, kidney, lung or heart allograft transplantation). The total daily dose of the XL capsules is proposed to be the same as approved for the IR capsules, but the XL capsules will be given as a single morning dose, whereas the IR capsules are given in two divided doses (morning and evening).

The starting dose is 0.075-0.30 mg/kg/day for adults and 0.15-0.30 mg/kg/day for children, corresponding, for example, to 5-20 mg/day for a 67 kg adult and 1.5-3.0 mg/day for a 10 kg child. Therapeutic drug monitoring is considered essential, with the aim of maintaining whole blood tacrolimus trough concentrations within specified 2 to 4-fold ranges (within the overall range 5-20 ng/mL) depending upon the type of transplant.

Tacrolimus is currently registered in Australia in 2 different dosage forms, Prograf immediate release oral capsules (0.5, 1 and 5 mg) and Prograf concentrated injection for the use as an adjunct to liver, kidney, heart and lung allograft transplantation in adults and children. In this submission, the sponsors seek approval of the new dosage form, Prograf-XL prolonged release oral capsules (0.5 mg, 1 mg, 5 mg), administered once daily for the same indication. Prograf-XL can be initiated in *de novo* patients immediately following organ transplantation or by conversion from twice daily Prograf therapy on a 1mg:1mg conversion ratio.

Regulatory Status

The data for the established formulation of tacrolimus (Prograf capsules) provide the basis for the efficacy of the prolonged-release formulation of tacrolimus. Tacrolimus is currently approved by the TGA in 2 different dosage forms, Prograf immediate release oral capsules (0.5, 1 and 5 mg) and Prograf concentrated injection for use as an adjunct to liver, kidney, heart and lung allograft transplantation in adults and children. Both tacrolimus dosage forms were first registered on the Australian Register of Therapeutic Goods in July 1997.

The first Marketing Authorisation for Prograf in the European Union (EU) was granted in 1994 by the United Kingdom. Subsequently, Prograf has been approved and marketed throughout the European Union except Estonia, Latvia and Lithuania. It is indicated for prophylaxis of transplant rejection in kidney, liver and heart allograft recipients and the treatment of allograft rejection resistant to treatment with immunosuppressive drugs.

Prograf XL has been approved in various EU countries (for prophylaxis of transplant rejection in adult kidney or liver allograft recipients, and treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.) and Canada (for kidney transplant prophylaxis), as well as in Argentina, Brazil, Chile, Colombia, Costa Rica, El Salvador, Guatemala, Mexico, Paraguay, Peru, Uruguay, Hong Kong, Japan, Korea, Taiwan, Ukraine, Macau, Armenia, Dominica and Russia,. The data packages submitted in Australia, EU, Canada and USA are essentially identical. In addition to the clinical study reports for Prograf-XL submitted in all countries, the EU package submitted in this application also included past study reports of tacrolimus with other formulations such as tacrolimus intravenous formulation and Prograf. These data have been cross-referenced in the data package submitted in Canada and the USA.

The US New Drug Applications (NDAs) for Prograf XL (tacrolimus extended release formulation) for prevention of rejection after solid organ transplantation was withdrawn by the US sponsor as of 30 January 2009, after considering the clinical challenges in performing additional studies necessary to meet FDA expectations to support approval.

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The drug substance is identical to that used in the registered dose forms.

Tacrolimus is practically insoluble in water (about 0.001%) but it is dissolved in ethanol during manufacture of the drug product, so particle size and polymorphic form are not relevant to the manufacture of the product.

Drug Product

Tacrolimus is mixed with ethylcellulose, hypromellose and lactose to form intermediate sustained release granules, which are milled to a specified particle size, blended with lactose and magnesium stearate then filled into hard gelatin capsule shells. The sustained release character of the granules is imparted by the ethylcellulose, which controls the rate of permeation of water into the granules. The three strengths of capsule are direct scales, manufactured by filling different amounts of the sustained release granules and other excipients into capsule shells.

Appropriate routine quality control dissolution tests are employed and appropriate limits are applied, based on results observed for a large number of batches used in Phase 2/3 clinical studies. An *in vitro-in vivo* correlation has not been established.

Two new impurities have been detected in Prograf-XL capsules that have not been observed in the registered products. Both are formed during manufacture of the intermediate granules. The limits applied to those adducts comply with International Conference on Harmonization (ICH) requirements.

The capsules are packaged in PVC/PVDC/Al blister packs, enclosed in an aluminium foil pouch together with desiccant. The agreed shelf life is 3 years below 25°C, which may include up to one year's storage after removal of the blister packs from the aluminium pouch.

Biopharmaceutics

Tacrolimus is a BCS Class II drug (high permeability, low solubility).[1] The absolute bioavailability of tacrolimus from Prograf immediate release capsules is 20-25%. Tacrolimus binds strongly to erythrocytes, so the drug is measured in whole blood rather than plasma.

Tacrolimus is extensively metabolised in the liver and intestinal wall, primarily by CYP-3A4. Several metabolites have been identified, but only one has immunosuppressive activity similar to tacrolimus. Blood levels of the metabolites are low, therefore they do not contribute significantly to the pharmacological activity of tacrolimus.

The elimination half life of tacrolimus is long and variable: approximately 43 hours in healthy subjects, 11-16 hours in transplant recipients.

Twelve bioavailability studies were submitted with the present application.

Single dose bioavailability studies

Study 99-0-060 showed that a prototype Prograf-XL 5 mg capsule formulation was bioequivalent in terms of the area under the curve (AUC) to the registered Prograf 5 mg capsule but had a 66% lower maximal plasma concentration (C_{max}). The C_{max} comparison is not particularly relevant because, in clinical practice, the Prograf dose would be divided into two doses given 12 hours apart.

Studies 00-0-076, 00-0-077 and 00-0-078 compared single doses of the 0.5, 1 and 5 mg Prograf-XL capsules proposed for registration with equal doses of the corresponding Prograf capsules. Although the 0.5 mg study demonstrated bioequivalence in terms of AUC, the other two studies showed that the Prograf-XL capsules had an approximately 30% lower AUC than the Prograf capsules. The sponsor has not been able to provide a convincing explanation for this anomaly. The three strengths of Prograf capsules have been shown to be bioequivalent at equal dose, and the three strengths of Prograf-XL capsules would be expected to be bioequivalent at equal dose given that their formulations are direct scales. The three studies used different dose levels of tacrolimus (1.5, 3 and 5 mg, respectively) which might in some way account for the different findings but solubility-limited absorption, for example, would be expected to affect the immediate release product more than the controlled release product. It is unlikely that the inconsistent bioavailability results are due to batch-to-batch variation in the Prograf-XL capsules because these three studies all used the same batch of intermediate granules.

[1] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

The results of studies 99-0-060 and 00-0-078 are directly contradictory: the former showing bioequivalence (with respect to AUC) of Prograf-XL and Prograf 5 mg capsules, the latter showing that the Prograf-XL capsules have an approximately 30% lower AUC.

Multiple dose studies

Two studies directly compared the 1 mg Prograf-XL capsules with the same daily dose of 1 mg Prograf capsules at steady state under the conditions of administration that would be applied in clinical practice, that is, once daily for Prograf-XL versus twice daily for Prograf. This is the most appropriate way of comparing the two products. Study FG-506-04-21 used a daily dose of 2 mg, but gave blood concentrations below normal therapeutic levels. Therefore, an additional study, Study FG-506-04-25, was performed using a daily dose of 4 mg.

The latter study is considered to be the most definitive study submitted. It demonstrated that the two dosage regimens are bioequivalent in terms of AUC and similar in terms of the trough serum concentration (C_{min}), but that Prograf-XL gives a 26% lower C_{max} than Prograf.

Again, the results of the two multiple dose studies are not entirely consistent, with a suggestion that the bioavailability of the Prograf-XL capsules is reduced relative to the Prograf capsules at higher dose (compared with the single dose studies, discussed above).

A possible confounding factor that could, in part, explain differences in results between the multiple dose and single dose studies is the significant diurnal effect on tacrolimus bioavailability; the same dose of Prograf capsules gives a lower AUC when administered in divided doses compared to administration as a single morning dose.

Food effect studies

Two food effect studies (01-0-123 and 02-0-153) showed that food causes a moderate reduction in both the rate and extent of absorption of tacrolimus from Prograf-XL capsules. Based on these studies, the product information (PI) recommends that the capsules be taken on an empty stomach, at least one hour before and 2-3 hours after a meal. There is no evidence of dose-dumping in these studies.

Other studies

Study FG-506E-04-31 assessed the effects of administering the Prograf-XL capsule contents as an aqueous suspension, either orally or via a nasogastric tube. Administration as an oral suspension did not affect the AUC but increased the rate of absorption slightly. Administration via a nasogastric tube also increased the rate of absorption, but decreased the AUC by about 17%.

Study 02-0-148 assessed diurnal effects on tacrolimus bioavailability. Administration in the evening reduced the AUC of both Prograf and Prograf-XL capsules by about 35% compared to administration in the morning. The rate of absorption of tacrolimus from Prograf capsules was decreased considerably (C_{max} reduced by about 60%) in the evening. There was a much smaller effect on the rate of absorption of tacrolimus from Prograf-XL capsules. The PI recommends that Prograf-XL capsules be taken in the morning.

Study FJ-506E-0001 showed that tacrolimus bioavailability is increased in Japanese subjects compared to Caucasians, although the effect is only moderate when adjusted for body weight.

Study FJ-506E-0002 assessed dose linearity of Prograf-XL capsules in Japanese subjects. Linearity of C_{max} and AUC was demonstrated after single doses in the range 1.5-10 mg (3 x 0.5 mg, 4 x 1 mg and 2 x 5 mg). This suggests also that the three capsule strengths are bioequivalent (at equal dose).

Justification for non-supply of bioequivalence data

No formal justification was provided for not performing a study to show that the three strengths of Prograf-XL capsules are bioequivalent at equal dose. However, the three strengths contain the same

modified release granules, mixed in the same ratio with the same excipients, and all have essentially identical dissolution profiles over the pH range 2-6. It is difficult to conceive, therefore, how the three strengths could not be bioequivalent at equal dose.

Quality Summary and Conclusions

There are no objections in respect of chemistry, manufacturing and controls to registration of Prograf-XL capsules.

The inconsistent results obtained in the various bioavailability studies are of some concern. The sponsor attributes these inconsistencies to the large inter- and intra-subject variability of tacrolimus pharmacokinetics, including the effects of genetic polymorphism and circadian variation. Although large variability may make it difficult to obtain statistically significant results, it is not clear how it can account for clear-cut differences between studies, for example, 90% confidence intervals for AUC of 83-103% in Study 00-0-076 compared to 66-76% in Study 00-0-077.

The company's arguments concerning the inconsistent bioavailability results were referred to the Delegate.

III. Nonclinical Findings

Introduction

The pharmacological, pharmacokinetic and toxicological profile of tacrolimus has been established during the development of Prograf. Thus, no additional nonclinical studies with the prolonged-release tacrolimus formulation (Prograf-XL) have been provided. In addition, according to the sponsor, "most of the nonclinical information has now been superseded by clinical data". The updated nonclinical overview provided for Prograf-XL was based on the expert report (1993) provided for Prograf/Prograft national registration procedures and published information becoming available post-dossier submission.

Pharmacokinetics

Dosage and Administration

In the draft Product Information document provided, it was noted that the recommended oral daily dose of Prograf should be administered as two divided doses, while the same dose of Prograf-XL should be administered once daily.

According to the sponsor's Clinical Overview, "in comparison with Prograf, tacrolimus administered as MR4 [Prograf-XL], results in an extended oral absorption profile with slightly lower C_{max} values. In addition, administration of total dose once daily for MR4 did not reportedly indicate any signs of dose dumping (that is, immediate release of tacrolimus from total dose resulting in high C_{max}) either in de novo transplant recipients or those converted from Prograf to MR4."

According to the sponsor, 12 bioequivalence studies have been submitted in the current data package for Prograf-XL. These studies reportedly examined the administration of Prograf/Prograf-XL at single dose and at steady state under fasting and fed condition and concluded that "Prograf-XL provides equivalent systemic exposure [defined by AUC] to twice daily Prograf."

Toxicology

Relative exposure and safety profile

On the basis of bioequivalence of the two formulations (Prograf and Prograf-XL) when administered at the same total daily dose, the extended oral absorption profile, and reported lower

C_{max} values for Prograf-XL, no remarkable alterations in either the toxicological profile or animal:human safety margins of tacrolimus are expected. Thus, no additional safety concerns are anticipated with the modified-release tacrolimus formulation. However, this is subject to confirmation of bioequivalence and the reported absorption profile of Prograf-XL by the clinical evaluator.

Nonclinical Summary and Conclusions

Subject to the confirmation of bioequivalence of the two formulations (Prograf and Prograf-XL) and the reported Prograf-XL absorption profile by the clinical evaluator, there are no nonclinical objections to the registration of the modified-release tacrolimus formulation.

IV. Clinical Findings

Introduction

The safety and efficacy of tacrolimus, administered twice daily as Prograf immediate release capsules for kidney, liver, heart and lung transplantation are well established and form the basis for the clinical trial development program for prolonged release Prograf-XL which allows once daily dosing. Prograf-XL was developed to assist patient adherence which is critical to long-term graft/ patient outcomes.

There were 12 bioequivalence studies which evaluated the systemic exposure of Prograf-XL compared with Prograf at single dose and at steady state under fasting and fed conditions. There were six conversion studies in stable liver, kidney and heart transplant patients, in which the patients were converted from twice daily Prograf to once daily Prograf-XL on a 1mg:1mg daily dose basis. Two Phase II studies in *de novo* liver and kidney transplant patients compared incidence of biopsy-confirmed acute rejection rates between Prograf-XL and Prograf over a 6-week study period. Three large Phase III studies **(02-0-158, FG-506E-11-03 and FG-506E-12-03)** compared the efficacy and safety of Prograf-XL with Prograf over a 12-month treatment period in kidney and liver transplant patients. Prograf-XL is designated as MR4 in the clinical studies.

All the studies were conducted in accordance with Good Clinical Practice (GCP) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Additionally, all regulatory approvals required by the regulatory authorities in each participating country were obtained.

Pharmacokinetics

Overview

Forty one studies, involving 1407 subjects, examined the pharmacokinetics (PK) of tacrolimus. Seventeen studies were conducted in 292 healthy subjects, 8 studies in 766 kidney transplant patients, 6 studies in 230 liver transplant patients, 4 studies in 107 heart transplant patients and 2 studies in 12 patients with liver dysfunction. Tacrolimus whole blood concentrations were determined using a validated liquid chromatography-mass spectrometer (LC/MS/MS) method. In some earlier studies tacrolimus levels were determined using a commercial enzyme-linked immunosorbent assay (ELISA).

Absorption, distribution, metabolism and elimination

Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

There were no reports provided on plasma protein binding, hepatic metabolism and drug interaction studies or studies using other human biomaterials.

Dissolution studies

The dissolution profiles of 5 mg, 1mg and 0.5 mg capsules of MR4 were examined in study **RAR040319**. Tests were performed at pH 2.0, 4.5 and 6.0 with sampling times at 1, 2, 6, 12 and 24 hours. The dissolution profiles for the 3 strengths of capsule were visually similar in the three media. The f_2[2] values, calculated using mean dissolution rates, were sufficiently high (77 to 96) and satisfied the acceptance criteria of > 50.

Using the method described in the previous study the dissolution profiles of the 5, 1 and 0.5 mg capsules of MR4 were examined (**Study Report No. RAR040320**) when the corresponding capsule amount to a 5 mg dose of tacrolimus was introduced to each vessel. The dissolution profiles for the three different capsule strengths (when given as 5 mg dose) were visually similar and the calculated f_2 values were higher than the acceptance criteria of $\geq$50 (f_2 ranged from 78.1 to 99.5).

Bioavailability in healthy subjects

A three-way treatment (0.01 mg/kg intravenous (IV) infusion over 4 hours, five 1 mg capsules and one 5 mg capsule), three-period, randomised block cross-over study (**Study No. 91-012**) examined the absolute bioavailability of tacrolimus capsules and evaluated the bioequivalence of five 1 mg dose and one 5 mg capsule in 27 healthy subjects (aged from 19 to 45 years). The subjects were randomly assigned into one of six dosing sequences with 6 subjects in each group. Treatments were separated by a 14-day wash-out period and blood samples were collected up to 72 hours post dosing for pharmacokinetic analysis. Based on the whole-blood AUC_t (area under the curve to last-time point with quantifiable tacrolimus concentration) the estimated bioavailability for the 5 x 1 mg regimen was 18% with 95% confidence intervals (CIs) of 14 – 23.2%, whereas the estimated bioavailability for the 1 x 5 mg regimen was 14% with 95% CIs of 10.3 – 18.7%; the estimated difference in bioavailability between the 5 x 1 mg and the 1 x 5 mg regimens was -22% with 95% CIs of -42.1 to 2.1. Although plasma data reached the lower limit of quantitation within a few hours of dosing and the area under the concentration time curve to infinite time (AUC_∞) could not estimated with confidence, based on the whole-blood AUC_∞, the estimated bioavailability for the 5 x 1 mg regimen was 17.4% with a 95% CI of 14.5 – 20.9%, whereas, the estimated bioavailability for the 1 x 5 mg regimen was 14.4% with a 95% CI of 11.7 – 17.7%. The estimated difference in bioavailability between the 5 x 1 mg and the 1 x 5 mg regimens was -17.1% with a 95% CI: -32.5 to 0.8. Using bioavailability estimates based on both AUC_t and AUC_∞, Schuirmann's two one-sided t-tests failed to reject the null hypothesis that the capsules differed in bioavailability by 20% or more at the significance level of 5%. The study's authors suggest that the failure to demonstrate bioequivalence may in part result from the high degree of inter- and intra-subject variability seen in this study. The C_{max} for the 5 x 1 mg regimen was significantly higher than for the 1 x 5 mg regimen using whole blood data (36.1 versus 29.5 ng/mL, p = 0.033) but not for the plasma data (1.32 versus 1.07 ng/mL, p = 0.09). There were no significant differences in T_{max} for the two dose regimens which ranged from 1.31 to 1.47 hours (p = 0.10) for the whole blood samples and 1.38 to 1.60 for the plasma samples (p = 0.22). Based on the whole blood data, the mean half life derived from the IV infusion data was 21.2 ± 8.5 hours, total body clearance (CL) was 0.043 ± 0.16 L/hr/kg and the volume of distribution (V) was 0.88 ± 0.31 L/kg. Although bioequivalence was not demonstrated between the 5 x 1mg and 1 x 5mg regimens these differences are unlikely to be clinically significant as therapeutic drug monitoring is routinely used in patients receiving tacrolimus, particularly during the early post transplant period and dose adjustments can easily be made.

The pharmacokinetics and metabolism of ^{14}C labelled tacrolimus after intravenous and oral administration in 6 healthy male volunteers, aged 49 to 67 years, was examined in an open, non-

[2] f_2 - Similarity factor - if there is absolute similarity between 2 formulations then f2=100

blinded, randomised crossover study (FG-4-01). Blood samples and urine were collected predose and up to 264 hours post dose. Faeces was collected pre-dose and up to Day 12 of the trial. Two methods were used to determine ^{14}C content: ELISA and liquid scintillation counter (LSC) with the lower limit of quantification (LLQ) for ELISA method being, 0.05 ng/mL for plasma and blood, 0.005 ng/0.1g faeces and 0.005 ng/0.1mL urine. The LLQ for the LSC method was 7.86 disintegrations per minute (dpm)/100 µl for whole blood, 9.63 dpm/100 µl for plasma, 10.95 dpm/100 mg faeces and 9.28 dpm / mL urine. Following single IV or oral dosing of C^{14}-tacrolimus between 78 and 95% of the administered dose were recovered in faeces and urine within 264 hours of administration. Elimination was primarily in the faeces (urine < 3%).

Bioavailability in target population

An open-label, 3 centre study (**FK506-7**) characterised the pharmacokinetics of intravenous tacrolimus and determined the bioavailability of oral tacrolimus capsules in 16 liver transplant patients (6 female) aged from 33 to 65 years. All patients in the study were treated with an initial intravenous dose of tacrolimus followed by the oral regimen. The intravenous dose was 0.05 mg/kg administered over a 12 hour period. Oral tacrolimus was administered at a dose of 0.15 mg/kg. Based on the whole blood concentration, mean elimination half-life was 11.7 hours (range: 6.1 - 20.9 hours) and the volume of distribution averaged 64.6 litres or 0.85 l/kg when normalised to body weight. The total body clearance averaged 4.05 l/hr, indicating low hepatic extraction. Based on plasma concentration, elimination half life averaged 6.5 hours (range 2.7 - 13.3 hours), the volume of distribution averaged 1094.5 litres or 16.1 l/kg when normalised to body weight. The total body clearance averaged 150.1 l/hr. Steady state was achieved within 3 days for most patients receiving the oral regimen. The bioavailability of tacrolimus averaged 21.8% (range 13.7 - 38.4%) based on whole blood and 30.4% (range 13.0 - 64.4%) based on plasma concentrations.

Effect of Food

The effect of food on the absorption of tacrolimus administered as a modified-release dosage form (MR4) was examined in a randomised, open-label, single dose, three-period, six sequence crossover study (**01-0-123**) in 21 healthy male volunteers aged 24 to 51 years. Subjects were randomised to one of six possible treatment sequences as shown in Table 1. In each period, subjects were administered 5 mg tacrolimus as: the MR4 capsule following a 10-hour fast, the MR4 capsule following a high-fat breakfast, or the commercially available Prograf capsule following a 10-hour fast. Administration of MR4 immediately following a high fat meal significantly reduced the rate and extent of tacrolimus absorption relative to the fasted state. The mean C_{max}, AUC_{0-24}, AUC_t and AUC_∞ were reduced by approximately 25% in the presence of food. The 90% confidence intervals (MR4fed/MR4fasted) for the natural log of the C_{max} (lnC_{max}), $lnAUC_{0-24}$, $lnAUC_t$, and $lnAUC_\infty$ were not contained within the level of bioequivalence (80%-125%). The presence of food also delayed median T_{max} from 2 hours post MR4 dosing in the fasted state to 3.5 hours in the fed state (p=0.0335, Wilcoxon signed-rank test). Despite the differences in the rate and extent of absorption, tacrolimus declined with an elimination half life of approximately 35 hours, regardless of formulation or dosing conditions.

Table 1: Report No. 2002010888-1 US / Study No. 01-0-123

	Period 1	Period 2	Period 3
Group A	MR4/fasting	MR4/high fat breakfast	Prograf/fasting
Group B	MR4/high fat breakfast	Prograf/fasting	MR4/fasting
Group C	Prograf/fasting	MR4/fasting	MR4/high fat breakfast
Group D	MR4/fasting	Prograf/fasting	MR4/high fat breakfast
Group E	MR4/high fat breakfast	MR4/fasting	Prograf/fasting
Group F	Prograf/fasting	MR4/high fat breakfast	MR4/fasting

The effects of meal time on the absorption of tacrolimus administered as a modified-release dosage form to 24 healthy male volunteers, aged 18 to 48 years, was examined in a single-centre, randomised, open-label, single-dose, four-treatment, four-period, four-sequence (block design) crossover study (**02-0-153**). Subjects were randomised to one of four treatment sequences as shown in Table 2. Each study period lasted 6 days and there was a 10 to 20 day washout between doses. Administration of MR4 1 hour prior to a high fat breakfast delayed the median T_{max} from 2 hours in the fasting state to 4 hours ($p<0.0001$) and decreased C_{max} by approximately 18%. By contrast, AUC_{0-t} and AUC_{0-inf} were bioequivalent under the two conditions and the median time to maximum exposure was observed at 2 hours post-dose for both treatments ($p=0.7432$). Administration of MR4 immediately after consuming a high-fat breakfast statistically significantly reduced both maximum concentration and systemic exposure by approximately 26% to 28% relative to the mean corresponding fasting values (C_{max} $p=0.0001$, AUC_t $p<0.0001$, and AUC_∞ $p<0.0001$). MR4 administration 1.5 hours after consuming a high-fat breakfast significantly reduced both maximum concentration and systemic exposure up to 36% relative to the corresponding mean fasting values (C_{max} $p=0.0003$, AUC_t $p<0.0001$, and AUC_∞ $p<0.0001$). MR4 administered 1.5 hours after consuming a high-fat breakfast also delayed the median T_{max} from 2 hours in the fasting state to 3 hours ($p<0.0001$). Despite differences observed among treatments in the rate and extent of exposure, the elimination half-life ($t_{1/2}$)was similar for all treatments ($t_{1/2}$ ± standard deviation [SD]: 36.6 ± 4.14 hours [Treatment A]; 35.2 ± 3.92 hours [Treatment B]; 36.0 ± 3.95 hours [Treatment C]; and 36.2 ± 4.61 hours [Treatment D]). Relative to fasting conditions, food affected the pharmacokinetics of a 5mg dose of MR4 when administered immediately or 1.5 hours after consuming a high fat breakfast. Systemic exposure to tacrolimus was greater when MR4 was administered under fasting conditions or 1 hour prior to breakfast than it was when administered with breakfast or 1.5 hours after consumption of a meal.

Table 2: Study Report No. 2003063753 / Study No. 02-0-153

Study Drug Sequence Schedule

Treatment Period:	Period 1	Period 2	Period 3	Period 4
Sequence	Treatment	Treatment	Treatment	Treatment
I	A	D	B	C
II	B	A	C	D
III	C	B	D	A
IV	D	C	A	B

Treatment A: MR4 administered under fasting conditions.
Treatment B: MR4 administered 1 hour prior to a high-fat breakfast.
Treatment C: MR4 administered immediately after consumption of a high-fat breakfast.
Treatment D: MR4 administered 2 hours† after consumption of a high-fat breakfast.

Effect of time of dosing on pharmacokinetics

Tacrolimus whole blood concentration-time profiles following a single morning dose versus a single evening dose of MR4 and following a single morning dose versus a single evening dose of Prograf, in 24 normal healthy males aged 19 to 44, were examined in an open-label, single-dose, 4-

treatment, 4-period, 4-sequence (block design) crossover study. Subjects were randomised to 1 of 4 treatment sequences as shown in Table 3. Each treatment period lasted 6 days and there was a 10 to 20 day washout between doses. Each subject received 1 dose of study drug (MR4, 5 mg or Prograf, 5 mg) on the first day of study periods 1, 2, 3, and 4. MR4 PM dosing significantly reduced both maximum concentration and tacrolimus exposures by approximately 10% and 35%, respectively (C_{max} $p<0.0001$, AUC_t $p<0.0001$, and AUC_∞ $p<0.0001$). The 90% confidence intervals around the geometric mean ratios (MR4 PM dose/MR4 AM dose for lnC_{max}, $lnAUC_t$, and $lnAUC_\infty$) were not within the level of bioequivalence and therefore the study's authors concluded that tacrolimus underwent a diurnal absorptive effect. A similar reduction in tacrolimus exposures (approximately 35%, AUC_t $p<0.0001$ and AUC_∞ $p<0.0001$) was observed following Prograf PM dosing relative to AM dosing. However, the reduction in maximum concentration (approximately 60%, C_{max} $p<0.0001$) was more pronounced than for MR4. The 90% confidence intervals around the geometric mean ratios (Prograf PM dose/Prograf AM dose for lnC_{max}, $lnAUC_t$, and $lnAUC_\infty$) were not bioequivalent and therefore a diurnal absorptive effect was also concluded for Prograf. The proposed product information recommends that Prograf-XL (MR4) be administered in the morning.

Table 3: Report No. 2003063443 / Study No. 02-0-148

Study Drug Sequence Schedule

Treatment Period:	**Period 1**	**Period 2**	**Period 3**	**Period 4**
Sequence	Treatment	Treatment	Treatment	Treatment
I	A	D	B	C
II	B	A	C	D
III	C	B	D	A
IV	D	C	A	B

Treatment A: MR4 AM dose (MR4 reference treatment).
Treatment B: MR4 PM dose (MR4 test treatment).
Treatment C: Prograf AM dose (Prograf reference treatment).
Treatment D: Prograf PM dose (Prograf test treatment).

Single dose pharmacokinetics

An open-label, randomised, three-period, three treatment crossover study (**99-0-060**) examined tacrolimus blood concentration-time profiles and comparative pharmacokinetics of tacrolimus following single oral dose administration of the current formulation (Prograf 5 mg capsule) and 2 different tacrolimus modified release formulations (MR3 and MR4 both 5 mg) in 12 male Caucasian subjects aged 20 to 46 years. Each treatment period lasted 4 days and there was at least a 10 day wash-out between each of the three treatment periods. There were six treatment period sequences with two subjects in each sequence and the dose administration order for each sequence is shown in Table 4**)**. For the MR4 and Prograf formulations the mean ratios for the log-transformed C_{max}, AUC_t and AUC_∞ were 34% (90% CI: 29 - 39) , 94% (90% CI: 82 - 107) and 97% (90% CI: 87 - 109), respectively, indicating that the MR4 and Prograf formulations had similar extents of tacrolimus exposure, however, the rate of absorption was considerably slower (ratio of T_{max} = 206%, 90% CI: 143 - 269) for the MR4 formulation. Overall, despite the low rate of absorption of the MR4 formulation the pharmacokinetic profiles of the MR4 and Prograf formulations were similar. The MR4 formulation used in this and the following clinical trials is the proposed marketing formulation.

Table 4: Report No. 2001021707-1-US/ Study No. 99-0-060

Treatment Period	Sequence 1	Sequence 2	Sequence 3	Sequence 4	Sequence 5	Sequence 6
1	Prograf®	MR-3	MR-4	Prograf®	MR-4	MR-3
2	MR-3	MR-4	Prograf®	MR-4	MR-3	Prograf®
3	MR-4	Prograf®	MR-3	MR-3	Prograf®	MR-4

An open-label, randomised, two period, two-treatment, cross-over, single-centre study (**00-0-076**) in 16 healthy male subjects aged 19 to 47 years examined the pharmacokinetics of tacrolimus following a single oral administration of 0.5 mg Prograf and 0.5 mg of the modified release formulation MR4. There was a 14-day wash-out between the two dose administrations and blood samples for pharmacokinetic determination were taken pre-dose and up to 120 hours post-dosing. The MR4 formulation had a slower rate of absorption than the Prograf (reference) formulation as indicated by its lower C_{max}, longer T_{max} and lower AUC_{0-24}. By contrast, the extent of absorption of the MR4 and Prograf formulations were similar (ratio of the log transformed AUC_{∞} = 92.6%, 90% CI: 83 – 103).

A prospective, open-label, single-dose, two-treatment, four-sequence, four-period cross over study (**00-0-077)** examined the tacrolimus blood concentration-time profiles and comparative pharmacokinetics of tacrolimus in 30 normal healthy adult males, aged 19 to 50 years, following single administrations of 3 mg tacrolimus in two dosage forms: the marketed 1 mg Prograf capsule and a 1 mg modified release (MR4) formulation. The subjects were randomly allocated to one of four treatment sequences as shown in Table 5. There was at least a 10 days wash-out between treatment periods and blood samples for pharmacokinetic analysis were taken predose and up to 120 hours post-dose in each treatment period. Although the T_{max} and $t_{1/2}$ parameters were similar for the two formulations, the log transformed mean C_{max} and AUC_{∞} values were approximately 70% (90% CI: 27 - 32) and 30% (90% CI: 66 - 76) lower, respectively, for the MR4 formulation than for the Prograf formulation; no explanation was given for the 30% lower systemic exposure to tacrolimus following MR4 (1 mg).

Table 5: Report No. 2001014216-US-1/ Study No. 00-0-077

	Period 1	Period 2	Period 3	Period 4
Sequence 1	Prograf®	Prograf®	MR-4	MR-4
Sequence 2	Prograf®	MR-4	Prograf®	MR-4
Sequence 3	MR-4	Prograf®	MR-4	Prograf®
Sequence 4	MR-4	MR-4	Prograf®	Prograf®

An open-label, randomised 2-period, 2-treatment crossover, single centre study (**00-0-078)** examined the tacrolimus blood concentration-time profiles and comparative pharmacokinetics of tacrolimus following single oral dose administrations of the 5-mg Prograf and 5-mg tacrolimus modified release formulation (MR4) in 15 healthy male subjects aged 19 to 50 years. Blood samples were collected over 120 hours after each dose pharmacokinetic analysis and there was at least a 10-day washout period between the 2 treatment periods. As in the previous study, the T_{max} and $t_{1/2}$ parameters were similar for the two formulations, but the log transformed mean C_{max} and AUC_{∞} values were approximately 67% (90% CI: 26 - 41) and 33% (90% CI: 53 - 84) lower, respectively, for the MR4 formulation than for the Prograf formulation.

A Phase I, open-label, randomised, balanced, three-period crossover study (**FG- 506-04-31**) investigated the relative bioavailability of single oral doses of capsule versus suspension formulations of MR4 in 20 healthy male subjects aged between 20 to 54 years. Subjects were randomly assigned to one of the following two treatment sequences as shown in Table 6 with a 14-

day interval between dosing periods. All subjects received MR4 at a dose level of 10 mg in each treatment period.

For the oral formulations of 10 mg MR4, the overall systemic exposure to tacrolimus, based on AUC_∞ was similar for the capsules and suspension (AUC_∞ = 350 and 334 ng.h/mL, respectively. However, maximum whole blood concentrations of tacrolimus were approximately 30% higher and occurred approximately 1 hour earlier for the oral suspension than for the capsules. For the nasogastric suspension of MR4, the overall systemic exposure to tacrolimus, based on AUC_∞ was approximately 17% to 21% lower compared to the oral formulations (capsules and suspension). However, maximum whole blood levels of tacrolimus occurred at the first sampling time point (0.5 hours post-dose) for the majority of subjects receiving the nasogastric dose and it appeared that the absorption phase was not fully defined and thus AUC_∞ may have been underestimated. The disposition kinetics of tacrolimus were similar for all three formulations, with the mean terminal elimination half-life of tacrolimus being approximately 33 hours for each formulation. Furthermore, inter-subject variability in the systemic exposure to tacrolimus for the three formulations was similar.

Table 6: Report No. 1339/123 / Study No. FG- 506-04-31

Treatment Period 1	Treatment Period 2	Treatment Period 3
Formulation C (nasogastric suspension)	Formulation A (oral capsules)	Formulation B (oral suspension)
Formulation C (nasogastric suspension)	Formulation B (oral suspension)	Formulation A (oral capsules)

Multiple dose pharmacokinetics

A randomised, two-period cross-over study (**FG-506-04-21**) examined the blood concentration-time profiles and comparative pharmacokinetics of tacrolimus following single and repeated dose administrations of 1 mg Prograf capsule and the modified release oral formulation 1 mg MR4 capsule in 14 normal healthy male subjects aged between 18 and 50 years. Multiple oral doses of tacrolimus were administered following a 2 hour fast, with subjects planned to receive two formulations, Prograf and MR4, in two treatment periods. Prograf (1 mg capsule) was administered twice daily for 10 consecutive days, an interval of 12 hours separating dose administrations on each dosing day. MR4 (2 x 1 mg capsules) was administered once daily for 10 consecutive days. A washout period of at least 14 days separated the two treatment periods. Following the first oral dose of Prograf on Day 1, tacrolimus was rapidly absorbed with maximum blood concentrations (mean C_{max} of 3.94 ng/mL) occurring at a median t_{max} of 1 hour (range 1 to 3 hours). Following the second daily dose of Prograf on Day 1, the rate of absorption of tacrolimus was markedly reduced, with a mean C_{max} of 1.92 ng/mL occurring at a median t_{max} of 21 hours after the second dose (range 15 to 23.8 hours). The overall systemic exposure was however, of a similar magnitude in the 12 - 24 hour period following the second dose of Prograf compared to the 0 - 12 hour period following the first dose of Prograf, the mean AUC values being 15.4 and 17.7 ng.h/mL respectively. Following oral administration of the MR4 capsule on Day 1, tacrolimus was also rapidly absorbed with maximum blood concentrations (mean C_{max} of 2.99 ng/mL) occurring at a median t_{max} of 2 hours (range 1 to 3 hours). A similar t_{max} was obtained on Day 10, with a median value of 2 hours (range 1 to 5 hours). Based upon AUC_{24}, there was approximately a 2- and 2.5-fold accumulation of tacrolimus in the blood following 10 days multiple dosing with Prograf and MR4 respectively. On Day 1, systemic exposure to tacrolimus, as assessed by AUC_{24}, was similar for the two formulations. Upon attainment of steady state, once daily dosing with 2 mg MR4 resulted in an 18% increase in 24 hour systemic exposure of tacrolimus when compared to twice daily dosing with 1 mg Prograf.

A randomised, balanced, two-period crossover study (**FG- 506-04-25**) compared the pharmacokinetics of tacrolimus following single and multiple oral doses of the MR4 formulation with Prograf at a total daily dose of 4 mg in 24 healthy male subjects, with an average age of 35 years. Twelve subjects were randomly assigned to receive each of the two treatment sequences (Prograf/MR4 or MR4/Prograf). Multiple oral doses of tacrolimus were administered after a 2 hour fast, with subjects receiving two formulations, Prograf and MR4, in two treatment periods. A washout interval of at least 14 days separated the two treatment periods. Prograf was administered twice daily for 10 consecutive days, with an interval of 12 hours separating dose administrations on each dosing day. On each dosing occasion, subjects received two 1 mg capsules of Prograf. MR4 was administered at the 4 mg dose level once daily in the morning with subjects receiving four 1 mg capsules on each dosing occasion. On Day 1, systemic exposure to tacrolimus, as assessed by AUC_{0-24}, was similar for the two formulations. Upon attainment of steady state, once daily dosing with 4 mg MR4 resulted in a systemic exposure to tacrolimus 93% of that following twice daily dosing with 2 mg Prograf, with the 90% confidence interval of this ratio (CI: 87 - 99) being within the limits of bioequivalence. Based upon both AUC_{0-24} and C_{max}, there was an approximate 2-fold accumulation of tacrolimus in the blood following 10 days multiple dosing with both MR4 and Prograf. Following morning administration, the rate of absorption of tacrolimus was rapid for both formulations, with a median t_{max} of approximately 1 and 2 hours being obtained for the Prograf and MR4 formulations, respectively. On Day 10, following the evening dose of Prograf, the rate and extent of absorption of tacrolimus was reduced, with total systemic exposure as assessed by AUC_t and C_{max} being 17 and 50% lower, respectively, following the evening dose compared to the morning dose. For both MR4 and Prograf, C_{min}(24 h) and AUC_{0-24} were highly correlated. This correlation was numerically slightly higher for the MR4 formulation, but was not statistically different for the two formulations. The elimination kinetics were similar for the two formulations, with a mean terminal elimination half-life of approximately 38 hours for both MR4 and Prograf.

Pharmacokinetics in special populations

Pharmacokinetics of MR4 was specifically evaluated in healthy Japanese subjects (FJ-506E-0002 and FJ506E-0001) and in patients with mild and severe hepatic impairment (92-0-0020).

Japanese Subjects

A randomised, open-label, uncontrolled, three-period crossover study (**FJ-506E-0002**) examined the pharmacokinetics of tacrolimus in 18 healthy Japanese adult males, aged between and 20 and 45 years, after single oral administration of MR4 capsule at 3 doses by cross-over method and assessed the dose linearity in the pharmacokinetics of MR4 capsule. Healthy adult male subjects received an oral dose of the study drug (MR4 capsule) at 3 doses (1.5 mg, 4 mg and 10 mg) in fasting state in three cross-over treatment periods with at least 14 days between drug administrations. T_{max} occurred approximately 2 hours after dosing for each dose, and the terminal elimination half-lives ($t_{1/2}$) were also similar (approximately 36 hours). The dose-normalised blood concentration-time profiles (AUC_∞/D) of tacrolimus for the 1.5, 4 and 10 mg doses were similar (50.07 – 51.63 ng.hr/mL). C_{max} and AUC_∞ increased dose-dependently, whereas there was no dose-dependency in the CL/F, MRT, nor Vdz/F. In power model analysis, the mean values of exponent term (β) were 1.0422 for AUC_∞ and 1.1082 for C_{max}. The 95% confidence intervals of β for AUC_∞ and C_{max} were estimated to be 0.9647-1.1197 and 1.0203-1.1960, respectively. Assuming that the dose of MR4 was doubled, the increase in the C_{max} value was estimated to be approximately 2.0283-2.2910 ($2^{1.0203}$-$2^{1.1960}$) times the original value, based on the calculated confidence interval. Analysis of variance (ANOVA) revealed that there was no significant difference in C_{max}/D between 1.5 mg versus 4 mg and 4 mg versus 10 mg, whereas a significant difference was observed between the 1.5 mg versus 10 mg doses (p=0.0425, 90% confidence interval: 1.03-1.46). No significant difference was noted among the 3 doses in AUC_∞/D, CL/F, MRT, Vdz/F or $t_{1/2}$. Overall, the pharmacokinetics

of tacrolimus after single oral administrations of MR4 at 3 different dose levels (1.5 mg, 4 mg, and 10 mg) demonstrated dose-linearity in the dose range of 1.5 mg to 10 mg.

An open-label, uncontrolled study (**FJ-506E-0001**) examined the pharmacokinetics of tacrolimus in 20 healthy Japanese adult males after a single oral administration of MR4 capsules and the results were compared with the pharmacokinetics of tacrolimus in Caucasian subjects from the previous study (Protocol No. 00-0-077) at the same dose. Each subject was administered an oral dose of the study drug (three MR4 capsules 1 mg) with 150 mL of water in fasting state at 09:00 AM. Overall, the whole blood tacrolimus concentrations in Japanese were 1.23 to 1.6 times higher than those in Caucasians. The ratios of Japanese to Caucasians for the geometric means of C_{max} and AUC_{0-24} were 1.406 and 1.353, respectively. The 90% confidence intervals were from 1.183 to 1.672 and from 1.101 to 1.662, respectively. The geometric means of C_{max} and AUC_{0-24} in Japanese were 30%-40% higher than those in Caucasians. By contrast, the Japanese to Caucasians ratio of the geometric mean of $t_{1/2}$ was 1.064 and the 90% confidence interval was within the levels of bioequivalence. The ratio of the whole blood tacrolimus concentration adjusted by dose per body weight was more similar and ranged from 1.00 to 1.34 (at 6 hours after dosing) for Japanese and Caucasians subjects. In addition, the ratios of Japanese to Caucasian subjects for the geometric means of dose per body weight adjusted C_{max} and AUC_{∞} were more similar (1.147 and 1.103, respectively), however, the upper bounds of the 90% confidence limits were once again outside the level of bioequivalence. These results suggest that although similar the pharmacokinetics of MR4 are not bioequivalent in healthy adult Japanese and Caucasian subjects and may indicate that a slightly lower dose of MR4 may be required for Japanese subjects.

Hepatic Impairment

A two treatment, two-period, open-label, randomised cross-over study (**92-0-0020, Report No: R95-0163-506-C4P-E**) examined the pharmacokinetics of tacrolimus in 6 patients (1 female), aged 62 to 64 years, with mild hepatic impairment (mean Child-Pugh score 6.2).[3] Each patient was administered tacrolimus as a single 4 hour IV infusion (0.02 mg/kg) and oral (0.12 mg/kg) dose after an overnight fast with a 14-day wash-out period between the two treatment periods. Although similar, the AUC, $t_{1/2}$ and Vd for the oral regimen were in general higher than for the IV regimen. The mean $t_{1/2}$was considerably longer (61 – 66 hours) than in normal volunteers (34 hours) and was accompanied by an increase in V_d (3.12 and 1.92 l/kg in hepatically impaired and normal subjects, respectively) By contrast, the mean clearance was similar in hepatically impaired and normal volunteers (0.042 and 0.040 l/hour/kg, respectively).

A two-treatment, two period, open-label, crossover, three centre study (**92-0-0020, Report No: R98-0012-506-C4P-E**) examined the pharmacokinetics of intravenous and oral tacrolimus in 6 patients (1 female), aged from 41 to 61 years, with severe hepatic impairment (Child-Pugh score >10). All doses were administered following a 10 hour fasting period and there was at least a 21-day wash-out between doses. Following equal oral doses of tacrolimus the AUC_{∞} ranged from 803 ng.hr/mL to 1339 ng.hr/mL, whereas the AUC_{∞} ranged from 322 ng.hr/mL to 1665 ng.hr/mL following equivalent IV doses. The $t_{1/2}$ following IV doses was approximately twice that seen following oral dosing (mean $t_{1/2}$ = 198 and 119, respectively) and the Cl and Vd following oral doses were 5 and 3 times greater respectively than with comparable IV doses. The pharmacokinetic parameters in patients with severe hepatic impairment differed markedly from those with mild hepatic dysfunction although the $t_{½}$ in severe hepatic patients was not statistically different than that in mild hepatic patients following both IV and oral administration (see previous study). Comparing CI and Vd in severe hepatic patients and mild hepatic patients after oral dosing revealed statistically

[3] The **Child-Pugh score** is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

significant differences in these parameters (0.079±0.016 versus 0.034±0.019 L/hr/kg, p=0.004 and 12.9±2.2 versus 3.72±4.70 L/kg, p=0.008, respectively). When compared to normal volunteers and patients with mild hepatic dysfunction, the present data clearly indicates that the degree of hepatic impairment has an effect upon the pharmacokinetic profile of tacrolimus.

Pharmacokinetics in target population

Pharmacokinetics in kidney transplant patients

Comparative PK Study FG-506E-12-01

A Phase II multi-centre, open, prospective, 1:1 randomised, comparative PK study (**FG-506E-12-01)** of MR4 versus Prograf investigated and compared the pharmacokinetics of tacrolimus in patients undergoing kidney transplantation treated with modified release tacrolimus (MR4) or Prograf-based immunosuppression regimen. The recommended first total daily oral dose of tacrolimus was 0.20 mg/kg for both MR4 and Prograf treatment arms. The first dose of MR4 was administered within 24 hours of reperfusion in the morning following transplantation. Subsequent doses of MR4 capsules were taken orally once daily in the morning. The first daily dose of Prograf was administered in two divided doses (0.10 mg/kg twice daily; once in the morning and once in the evening approximately 12 hours apart), with dosing starting within 24 hours of reperfusion on the morning following transplantation. Subsequent doses of Prograf capsules were taken orally twice daily. Methylprednisolone (or equivalent) was given prior to reperfusion as a 500 to 1000 mg intravenous bolus. A second intravenous dose of 125 to 250 mg was administered in conjunction with the first dose of tacrolimus (MR4 or Prograf). Administration of oral prednisone (or equivalent) was also permitted with recommended doses of 15 to 20 mg/day in the first month and tapered doses thereafter. A standardised regimen for mycophenolate mofetil (MMF) was used for this study with a starting dose of 2 g/day. Following maintenance for 14 days, the dose was reduced to 1 g/day in clinically stable patients.

The mean total daily doses of both MR4 and Prograf generally remained stable during the study, and were similar for the two treatment arms for the first 7 days post-transplant. Thereafter the total daily doses of MR4 were slightly higher than the corresponding doses of Prograf. Whole blood tacrolimus trough levels in the two treatment arms were comparable; however, there was a tendency for levels to be higher in the Prograf-treated patients than in the MR4-treated patients.

The systemic exposure to tacrolimus (AUC_{0-24}) on Day 1 was approximately 32% lower for MR4 than for Prograf at comparable mean daily doses of 0.189 and 0.185 mg/kg respectively. However, on Day 14 and Week 6, the exposure for MR4 was comparable to that for Prograf. The 90% confidence intervals for $\ln(AUC_{0-24})$ on Day 14 was within the equivalence range of 80% to 125%. At Week 6, the lower limit of the confidence interval was slightly outside the 80% limit at 79%. There was good correlation between AUC_{0-24} and C_{24} for MR4 and Prograf (r=0.83 and r=0.94, respectively). The systemic exposure to tacrolimus was also evaluated using dose normalised parameters (dose normalised to dose of 0.1 mg/kg). When normalised to an equivalent dose for both formulations, the $\ln(AUC_{0-24})$ ratio of MR4:Prograf was 98.0% and 82.4% on Day 14 and at Week 6, respectively.

PK Conversion Study FG506E-12-02

A Phase II, open-label, multi-centre, single-sequence, four period cross-over replicate design study (**FG-506E-12-02**) assessed the pharmacokinetics of tacrolimus in stable kidney transplant patients converted from a Prograf-based immunosuppression regimen to a tacrolimus modified release (MR4) based immunosuppression regimen. The study was performed in stable, adult kidney transplant recipients (at least 6 months post-transplant), who were receiving Prograf-based treatment at the time of screening. A total of 60 patients, aged between 18 and 65 years, completed four evaluable pharmacokinetic profile assessments without any major PK relevant protocol

violations. After entry into the study and a screening phase of 2 weeks, treatment with tacrolimus was converted three times, each conversion being performed on a 1:1 (mg:mg) total daily dose basis compared to the treatment on the day prior to the conversion. Each treatment period lasted 14 days. On Day 1, a twice daily, stable dose commercial Prograf regimen was replaced by a twice daily Prograf (as study medication) regimen. On Day 15, the treatment was converted to a once daily MR4 regimen. On Day 29, the treatment was converted back to a twice daily Prograf regimen, and on Day 43, the treatment was converted for a second time to a once daily MR4 regimen. At the end of this study (Day 56), patients were able to continue treatment with MR4 as part of a long-term extension study (FG-506-14-02). Four 24-hour PK profiles were collected, with each profile starting on the last day of each treatment period. These were two 24-hour PK profiles for Prograf starting in the morning of Day 14 and Day 42, and two 24-hour PK profiles for MR4 starting in the morning of Day 28 and Day 56.

The AUC_{0-24} of tacrolimus was comparable for Prograf and MR4, with the 90% confidence intervals for $ln(AUC_{0-24})$ being contained within the bioequivalence range of 80% to 125%. By contrast, the C_{max} for the MR4 formulation was lower (15.99 and 21.84 ng/mL for the MR4 and Prograf formulations, respectively, 90% CI: 68 to 79%). There was good correlation between AUC_{0-24} and C_{24} for both Prograf and MR4 (r=0.82 and r=0.88, respectively). The inter- and intra-subject variability for $ln(AUC_{0-24})$ were similar for both MR4 and Prograf. The equivalence in exposure (AUC_{0-24}) to Prograf and MR4, and the strong correlation between C_{24} and AUC_{0-24} for the two formulations, suggests that stable kidney transplant recipients on twice daily Prograf therapy can be safely converted to once daily MR4 therapy on a 1:1 (mg:mg) basis.

PK Conversion Study 02-0-131

A Phase II, open-label, multi-centre study (**02-0-131**) assessed the pharmacokinetics, long-term safety and tolerability of tacrolimus in 70 stable kidney transplant patients (age 22-71 years; 24 females) converted from a Prograf-based immunosuppression regimen to a modified release (MR4) tacrolimus-based immunosuppression regimen. Patients were enrolled into the study on their stable twice-daily (bd) dose of Prograf on Day 1. Patients continued to receive a stable bd dose of Prograf through the evening of Day 7. On the morning of Day 8, patients were converted to MR4 on a 1:1 (mg:mg) basis for their total daily dose. MR4 was administered once-daily (qd) in the morning. The duration of the Prograf pharmacokinetic treatment period was 1 week, and the MR4 pharmacokinetic treatment period was 4 weeks. Patients who completed the 4-week MR4 pharmacokinetic treatment period were eligible to continue receiving MR4 as part of the MR4 extension treatment period of the study and will continue until commercial availability of the study drug or notification of study discontinuation.

As seen in other studies the mean C_{max} was higher for Prograf than for MR4, consistent with the extended-release formulation of MR4, whereas the 90% CIs for AUC_{0-24} and $ln(AUC_{0-24})$, the primary measure of exposure for MR4 and Prograf at steady state, were 90.34-98.54 and 90.72-99.41 respectively, and were completely contained within the 80% to 125% limits. These data indicate equivalence of exposure when comparing steady state between MR4 and Prograf. An analysis using dose-adjusted parameters gave similar results.

The correlation coefficients for AUC_{0-24} versus C_{min} were 0.80 on Day 1 and 0.84 on Day 7 for Prograf steady state, and 0.92 on Day 14 and 0.86 on Day 21 for MR4 steady state. Thus, trough (C_{min}) and exposure (AUC_{0-24}) measures correlated strongly during both Prograf and MR4 treatment periods; with numerically greater correlation coefficients observed for MR4. Intra-subject variability for $ln(AUC_{0-24})$ and dose-adjusted $ln(AUC_{0-24})$ were less for MR4 than for Prograf. The ratio of MR4 to Prograf intra-subject variability for non-dose-adjusted values was 0.805 (p-value = 0.384). The ratio of MR4 to Prograf intra-subject variability for dose-adjusted values was 0.701 (p-value = 0.155). Inter-subject variability for $ln(AUC_{0-24})$ was less for MR4 than for Prograf: 0.054

for MR4 and 0.062 for Prograf without adjustment for dose, and 0.300 for MR4 and 0.345 for Prograf with adjustment for dose.

An analysis of data comparing exposure among black and white patients indicated there was equivalence in exposure within each race when comparing steady states between MR4 and Prograf, suggesting both blacks and whites can be successfully converted 1:1 (mg:mg) from Prograf to MR4. Additionally, the data indicated that the intra-subject variability for black patients was significantly less (p-value = 0.02) during steady state with MR4 than steady state with Prograf. The intra-subject variability of $\ln(AUC_{0-24})$ and $\ln(C_{max})$ for steady state MR4 within black patients was similar to the intra-subject variability seen for white patients; whereas for Prograf steady state, black patients had greater intra-subject variability when compared to white patients.

The 90% CIs for $\ln(AUC_{0-24})$ were completely contained within the 80% to 125% limits when exposure was analysed by gender. These data indicate equivalence of exposure when comparing steady state between MR4 and Prograf for both males and females. As seen previously higher mean C_{max} values were observed with Prograf.

Comparison of $\ln(AUC_{0-24})$ for Prograf and MR4 in patients with diabetes or post transplant diabetes mellitus showed that the 90% CIs for $\ln(AUC_{0-24})$ (84.79, 99.73) were within the 80% to 125% limits of bioequivalence. The results for dose-adjusted $\ln(AUC_{0-24})$ were also within the 80% to 125% limits. These data indicate that there was equivalence in exposure for patients with diabetes or post-transplant diabetes mellitus when comparing steady states between MR4 and Prograf. The 90% CIs for patients with diabetes or post-transplant diabetes mellitus were comparable for $\ln(C_{max})$ and ln(Cmin) respectively, for both dose-adjusted and non-dose adjusted parameters.

The 90% CIs for $\ln(AUC_{0-24})$ were completely contained within the 80% to 125% limits when exposure between the first day of MR4 (Day 8) was compared to the last day of Prograf (Day 7). These data suggest that a 1:1 (mg:mg) conversion from Prograf to MR4 will yield equivalent exposures, even during the first day of exposure to MR4.

Overall, as has been indicated in other studies, higher mean C_{max} concentrations were observed with Prograf. The study's authors state that this finding is significant from a safety perspective since it has been shown that tacrolimus can cause neurotoxicity and nephrotoxicity, particularly when used at high doses, but it is not stated whether the reported toxicity is related to the maximum blood levels or exposure.

PK Conversion Study FJ-506E-KT01

An open-label study (**FJ-506E-KT01**) compared the pharmacokinetics of tacrolimus in 37 kidney transplant patients who were initially on immunosuppressive therapy with Prograf capsules and were then converted to treatment with the MR4 formulation. The pharmacokinetics-evaluable set comprised 35 patients (14 female), aged from 20 to 55 years (2 patients were excluded because of withdrawal from the study due to adverse events before administration of MR4 capsules). The subjects in the present study had undergone kidney transplantation at least 6 months before and had continuously received Prograf capsules for at least for 3 months before the day of submitting the informed consent. Prograf capsules were administered twice-daily, that is, in the morning and evening for 1 week with the same daily dose as that of Prograf given just before the hospitalisation period to enable the determination of the pharmacokinetics of Prograf at steady state. Patients were then converted to MR4 capsules which were administered once-daily in the morning with the same daily dose as that of Prograf given 1 day before conversion to MR4 capsules. After discharge from the hospital MR4 capsules were administered once in the morning with the same daily dose as that of Prograf given on the day of discharge from the hospital.

As in other studies, AUC_{0-24} (138 and 130 ng.hr/mL) and C_{min} (3.71 and 3.71 ng/mL) were similar for Prograf and MR4, respectively, whereas the C_{max} was lower for MR4 (14.6 and 9.7 ng/mL for

Prograf and MR4, respectively) and t_{max} was delayed for the MR4 formulation. The geometric mean ratio of MR4 capsules/Prograf capsules for AUC_{0-24} was 0.95 (90% CI: 0.88-1.03), and the 90% CIs were contained entirely within the 0.80 to 1.25 limits. Dose-normalized PK parameters were also calculated, since the dose of MR4 capsules was changed in 1 patient during the pharmacokinetics evaluation period. The geometric mean ratio of MR4 capsules/Prograf capsules for AUC_{0-24}/dose was 0.93 (90% CI: 0.87-1.00) and the 90% CI was contained entirely within the 0.80 to 1.25 limits.

A high correlation was observed between AUC_{0-24} and C_{min} for both Prograf capsule administration and MR4 capsule administration, coefficients of correlation being 0.898 and 0.934 respectively. In addition, eleven of 34 patients (32.4%) who responded to the patient questionnaire to investigate the usefulness of MR4 capsules answered that he/she felt it has become easier to remember taking the drug, indicating a possibility of better drug compliance with MR4 capsules than Prograf capsules. Overall, this study indicates that there was equivalence in exposure (AUC_{0-24}) at steady state between MR4 and Prograf capsules with lower C_{max} and later t_{max} for MR4 capsules.

PK Study (oral versus IV tacrolimus)

The pharmacokinetics of tacrolimus following oral and IV administration in patients prior to and following kidney transplantation were examined in an open-label, two treatment randomised cross-over trial (**FK506-10**). Two groups of patients were used in this trial - those awaiting kidney transplantation or pre-transplant patients (12 patients, 6 females, ages ranging from 25 to 65 years) and 26 kidney transplant patients (11 females), aged from 19 to 66 years. This study was conducted in 1993 and was done to provide PK predictors and strategies to aid in initiating and adjusting tacrolimus therapy following kidney transplantation. Although MR4 was not evaluated, the study results of this have been discussed for completeness as it was submitted in this dossier. Pre-transplant patients were randomised to two dosing sequences: IV followed by oral or oral followed by IV. Six patients received a single 0.02 mg/kg dose of tacrolimus administered intravenously over 4 hours. Seven days after the IV dose, the same patients received a single 0.08 mg/kg oral dose of tacrolimus. On a separate occasion, 6 additional subjects received the treatments in the reverse order.

The post-transplant patients, 2 to 4 days following renal transplantation, received a single intravenous 0.02 mg/kg dose of tacrolimus administered over 4 hours. Subsequently, in parallel, the patients were randomised to initially receive one of three dosage regimens (low, 0.1 mg/kg/12 hours; medium, 0.15 mg/kg/ 12 hours; high, 0.2 mg/kg/12 hours) followed by the necessary dosage adjustments to yield a defined range of tacrolimus trough whole blood concentrations (low,5 -14 ng/mL; medium 15-25 ng/mL; high, 26-40 ng/mL). There were clear differences in the pharmacokinetics of tacrolimus in the two groups of subjects. Compared to the pre-transplant subjects, the half life and the IV $AUC_{¥}$ were decreased (although these did not reach significance) and total body clearance (0.083 and 0.038 l/hour/kg) and volume of distribution (1.41 and 1.07 l/kg) were significantly increased in the post-transplant patients. As a result of these changes in total body clearance and volume of distribution, it is clear that the initial dosing of tacrolimus for patients following renal transplantation cannot be estimated using pre-transplant pharmacokinetic data. However, the objective of this study was not clear as Prograf (and Prograf XL) are to be administered only in the post-transplant setting.

PK Comparative Study

An open multi-centre, randomised, parallel-group study (**FG-02-02**) compared the efficacy and safety of a Prograf-based immunosuppressive regimen with a conventional cyclosporin-based therapy in renal transplant recipients over a 12 month period. A total of 448 patients were recruited and 303 were randomised to receive treatment with Prograf. The other 145 patients were allocated Sandimmun (cyclosporin) therapy (aged 18 to 72 years and 107 subjects were female). The objectives of the study were to examine the time-dependent changes in dosing and blood

concentrations of tacrolimus and to examine any relationship between efficacy and toxicity with dose or blood levels of tacrolimus. This study was conducted in 1996 and although the MR4 formulation was not evaluated, results have been discussed briefly in the following sections.

The mean oral tacrolimus dose was stable for the first two week period at 0.26 mg/kg on both Day 1 and at Week 2. Corresponding mean blood levels were 19.6 and 12.9 ng/mL respectively. The apparent increase in relative clearance was found to correlate with changes in haematocrit ($r = 0.84$, $p= 0.017$) and with plasma albumin ($r = 0.74$, $p = 0.047$). There was 54% decrease in tacrolimus oral dose from 0.26 mg/kg (Week 4) to 0.12 mg/kg (month 10 - 12). Corresponding values for blood levels were 13.3 and 9.4 ng/mL, a reduction of 29%. This apparent decrease in clearance was shown to correlate with decreasing doses of oral corticosteroid doses ($r = 0.94$, $p = 0.017$). Therefore, a decrease in steroid usage may need to be accompanied by a decrease in tacrolimus dose to maintain similar target blood levels.

Cox's regression analysis showed a correlation between trough levels of tacrolimus and adverse events related to glucose metabolism disorders (GMD) and a more clinically relevant parameter - insulin dependent diabetes (IDDM), defined as a subset of patients who received ³ 30 days of insulin for diabetes but precludes those subjects who had pre-existing GMD. Step-wise Cox's regression used to analyse other covariates showed that for GMD and IDDM, whole blood tacrolimus levels and steroid dosage were significant explanatory variables. In addition, baseline age and patient weight were also positively correlated with GMD and IDDM.

PKs following combination treatment with Tacrolimus and Mycophenolate Mofetil (MMF)

The pharmacokinetics of tacrolimus and mycophenolate mofetil (MMF) when used in combination in stable renal transplant patients were examined in a three-centre, non-randomised, dose escalation study (**95-0-004**) involving 18 stable renal transplant patients (7 female), aged 17 to 61 years, receiving tacrolimus, azathioprine and corticosteroids. Three groups of 6 patients were enrolled and treated sequentially based on the bd MMF dose: Group I 500 mg MMF orally bd; Group II 750 mg MMF orally bd and Group III 1000 mg MMF orally bd.

All subjects maintained their current dose of tacrolimus and corticosteroids. The mean tacrolimus dose was consistent throughout the study and was within the recommended therapeutic range (5-15 ng/mL).

The dose of tacrolimus across the three groups was similar and ranged from 4.2 - 4.8 mg, however, there was far greater variability in AUC_{0-12} ranging from 87 - 143 ng.hr/mL. There was a trend towards ($p > 0.10$) an increased AUC_{0-12} of tacrolimus in all three patient groups following administration of MMF in combination with tacrolimus (AUC_{0-12} ranging from 115 - 183 mg.hr/mL).

PKs in Phase III non-inferiority study (MR4 versus Prograf)

A multi-centre, 1:1 randomised, double blind, double dummy, two arm parallel group Phase III study (**FG-506E-12-03**) compared the pharmacokinetics of tacrolimus during the first two weeks after transplantation in kidney transplant patients treated with modified release tacrolimus (MR4) or Prograf-based immunosuppression regime. Thirty four subjects were evaluable for analysis (17 in the MR4 treatment arm and 17 in the Prograf treated arm). The pre-operative dose of MR4 was 0.1 mg/kg given orally in one dose, at any time of the day. The initial post-operative MR4 dose was 0.2 mg/kg/day given orally in one dose, preferably in the morning. The pre-operative dose of Prograf was also 0.1 mg/kg given orally in one dose, at any time of the day (within 12 hours prior to reperfusion). The initial post-operative Prograf dose was 0.2 mg/kg/day given orally in two doses (equal to 0.1 mg/kg twice daily). In the Prograf arm there were 6 females and in the MR4 arm there were 10 females and the mean ages (PK Analysis Set) were 47.4 and 41.4 years for the Prograf and the MR4 treatment arms, respectively.

In the PK Analysis Set, the mean total daily doses of MR4 on days 1, 3, 7 and 14 were 0.188 mg/kg, 0.183 mg/kg, 0.180 mg/kg and 0.173 mg/kg, respectively. Corresponding values for Prograf were 0.185 mg/kg, 0.184 mg/kg, 0.162 mg/kg and 0.172 mg/kg on days 1, 3, 7 and 14 respectively.

The systemic exposure to tacrolimus [$\ln(AUC_{0-24})$] on Day 1 was approximately 16% lower for MR4 than for Prograf, although the mean total daily dose (mg/kg) was approximately the same. Although the mean total daily doses (mg/kg) of MR4 were approximately the same as the corresponding mean Prograf doses on Days 3, 7 and 14, the $\ln(AUC_{0-24})$ for MR4 was 5%, 22% and 22% higher than that for Prograf, with the 90% confidence intervals for $\ln(AUC_{0-24})$ being outside the equivalence range of 80% to 125%. Dose normalised $\ln(AUC_{0-24})$ of tacrolimus for MR4 compared to Prograf was approximately 81%, 106%, 107% and 116% on days 1, 3, 7 and 14, respectively. However, the values were outside the level of bioequivalence on days 3, 7 and 14. There was good correlation between C_{24} and AUC_{0-24} for both MR4 (r=0.87) and Prograf (r=0.92).

Pharmacokinetics in liver transplant patients

PKs in Phase II study (MR4 versus. Prograf)

A Phase II, multi centre, open, prospective, 1:1 randomised, comparative PK study (**FG-506-11-01**) of MR4 versus Prograf investigated and compared the pharmacokinetics of tacrolimus in patients undergoing primary liver transplantation treated with modified release tacrolimus (MR4) or Prograf-based immunosuppression regimens. Following transplantation, patients received either MR4-based or Prograf-based immunosuppression. Three 24-hour whole blood concentration-time profiles were taken during the study: one following the first administration of tacrolimus, and two under steady state conditions for tacrolimus, Day 14 (+7) after transplantation and at Week 6 (± 7 days). A total of 133 patients (69 MR4, 64 Prograf) were randomised into the study to achieve this target. Four patients did not receive study medication, thus the Full Analysis Set (FAS)comprised 129 patients (67 MR4, 62 Prograf). Nineteen of the PK evaluable set were female and the ages of the subjects ranged from 26 to 65 years. The first daily dose of Prograf was administered orally in two divided doses (0.05 to 0.075 mg/kg twice daily; once in the morning and once in the evening approximately 12 hours apart), with dosing starting within 6 to 12 (up to 18) hours after skin closure (morning after transplantation). Subsequent doses of Prograf capsules were taken orally twice daily.
On Day 1, the systemic exposure to tacrolimus (AUC_{0-24}) was approximately 50% lower for MR4 than for Prograf, although the mean total daily dose was comparable for the two formulations. On Day 14 and at Week 6, the AUC_{0-24} for MR4 was 13% and 21% higher than that for Prograf, with the 90% confidence intervals for $\ln(AUC_{0-24})$ being just outside the equivalence range of 80% to 125%. However, the mean total daily dose of MR4 was approximately 25% higher than the corresponding Prograf dose at the time of the Day 14 and Week 6 profiles. As seen in other studies there was good correlation between AUC_{0-24} and C_{24} for MR4 and Prograf (r=0.92 and r=0.83, respectively).

When normalised to an equivalent dose for both formulations, the $\ln(AUC_{0-24})$ ratio of MR4:Prograf was 88.3% and 91.4% on Day 14 and at Week 6, respectively, however the 90% CIs were still a little outside the limits for bioequivalence suggesting lower exposure to MR4 compared to Prograf in patients undergoing primary liver transplantation.

PK Conversion Study 02-0-152

A Phase II, open-label, multi-centre study (**02-0-152**) assessed the pharmacokinetics, long-term safety, and tolerability of tacrolimus in stable liver transplant patients converted from a Prograf-based immunosuppression regimen to a modified release (MR4)-based immunosuppression regimen. Seventy patients are included in the FAS. Of these 70 patients, eight (8/70, 11.4%) did not complete all four pharmacokinetic profiles and were not included in the pharmacokinetic

evaluable set of 62 subjects (26 female) aged from 24 to 68 years. Patients were enrolled into the study on their stable twice-daily (bd) dose of Prograf on Day 1. Patients received Prograf bd on Days 1 through to 14 and Days 29 through to 42. Patients received MR4 on a 1:1 (mg:mg) basis for their total daily dose once daily (qd) in the morning on Days 15 through to 28 and Days 43 through to 56. The mean total daily dose of Prograf and MR4 was comparable for the FAS and the pharmacokinetic evaluable set and was consistent throughout the pharmacokinetic treatment period. For the pharmacokinetic evaluable set, the mean ± SD dose of Prograf was similar on Day 14 (5.2 ± 3.48 mg) and Day 42 (5.3 ± 3.36 mg). Consistent with the 1:1 (mg:mg) conversion from Prograf to MR4, the mean ± SD of MR4 on Days 28 and 56 was similar to that of Prograf on Days 14 and 42, respectively.

As seen in other studies, higher mean C_{max} values were observed with Prograf than with MR4. For the primary measure of exposure, $\ln(AUC_{0-24})$, numerically smaller intra-subject variability was observed with MR4 at steady state compared to Prograf at steady state, which may be an additional benefit for patients converted to MR4. For the trough evaluable set, the highest mean trough concentration observed was 7.15 ng/mL (Day 1, Prograf), and the lowest mean trough concentration observed was 5.54 ng/mL (Day 28, MR4). The difference between mean tacrolimus whole blood trough (C_{min}) concentrations across all days observed was < 1.70 ng/mL for non-dose-adjusted values, and < 0.5 ng/mL/mg for dose-adjusted values when comparing MR4 to Prograf suggesting that the difference in trough values between Prograf and MR4 is not clinically significant, considering the therapeutic range is 5 to 20 ng/mL.

The 90% CIs for $\ln(AUC_{0-24})$, at steady state, was (85.42, 92.29) and contained within the 80% to 125% limits, indicating equivalence of exposure. AUC_{0-24} and C_{min} (trough) for MR4 were strongly correlated, with MR4 having correlation coefficients that were comparable to those for Prograf on the steady state days analysed (Days 28 and 56 for MR4; Days 14 and 42 for Prograf).

Although there was a 16% decrease in C_{min} for MR4, the statistical analysis of exposure at steady state for MR4 (Days 21, 28, 49, and 56) versus Prograf (Days 1, 7, 14, 35, and 42) showed that the 90% CIs for $\ln(C_{min})$ were entirely contained within the 80% to 125% limits, regardless of adjustment for dose. Results suggest that the therapeutic monitoring system used for Prograf (that is, monitoring tacrolimus whole blood trough concentrations as a surrogate for overall tacrolimus exposure) can also be effectively used as the therapeutic monitoring system for patients once they are converted to MR4.

The 90% CIs for $\ln(AUC_{0-24})$ were completely contained within the 80% to 125% limits when exposure was analysed by gender, indicating that there is equivalence of exposure when comparing steady state between MR4 and Prograf for both males and females.

In patients with diabetes, exposure to MR4 was approximately 20 % lower (based on C_{max}, AUC and Cmin) when compared with Prograf and the 90% CIs for $\ln(AUC_{0-24})$ and $\ln C_{min}$ were not completely contained within the 80% to 125% limits. In spite of this, the AUC_{0-24} and C_{min} correlated strongly for patients with diabetes; therefore, regardless of whether or not these parameters were within the equivalence limits, the data suggest that trough levels are still a reliable indicator of overall tacrolimus exposure for patients with diabetes.

Effect of bile on tacrolimus PKs

The effect of presence and absence of bile on the absorption of tacrolimus was evaluated in a single centre clinical trial (**FG-506-01-10**) in liver transplant patients. The number of patients enrolled in the study was 43, of which 32 provided evaluable profiles for pharmacokinetic analysis (17 cyclosporin, 15 tacrolimus), the study report provides the data for tacrolimus only. Of the 15 patients receiving tacrolimus, 5 were female and the ages of all patients ranged from 15 to 65 years. Dosing in all patients commenced orally and the initial dose of tacrolimus was administered within 6 hours of transplantation in all cases.

The increase in mean maximum concentration (13.1 to 15.1 ng/mL) that was observed after the closure of the T-tube (in the absence of bile) was not significantly different (using a paired two sample for means test). The t_{max}, AUC_{0-12} and C_{min} were virtually identical for both pharmacokinetic profiles. These results suggest that bile has little effect on the pharmacokinetics of tacrolimus.

PKs in Phase III, non-inferiority Study (MR4 versus Prograf).

A multi-centre, 1:1 randomised, double blind, double dummy, two arm parallel group Phase III study (**FG-506E-11-03**) compared the pharmacokinetics of a dual modified release MR4 / steroid regimen with a standard tacrolimus (Prograf)/ steroid regimen in 25 primary liver allograft transplantation patients with a mean age of 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. The initial dose of MR4 was 0.2 mg/kg/day given orally once daily 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 patient's dose was adjusted so that the whole blood trough levels were maintained between the range 10-20 ng/mL during the PK section of this study. For inclusion into the pharmacokinetic analysis set, all patients must have completed treatment up to Day 14 (±3 days). The co-administered steroids were methylprednisolone (or equivalent) 500 to 1000 mg IV which was administered perioperatively.

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 0.151 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 0.227 mg/kg and 0.179 mg/kg respectively.

Following the oral administration of Prograf, tacrolimus was generally rapidly absorbed, with median T_{max} occurring at approximately 1 to 2 hours post-dose. The rate of absorption of tacrolimus following the evening dose of Prograf was slower compared to the morning dose resulting in a delayed T_{max} (medians, Day 1: 4 hours, Day 3: 2 hours, Day 7: 2.5 hours, Day 14: 3.5 hours) for all profiles and a lower C_{max} on Days 7 and 14. This effect did not have any marked influence on overall systemic exposure, with mean AUC_{0-24} values of 217 (Day 1), 318 (Day 3), 249 (Day 7) and 283 (Day 14) ng.h/mL which were approximately double the corresponding AUC_{0-12} values of 83 (Day 1), 161 (Day 3), 135 (Day 7) and 156 (Day 14) ng.h/mL. Following the administration of MR4, the T_{max} occurred later than that for Prograf reflecting the modified release characteristics of the formulation resulting in extended absorption of tacrolimus compared to Prograf.

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) of MR4 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.

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). When dose-normalised the $\ln(AUC_{0-24})$ ratio of MR4: Prograf was 77.4%, 87.9%, 116.6% and 84.3% on Days 1, 3, 7 and 14 respectively and none of the 90% confidence intervals fell within the 80% to 125 % equivalence range.

These results suggest that Prograf and MR4 are not bioequivalent when given to liver allograft transplantation patients co-administered a steroid regimen.

PKs in comparative study (tacrolimus versus. cyclosporin-based immunosuppression)

An international, multi-centre, open-label prospectively randomised, parallel-group study (**GHBA-157**) evaluated the efficacy and safety of tacrolimus combined with corticosteroids as prophylactic immunosuppressive therapy compared with conventional cyclosporin A-based immunosuppressive regimens (CBIR) in patients receiving a primary liver allograft. The proposed MR4 formulation was not evaluated in this study.

Of the 267 patients that received tacrolimus, pharmacokinetics was evaluated in 245 patients. The daily IV doses of tacrolimus ranged from 0.15 to 15.9 mg and the daily oral doses from 0.5 to 30 mg. The observed blood concentrations ranged from 0.5 – 397 ng/mL and 0.5 – 616 ng/mL after the IV and oral doses respectively. Concentrations in the range of 0.5 to 30 ng/mL, the limit of quantification (LOQ) and the higher limit of quantification (HOQ) of the assay accounted for 93% of all measurable concentrations The corresponding plasma levels ranged from 0.05 – 56 ng/mL and 0.05 – 104 ng/mL, respectively.

During the 4 week post-transplant period, there was considerable intra-subject variability in daily trough blood levels. Following this, the blood levels tended to be more stable, with 95% of the values in the range of 0.5 to 20 ng/mL. There was a decrease in the mean oral dose from 9.9 mg (0.159 mg/kg) in Week 4 to 7.3 mg (0.115 mg/kg) in Month 6. However, the mean blood concentrations of tacrolimus remained relatively stable within the range of 6.8 – 9.2 ng/mL throughout this period. There was poor correlation between blood and its corresponding plasma values. The blood to plasma concentration ratio ranged from 1.1 – 1014 (mean 56), the variation being largely due to a much greater spread of plasma concentrations, with mean values 0.42 ng/mL (coefficient of variation [CV] = 445%) in plasma and 15.3 ng/mL (CV = 157%) in blood. Regression of blood values as the dependent variable against plasma as the independent variable gave a significant intercept of 8.2 ng/mL ($P < 0.001$). This indicated that when no measurable concentrations of tacrolimus could be detected in plasma, measurable levels were detected in blood.

The population mean concentrations of tacrolimus in blood up to 20 ng/mL tended to increase more linearly with increasing daily oral dose (mg/day) than the values greater than 20 ng/mL. Based on population pharmacokinetic analysis (NONMEM) of blood level data from 7 patients, the total body clearance was estimated at 6.8 l/hour, volume of distribution at 90 litres, absorption rate constant at 2.5/hours and bioavailability of tacrolimus at 22%.

Pharmacokinetics in heart transplant patients

PK Conversion Study FG506-15-02

A Phase II, open-label, multi-centre study (**FG-506-15-02**) assessed the pharmacokinetics, safety and tolerability of tacrolimus in stable heart transplant patients converted from a Prograf-based immunosuppression regimen to a modified release tacrolimus, MR4, based immunosuppression regimen. The PK Evaluable Set comprised 45/85 (52.9%) patients (6 female), aged 30 to 65 years, from the FAS who received all doses of study medication and provided five evaluable PK profiles without major PK relevant protocol violations. An additional 14 patients who had five evaluable PK profiles and who had dose adjustments during the PK phase of the study (but not within 3 days prior to a PK profile) were added to the patients of the PK Evaluable Set to form the Extended PK Set (59/85 [69.4%] patients). There was an approximately 2-week screening period, during which time patients received a stable dose of Prograf, maintained in a therapeutically appropriate range of whole blood tacrolimus trough concentrations. On Day 1, this twice daily Prograf regimen was replaced by a twice daily Prograf (as study medication) regimen. On Day 8, the treatment was converted to a once daily MR4 regimen on a 1:1 (mg:mg) basis for 4 weeks. In the Extended PK Set, the mean dose of Prograf was 0.065 mg/kg/day and increased following conversion to MR4 to 0.069 mg/kg/day by Day 21. During MR4 administration 18/59 patients (30.5%) had dose adjustments (17 patients had increases in dose and 1 patient had a decrease in dose).

For the PK Evaluable Set (N=45), the AUC_{0-24} of tacrolimus was comparable for MR4 and Prograf, with the 90% confidence intervals for $ln(AUC_{0-24})$ being contained within the equivalence range of 80% to 125%. There was good correlation between AUC_{0-24} and C_{24} for MR4 and Prograf (r=0.94 and r=0.91, respectively). The inter- and intra-subject variability for $ln(AUC_{0-24})$ were similar for both MR4 and Prograf. In the Extended PK Set, both the observed and dose normalised AUC_{0-24} values of tacrolimus were comparable for MR4 and Prograf, with the 90% confidence intervals for $ln(AUC_{0-24})$ being contained within the equivalence range of 80% to 125%.

PKs in Phase II dose-finding study

The pharmacokinetics of intravenous and oral tacrolimus in primary orthotopic heart transplant recipients were examined in a subgroup of patients enrolled into an open, multi-centre, prospective, randomised, parallel group, Phase II dose-finding study (**FG506-05-03**). Twenty-one patients were enrolled into the pharmacokinetic part of the study. Samples from eight patients were lost due to technical reasons and another patient was excluded from the final analysis because only a 4 hour infusion was performed. Therefore, only results from 12 patients (1 female), aged from 33 to 67 years were reported. Two pharmacokinetic profiles were assessed during the study period, one during the intravenous infusion and one at steady-state conditions.

True clearance values could not be calculated because the first oral dose was administered immediately upon cessation of the infusion and therefore no elimination phase and hence no AUC to infinity could be calculated. Instead, an estimate of clearance was obtained by dividing the total dose over the infusion period by the AUC over the same period.

The mean intravenous clearance (Cl) of tacrolimus was calculated to be 3.8 L/hour, higher than that observed in healthy subjects, 2.25 L/hour (Möller et al., 1999).[4] Comparative values in liver and renal transplant recipients were 4.05 and 6.7 L/hour respectively (Lee et al. 1993; Mekki et al. 1993).[5,6] Only metabolites I and III, both inactive, were detected in blood. Metabolite II, the active metabolite was not detected and therefore metabolites do not contribute to overall pharmacological activity of tacrolimus.

An open, multi-centre, prospective, randomised, parallel group, Phase II dose-finding study (**FG506-05-04**) in primary orthotopic heart transplant adult patients receiving oral tacrolimus based immunosuppressive regimen was undertaken to optimise the dose of oral tacrolimus in heart transplant recipients. Tacrolimus was initiated either at a low dose of 0.075 mg/kg/day or a high dose of 0.15 mg/kg/day, following antibody induction. Two pharmacokinetic profiles were assessed during the study period, one following the first oral dose and one under steady-state conditions, (which was defined as a minimum of 7 days of oral tacrolimus dosing, and in addition the patient must have been maintained on a constant dose for 3 days immediately prior to the pharmacokinetic profile).

As expected, the mean AUC for the low dose group was lower than that for the high dose group (AUC_t 83 and 142 ng/mL respectively; AUC_∞ 192 and 278 ng/mL respectively). The mean AUC_t also increased between profile 1 and profile 2 for both dose groups (83 to 184 ng.h/mL and 142 to 198 ng.h/mL). Metabolite concentrations were generally low and no pharmacokinetic parameters were calculated for any metabolite. There was a very good correlation ($r > 0.88$) between minimum concentration and the overall exposure to the drug (as measured by AUC_t) for both profiles.

[4] Möller A, Iwasaki K, Kawamura A et al. Drug Metabolism and Disposition 1999; 27: 633.

[5] Lee C, Jusko W, Shaefer M et al. Clinical Pharmacology and Therapeutics 1993; 53: 181.

[6] Mekki Q, Lee C, Aweeka F et al. Clinical Pharmacology and Therapeutics 1993; 53: 238.

PKs following conversion from IV to oral tacrolimus

A multi-centre, open, single arm, Phase II study (**FG-506-05-05)** examined the pharmacokinetics of tacrolimus after IV and subsequent oral administration in patients undergoing primary orthotopic heart transplantation. Tacrolimus was administered in combination with steroids and mycophenolate mofetil (MMF), with or without antibody induction therapy. Blood concentration-time profiles to elucidate the IV and oral pharmacokinetics of tacrolimus (PK-profiles) were taken on three occasions; once for the IV dose and twice after oral doses (first dose and at steady-state). Efficacy, in terms of prevention of acute rejection, and safety parameters were assessed as secondary objectives. Tacrolimus doses were adjusted throughout the study as clinically indicated, aided by blood level monitoring. A total of 23 patients were enrolled onto the study and received at least one dose of tacrolimus (FAS).

There were a total of 11 patients (2 female), aged from 33 to 66 years, considered to have valid pharmacokinetic profiles (PK Evaluable Set). Intravenous infusion of tacrolimus began within 24 hours of skin closure in the absence of antibody induction therapy, and within 5 days of skin closure where antibody induction therapy was administered. The infusion of tacrolimus lasted for a minimum of 72 hours and a maximum of 7 days. Intravenous tacrolimus was administered as a continuous infusion over 24 hours at an initial dose of 0.01 mg/kg/day. Subsequent doses were adjusted to maintain tacrolimus concentrations in the range 12 to 18 ng/mL. Conversion to oral tacrolimus began as soon as the patient was extubated, full gastro-intestinal motility resumed and the patient was being fed by mouth, but no earlier than following 72 hours of IV tacrolimus. The initial daily oral dose of tacrolimus was 0.075 mg/kg administered in two doses (morning and evening).

In the PK Evaluable Set, the median initial day of first IV tacrolimus administration was Day 2, with the median duration of IV dosing being 5 days. During Week 1, the mean daily IV dose was 0.012 mg/kg. The median day of the initial oral dose was Day 6, with a mean initial oral dose of 0.036 mg/kg. The mean total daily oral dose rose from 0.071 mg/kg during Week 1 to a maximum of 0.121 mg/kg during Week 5. Mean whole blood trough levels of tacrolimus following oral dosing ranged from 10.71 ng/mL during Week 2 to 13.91 ng/mL during Week 6.

The AUC_{∞} following intravenous dosing was approximately 5 times higher than following initial oral dosing, 1189 and 250 ng.h/mL respectively, whereas the C_{max} was similar 14.7 and 16.5 ng/mL respectively. The mean intravenous clearance of tacrolimus in primary orthotopic heart transplant patients was calculated to be 3.9 L/hour with a bioavailability of approximately 20%. The oral bioavailability of 20% suggests that in patients where it is not possible to administer tacrolimus orally, therapy can be initiated by the intravenous route at a dose approximately 1/5th of the recommended oral dose.

Pharmacokinetics in paediatric liver transplant patients

A Phase II, open-label, multi-centre study (**03-0-160**) assessed the pharmacokinetics, long-term safety and tolerability of tacrolimus in 19 stable paediatric liver transplant patients converted from a Prograf-based immunosuppression regimen to a modified release (MR4) tacrolimus-based immunosuppression regimen. The Pharmacokinetic Evaluable Set comprised 18 subjects (13 female) aged from 5 to 13 years. Patients were enrolled into the study on their stable bd dose of Prograf on Day 1. Patients continued to receive a stable bd dose of Prograf through the evening of Day 7. On the morning of Day 8, patients were converted to MR4 on a 1:1 (mg:mg) basis for their total daily dose. MR4 was administered once-daily (qd) in the morning. The duration of the pharmacokinetic treatment period was 2 weeks; 1 week of Prograf administration, followed by 1 week of MR4 administration.

For the pharmacokinetic evaluable set, the mean ± SD total daily dose of Prograf remained unchanged between days 1 and 7 (5.3 ± 3.27 mg/day). Consistent with the 1:1 (mg:mg) conversion

from Prograf to MR4, the mean ± SD of MR4 total daily dose on Day 8 (5.3 ± 3.34 mg/day) was very similar to that of Prograf on Day 7. The difference in the range of total daily dose of tacrolimus from Day 7 (Prograf) to Day 14 (MR4) was due to an inadvertent dosing error (Patient Number 00190603), which was corrected the following day. On Day 14, the total daily dose of MR4 had increased very slightly (5.4 ± 3.40 mg/day) from the total daily dose of Prograf on Day 7.

Overall, the results were similar to those previously seen following the twice daily administration of Prograf versus the once daily administration of MR4. Median T_{max} was 1.0 hour for Prograf and 2.0 hours for MR4. Mean C_{max} was higher for Prograf (20.7 ng/mL) than for MR4 (15.2 ng/mL). For the primary measure of exposure, ln(AUC_{0-24}), the 90% CI for the comparison between MR4 and Prograf at steady state within the pharmacokinetic evaluable set (90.8, 112.1) was entirely contained within the 80% to 125% limits. The data, therefore, suggest equivalence of exposure between Prograf and MR4 at steady state. The 90% CIs for dose-adjusted ln(AUC_{0-24}) was also entirely contained within the 80% to 125% limits.

The correlation coefficients for AUC_{0-24} versus C_{min} were 0.94 on Day 7 for Prograf steady state and 0.90 on Day 14 for MR4 steady state. Therefore, trough (C_{min}) and exposure (AUC_{0-24}) measures correlated strongly during both the Prograf and MR4 treatment periods.

The 90% CIs for the primary measure of exposure for MR4 and Prograf at steady state, ln(AUC_{0-24}), were (84.5, 119.1) for black patients and (86.9, 118.1) for white patients, and both were contained within the 80% to 125% bioequivalence limits. The results for dose-adjusted ln(AUC_{0-24}) also showed both CIs to be within the 80% to 125% limits. These data suggest that equivalence in MR4 and Prograf exposure was observed between black and Caucasian patients at steady state.

Comparison of ln(AUC_{0-24}) for Prograf and MR4 by gender showed that the 90% CI for ln(AUC_{0-24}) was (96.2, 117.5) for females and (63.0, 123.4) for males. Results for dose adjusted ln(AUC_{0-24}) were similar. These data suggest that there was equivalence in exposure for female patients when comparing steady states between MR4 and Prograf. The 90% CIs for males were not within the 80% to 125% confidence limits; however, the number of males (n = 5) included in the analysis was small.

It must be noted that study numbers (n= 18) were too low to extrapolate the results seen for gender and race in this study to the wider population.

Drug Interactions

The effects of the anti-fungal agent and potent CYP3A4 inhibitor ketoconazole on the pharmacokinetics of tacrolimus, which is metabolised by the cytochrome P450 system, were examined in 6 healthy subjects (2 female), aged from 25 to 38 years, in a four dose study (**94-0-015**); each subject received single doses of tacrolimus alone (0.1 mg/kg orally and 0.025 mg/kg IV) and with concomitant ketoconazole (200 mg administered at bedtime for 12 days). The dose of tacrolimus was reduced during the ketoconazole phase (0.04 mg/g orally and, 0.01 mg/kg IV). The tacrolimus and ketoconazole doses were separated by approximately 10 hours and there was a 6 day wash-out period between doses. Concomitant ketoconazole administration caused no significant change in tacrolimus clearance (0.056 and 0.042 l/hour/kg without and with ketoconazole, respectively) or steady state volume of distribution (0.99 and 0.93 l/kg, respectively). However, the bioavailability of tacrolimus (F_{meas}) increased significantly (from 14% to 30%) when ketoconazole was administered concomitantly, whereas hepatic bioavailability (F_H) was unchanged. The study's authors suggest that as ketoconazole did not affect the F_H, the increase in F_{meas} may have been due to a local inhibitory effect of ketoconazole on tacrolimus gut metabolism and/or on intestinal p-glycoprotein activity and therefore the dose of tacrolimus may need to be decreased when co-administered with ketoconazole.

The effects of antacids (aluminium hydroxide or milk of magnesia) on the absorption of tacrolimus were determined in a single-dose, three-period, randomised, crossover study (**96-0-19**) in 9 healthy subjects (4 female) aged from 28 to 68 years. Drugs were administered following an overnight fast; treatment A was a single oral dose of five 1 mg tacrolimus capsules; treatment B was a single oral dose of 10 mL Goldline (aluminium hydroxide) followed immediately by five 1 mg capsules of tacrolimus; and treatment C was a single oral dose of 10 mL Phillips Milk of Magnesia followed immediately by five 1 mg capsules of tacrolimus.

None of the tacrolimus pharmacokinetic parameters were significantly affected by co administration of aluminium hydroxide or milk of magnesia ($P > 0.05$). For the comparison of aluminium hydroxide to the reference treatment, the log transformed 90% confidence intervals for C_{max} and AUC_t were 81.4 – 136% and 84.5 – 127% respectively. For the milk of magnesia versus reference treatment these 90% CIs were 71.4-119% and 94.6 – 142% respectively.

The pharmacokinetic interaction between tacrolimus, which is extensive metabolised by CYP3A4 and p-glycoprotein, and rifampin, a potent inducer of CYP3A4 and p-glycoprotein, was evaluated in a randomised study (**94-0-017**) comprising 6 healthy male subjects aged 25 to 42 years. Serial blood samples were collected over 96 hours following 0.1 mg/kg oral and 0.025 mg/kg/4 hours IV administrations over an 18 day rifampin dosing phase. There was a six day wash-out between tacrolimus dosing periods. Co-administration of rifampin significantly increased tacrolimus clearance (0.036 versus 0.053 l/hour/kg, $p = 0.03$) and decreased the AUC (654 versus 427 ng.hr/mL, $p = 0.03$) and bioavailability (14.4% versus 7%, $p = 0.03$) of tacrolimus. These changes are most likely to occur through the induction of CYP3A4 and P-glycoprotein by rifampin.

Summary of pharmacokinetics

MR4 was developed with the aim of having a prolonged tacrolimus absorption profile compared to Prograf. The pharmacokinetics of tacrolimus have been characterised in healthy subjects, and adult kidney, liver and heart transplant recipients, and paediatric liver transplant recipients.

Tacrolimus has been shown to be rapidly absorbed with the mean time to maximum concentration (T_{max}) ranging from 1 to 3 hours. Absorption of tacrolimus in liver transplant patients has been shown to be independent of bile flow.

The elimination half-life ($t_{½}$) of tacrolimus administered as Prograf in healthy subjects was estimated to be approximately 43 hours; the steady state $t_{½}$ of tacrolimus administered as the proposed MR4 to healthy volunteers ranged from 38 to 41 hours.

Administration of MR4 immediately following a high fat meal significantly reduced the rate and extent of tacrolimus absorption relative to the fasted state. The mean C_{max}, AUC_{0-24}, AUC_t and AUC_∞ were reduced by approximately 25% in the presence of food. The presence of food also delayed median T_{max} from 2 hours post MR4 dosing in the fasted state to 3.5 hours in the fed state ($p=0.0335$, Wilcoxon signed-rank test), whereas the elimination half life was approximately 35 hours, regardless of formulation or dosing conditions. Dosing recommendations in the proposed PI appropriately mention dosing on an empty stomach 1 hour before or 2 hours after meals.

The time of dosing affects the $\ln C_{max}$, $\ln AUC_{0-t}$, and $\ln AUC_{0-inf}$ of both Prograf and MR4 and a diurnal absorptive effect was identified for both formulations. Hence, once daily dose of the new prolonged release tacrolimus formulation is to be given in the morning as mentioned in the proposed PI.

In comparison to Prograf, tacrolimus administered as MR4, a prolonged-release formulation, results in an extended oral absorption profile. Once daily administration of MR4 results in consistently lower maximum concentration (C_{max}) values when compared to twice daily administration of Prograf.

In addition, pharmacokinetic profiles for tacrolimus prolonged-release formulation did not indicate signs of dose dumping (that is, complete dose was not more rapidly released from the dosage form).

The geometric means of the C_{max} and AUC_{0-24} in healthy Japanese subjects were 30%-40% higher than those in healthy Caucasian subjects. By contrast, the Japanese to Caucasian ratio of the geometric mean of $t_{1/2}$ was 1.064 and the 90% confidence interval was within the levels of bioequivalence. No data have been presented specifically examining the pharmacokinetics of MR4 in either black or Hispanic subjects.

Data from stable kidney, liver and heart transplant recipients converted from Prograf to MR4 on a 1:1 (mg:mg) total daily dose basis suggest equivalence in tacrolimus exposure (AUC) at steady state.

The oral bioavailability of 20% suggests that in patients undergoing primary orthotopic heart transplantation where it is not possible to administer tacrolimus orally, therapy can be initiated by the intravenous route at a dose approximately one-fifth of the oral recommended dose as has been mentioned in the PI.

In primary orthotopic heart transplant recipients, the mean intravenous clearance of tacrolimus was calculated to be 3.8 L/hour, which was higher than that observed in healthy subjects, 2.25 L/hour. Comparative values in liver and renal transplant recipients were 4.05 and 6.7 L/hour respectively.

A strong correlation exists between AUC and whole blood trough levels (C_{24}) at steady state for MR4 and Prograf. Moreover, the slope of the line of best fit was similar for both formulations indicating that for therapeutic drug monitoring, the same whole blood trough concentration range can be targeted for both formulations.

In non-transplant patients with mild hepatic impairment (mean Child-Pugh score = 6.2), $t_{½}$ and volume of distribution were increased, however, the absence of effects on clearance suggests that the overall disposition of tacrolimus was not substantially different from that in healthy subjects and liver transplant patients.

The pharmacokinetic parameters in patients with severe hepatic impairment (Child-Pugh score >10) differed markedly from those with mild hepatic dysfunction, although the $t_{½}$ was not statistically different between the two groups. Clearance and volume of distribution were significantly higher in patients with severe hepatic impairment. When compared to normal volunteers and patients with mild hepatic dysfunction, the data clearly indicate that the severe hepatic impairment has an effect on the pharmacokinetic profile of tacrolimus and a note regarding dosing in this patient group has been included in the proposed Product Information.

Concomitant administration of ketoconazole and tacrolimus caused no significant change in tacrolimus clearance or steady state volume of distribution; however, a significant increase in tacrolimus bioavailability was observed.

Concomitant administration of rifampin and tacrolimus resulted in a significant increase in tacrolimus clearance (from 36.0 mL/h/kg to 52.8 mL/h/kg p=0.03), and tacrolimus bioavailability was significantly decreased from 14.4% to 7.0% (p=0.03). Rifampin appears to induce both intestinal and hepatic metabolism of tacrolimus, most likely through induction of CYP3A4 and P-glycoprotein in the liver and intestine.

Two antacids, aluminium hydroxide and milk of magnesia, did not significantly alter the absorption of tacrolimus.

Across all studies in kidney, liver and heart transplantation, where adults were converted from twice daily Prograf to once daily MR4, the systemic exposure of tacrolimus following administration of MR4 was between 5% and 11% lower than that following administration of Prograf. The 90%

confidence intervals across these studies were all contained within the equivalence limits of 80% and 125%.

Pharmacodynamics

Mode of Action

Tacrolimus, a macrolide lactone, is a fermentation product of *Streptomyces tsukubaensis* belonging to the pharmacological class known as calcineurin inhibitors. Tacrolimus mediates its activity by the inhibition of formation of cytotoxic lymphocytes which are mainly responsible for graft rejection, T-helper cell dependent B-cell proliferation as well as formation of lymphokines such as interleukins 2 and 3, gamma interferon and expression of the interleukin (IL)-2 receptor.

No new studies were submitted that examined the mode of action of tacrolimus. A single study examined the pharmacodynamics (PD) of tacrolimus in six healthy subjects. Five efficacy/safety studies of tacrolimus in 890 transplant patients (119 kidney transplant, 739 liver transplant and 32 heart transplant) provided pharmacodynamic data in the target population.

Healthy Subjects PD

FK506-PK-1 (90-0002) evaluated the reversibility of immunosuppressive effects, possible renal effects, electrocardiogram (ECG) changes and pharmacokinetic parameters following first time administration of tacrolimus in five healthy male subjects (aged 19 to 39 years). The proposed tacrolimus formulation (MR4) was not evaluated in this study. A single dose of 0.03 mg/kg was administered intravenously over four hours and immunological parameters were monitored at screening, during a 24 hour baseline period and at regular intervals for four weeks after the administration of tacrolimus. A single IV dose of tacrolimus caused no allergic reaction, no clinically significant changes on 24 hour Holter ECG or in routine laboratory measurements (haematology, serum chemistries and urinalysis). Creatinine clearance decreased from a baseline rate of 110 ± 7 mL/min (mean ± SD) to 89 ± 19 mL/min (Day1), which may be an issue in patients with pre-existing kidney dysfunction. Whole blood concentrations of tacrolimus were approximately 20 times higher than plasma concentrations. Tacrolimus was not detectable after seven days in whole blood or plasma and was eliminated from whole blood with a half-life ($t_{1/2}$) of 32 hours. The total body clearance of 2 ± 0.45 l/hour indicated a low hepatic extraction ratio. The steady state volume of distribution was 65.7 ± 13.8 litres.

Pharmacodynamics in transplant patients administered MR4 immediately following transplantation

Kidney Transplant

A Phase II, multi-centre, open, prospective, 1:1 randomised, comparative PK study (**FG-506E-12-01)** investigated and compared acute rejection in patients undergoing kidney transplantation treated with modified release tacrolimus, MR4, or normal release tacrolimus based immunosuppression regimen. Whole blood tacrolimus trough levels between 10 to 20 ng/mL (Day 1 to Day 14 post-transplant) and between 5 to 15 ng/mL (Day 15 to Week 6 post-transplant) were recommended. The patients were also receiving an immunosuppression regimen of corticosteroids and mycophenolate mofetil.

In the FAS, comprising 119 patients (60 MR4, 59 Prograf), the frequency of biopsy-proven acute rejection over 6 weeks was comparable in MR4 (13.3%) and Prograf-treated (15.3%) patients (Table 7). The Kaplan-Meier estimates for freedom from acute rejection at Week 6 were also comparable, with values of 86.2% and 83.1% for MR4 and Prograf, respectively. Renal function, evaluated by return to long term dialysis or ongoing dialysis, incidence of delayed graft function and never functioning graft, serum creatinine levels and creatinine clearance were comparable for

MR4 and Prograf during this 6-week study, with the exception of non-significantly lower serum creatinine values for MR4-treated patients at Week 6. Incidences of graft loss were infrequent, with Kaplan-Meier estimated graft survival rates at Week 6 of 98.3% and 93.1% for MR4 and Prograf, respectively. There were no deaths during the study. However, the duration of the study was too short to enable relevant interpretation of graft and patient survival.

Table 7: Report No. FG-506E-12-01-R-PK / Study No. FG-506E-12-01

Main Efficacy Results – Study FG-506E-12-01

	6 weeks	
	MR4	Prograf
	N = 60	N = 59
Incidence	**No. Patients (%)**	
Acute rejection	12 (20.0)	10 (16.9)
Biopsy-confirmed acute rejection	8 (13.3)	9 (15.3)
Kaplan-Meier Estimate	**% of Patients**	
Freedom from acute rejection	78.5	81.2
Freedom from biopsy-confirmed acute rejection	86.2	83.1
Patient survival	100	100
Graft survival	98.3	93.1

Patient base: Full Analysis Set (all patients randomised to treatment who received at least one dose of study drug).

MR4: Modified release tacrolimus

Liver Transplant

An international, multi-centre, open prospectively randomised, parallel-group study (**GHBA-157**) evaluated the efficacy and safety of tacrolimus combined with corticosteroids as prophylactic immunosuppressive therapy compared with conventional cyclosporin A-based immunosuppressive regimens (CBIR) in patients receiving a primary liver allograft. The new MR4 form was not evaluated in this study.

Overall, 545 patients were recruited and subsequently randomised to treatment (Intent to Treat Population), of whom 270 were randomised to receive treatment with tacrolimus and 275 were randomised to receive CBIR therapy. The Efficacy Population comprised 540 patients, of whom 267 were randomised to treatment with tacrolimus and 273 to CBIR therapy. Five patients were excluded due to incorrect randomisation.

Of the 267 patients randomised to treatment with tacrolimus, 245 received an initial IV infusion of tacrolimus, while 17 patients commenced oral therapy and 5 patients did not receive treatment. The median initial IV dose was 0.038 mg/kg (2.4 mg) with a range of 0.003 – 0.091 mg/kg. Seventy one patients received their initial intravenous tacrolimus infusion over a four hour period and 107 patients had an initial infusion period of 12 hours. The initial IV dose was administered within 5 hours of surgery (that is, after closure of the abdominal wall). On Day 2 after surgery, 106 patients in the tacrolimus treatment group were receiving oral medication, which increased to 212 patients by Day 7. From Day 7 (mean of 0.165 mg/kg) through to Week 4 (mean of 0.159 mg/kg), the total daily dose remained relatively stable but subsequently the doses were progressively reduced to a mean of 0.115 mg/kg by Month 6.

The rate of biopsy-confirmed acute rejection was highest during the first month of the study; 91 and 107 patients with one or more events in the tacrolimus and cyclosporin groups, respectively (Kaplan-Meier estimate of survival was 63.9% and 57.6% in the tacrolimus and cyclosporin groups, respectively) during this period. The difference in the Kaplan-Meier rates between the two groups was significantly in favour of tacrolimus over 12 months ($p = 0.004$) and 36 months ($p = 0.006$) (Table 8).

There was no association between 5 selected adverse experiences (hyperglycaemia, diabetes mellitus, tremor, hypertension and infection) and blood concentrations of tacrolimus; this may have

been in part due to the inability to correlate all the incidences of adverse experiences with a blood concentration in the specified time window. However, patients who experienced diabetes mellitus received on average a significantly higher mean oral dose (0.03 mg/kg , p = 0.03) in the seven days prior to the onset of the event than those patients who did not experience this adverse event. By contrast, patients who experienced hypertension received on average a significantly lower mean oral dose (0.03 mg/kg, p = 0.01) in the seven days prior to the onset of the event than those who did not experience this adverse event. The study's authors could not provide a clear explanation for this discrepancy.

Table 8: - Report No. GHBA-157/PK / Study No. GHBA-157

Main Efficacy Results – Study GHBA-157

Time post-transplant	12 months		36 months	
	Tacrolimus (N = 264)	Ciclosporin (N = 265)	Tacrolimus (N = 264)	Ciclosporin (N = 265)
Incidence	**No. Patients (%)**			
Biopsy-confirmed acute rejection	107 (40.5)	132 (49.8)	110 (41.7)	132 (49.8)
Kaplan-Meier Estimate	**% of Patients**			
Freedom from BCAR	56.6*	46.4*	54.6†	44.9†
Patient survival	82.9	77.5	77.0	69.7
Graft Survival	77.5	72.6	70.6	65.2

Patient base: Efficacy population (all randomised patients who received at least one dose of study drug according to actual treatment received).

BCAR: Biopsy-confirmed acute rejection

* p = 0.004 (Wilcoxon test).

† p = 0.006 (Wilcoxon test).

Overall, there was no correlation between creatinine clearance (CL_{CR}) and blood concentrations of tacrolimus. The mean concentrations of albumin and protein increased steadily to reach normal levels in 4 – 8 weeks post–transplant. However, corresponding concentrations in patients withdrawn owing to adverse experiences remained considerably lower throughout their participation in the study.

A Phase II, multi centre, open, prospective, 1:1 randomised, comparative PK study (**FG-506-11-01**) investigated and compared the incidence of acute rejection in patients undergoing primary liver transplantation treated with MR4 or Prograf-based immunosuppression regimen. The recommended first total daily oral dose of tacrolimus was in the range of 0.10 to 0.15 mg/kg for both the MR4 and Prograf treatment arms. The subjects were also receiving a corticosteroid immunosuppression regimen. In the FAS (129 patients - 67 MR4, 62 Prograf), the frequency of biopsy-proven acute rejection over 6 weeks was comparable in MR4 and Prograf-treated patients with values of 26.9% and 27.4%, respectively (Table 9). The Kaplan-Meier estimates for freedom from acute rejection at Week 6 were also comparable (70.1% and 68.8% for MR4 and Prograf, respectively). The incidences of graft loss were infrequent in the study, with Kaplan-Meier estimated graft survival rates at Week 6 of 96.9% and 93.3%, respectively. There was a single patient death in each of the MR4 and Prograf groups (Kaplan-Meier estimates of patient survival were 98.4% and 98.1%, respectively). However, study duration was too short to enable a conclusion on graft and patient survival rates.

Table 9: - Report No. FG-506-11-01-R-PK / Study No. FG-506-11-01

Main Efficacy Results – Study FG-506-11-01

	6 weeks	
	MR4	Prograf
	N = 67	N = 62
Incidence	**No. Patients (%)**	
Acute rejection	19 (28.4)	18 (29.0)
Biopsy-confirmed acute rejection	18 (26.9)	17 (27.4)
Kaplan-Meier Estimate	**% of Patients**	
Freedom from acute rejection	68.4	67.5
Freedom from biopsy-confirmed acute rejection	70.1	68.8
Patient survival	98.4	98.1
Graft survival	96.9	93.3

Patient base: Full Analysis Set (all patients randomised to treatment who received at least one dose of study drug).

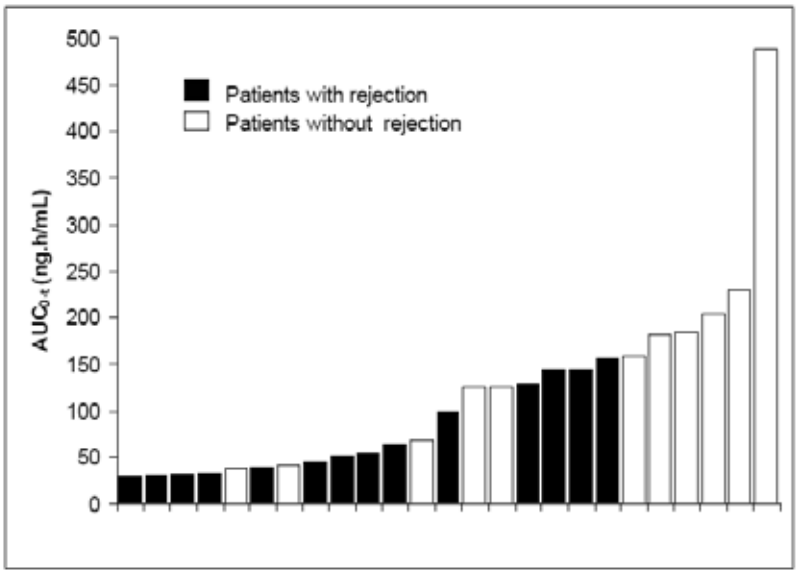
MR4: modified release tacrolimus

Heart Transplant

An open, multi-centre, prospective, randomised, parallel group, Phase II dose-finding study (**FG506-05-04**) in primary orthotopic heart transplant patients receiving oral tacrolimus based immunosuppressive regimen examined the association between the occurrence of rejection in the first three months and the systemic exposure (AUC) following first oral dose. Following antibody induction, tacrolimus was initiated either at a low dose of 0.075 mg/kg/day or a high dose of 0.15 mg/kg/day. Thirty two patients were enrolled into the pharmacokinetic sub-study of whom 27 provided two complete profiles. The analysis shows a higher incidence of rejection to be associated with lower AUC values of tacrolimus (Figure 1). The mean AUC of tacrolimus was significantly lower in patients who experienced acute rejection than in those who remained rejection free (76 versus. 168 ng.h/mL, p = 0.017).

Figure 1: Report No. FG506-05-04-R-PK-1 / Study No. FG506-05-04)

AUC0-t values following first oral dose in patients with and without a rejection episode



Pharmacodynamics in transplant patients converted from Prograf to MR4

A Phase II, open-label, multi-centre study (**02-0-152**) assessed the pharmacokinetics, long-term safety, and tolerability of tacrolimus in 70 stable liver transplant patients converted from a Prograf-based immunosuppression regimen to the proposed modified release (MR4) tacrolimus-based immunosuppression regimen. Seventy patients comprised the FAS. Patients received Prograf twice daily (bd) on Days 1 through to 14 and Days 29 through to 42. Patients received MR4 on a 1:1 (mg:mg) basis taken once daily (qd) in the morning on Days 15 through 28 and Days 43 through 56. All other immunosuppressants (mycophenolate mofetil, azathioprine, etc.) used in combination with Prograf at baseline were to be maintained at constant doses throughout the treatment period of 56 days.

There were no graft losses or patient deaths during the initial 2 week pharmacokinetic treatment period (Prograf only) and there were three instances of liver dysfunction in two patients during the MR4 treatment period.

Summary of Pharmacodynamics

Tacrolimus belongs to the pharmacological class known as calcineurin inhibitors and mediates its activity by the inhibition of cytokine gene transcription, suppression of T-cell activation and formation of cytotoxic lymphocytes which are mainly responsible for graft rejection. No new mechanism of action studies were included in this submission.

There were no differences in biopsy-confirmed acute rejection rates in patients undergoing primary liver or kidney transplantation treated with modified release tacrolimus (MR4), or Prograf-based immunosuppression regimen over a 6 week study period. The overall safety profile of MR4 was comparable to that of Prograf, the adverse events reported during the study were consistent with the known safety profile of Prograf, and no unexpected adverse events were reported.

In primary orthotopic heart transplant patients receiving oral tacrolimus, a higher incidence of rejection was associated with lower AUC values of tacrolimus and the mean AUC of tacrolimus was significantly lower in patients who experienced acute rejection than in those who remained rejection free (76 versus. 168 ng.h/mL, p = 0.017).

Efficacy

The efficacy of MR4 for the prophylaxis of organ rejection was evaluated in the large, pivotal, Phase III, comparative study **(02-0-158)** of MR4/mycophenolate mofetil (MMF), Prograf/MMF and cyclosporin (Neoral)/MMF, in combination with corticosteroids and basiliximab induction, in 668 *de novo* kidney transplant recipients. Two other Phase III non-inferiority studies compared the efficacy and safety of MR4 with Prograf in 475 liver transplant patients (study **FG506E-11-03**) and 669 kidney transplant patients (study **FG506E-12-03).** Supportive efficacy data for MR4 were provided by two Phase II pharmacokinetic studies: **FG-506E-12-01** in 119 *de novo* kidney transplant recipients and **FG-506-11-01** in 129 *de novo* liver transplant recipients. Longer term follow-up data of patients who received MR4 during Studies **FG-506E-12-01** and **FG-506-11-01** are being captured on an ongoing basis in Study **FG-506-14-02**, with results of a 1-year interim analysis presented in this submission.

The additional claim of "Conversion from Prograf capsules taken twice daily to Prograf MR prolonged-release capsules taken once daily in adult allograft recipients" was supported by some preliminary efficacy results from six Phase II, pharmacokinetic studies in stable kidney transplant recipients **(02-0-131, FG-506E-12-02** and **FJ-506E-KT01)**, stable adult liver transplant recipients **(02-0-152),** stable paediatric liver transplant recipients **(03-0-160)** and stable adult heart transplant recipients **(FG-506-15-02)**; these studies investigated pharmacokinetics and patient/ graft survival following conversion from Prograf capsules to MR4 capsules (1mg:1 mg). This is especially

important in clinical practice as this will be a frequently encountered situation when both products are on the market together.

Selected key studies and/or literature to support the use of Prograf as rescue therapy for treatment of allograft rejection resistant to treatment with other immunosuppressive drugs were also submitted. However, there are currently no data available on the use of MR4 in this indication.

Prophylaxis studies

Phase III pivotal study 02-0-158

This was a Phase III, randomised, open-label, non-inferiority study that was conducted in 668 *de novo* kidney transplant recipients (638 patients were included in the FAS) at 60 centres in the United States, Canada and Brazil. The aim of the study was to evaluate the efficacy and safety of Prograf-based immunosuppression and MR4-based immunosuppression, compared to cyclosporin (Neoral)-based immunosuppression. All regimens included MMF, corticosteroids and basiliximab induction. Prograf was initially administered as oral doses of 0.075 to 0.10 mg/kg twice daily. MR4 was initially administered as oral doses of 0.15 to 0.20 mg/kg once daily as a single dose in the morning. Neoral was initially administered as oral doses of 4 to 5 mg/kg twice daily. All patients were treated with MMF at a dose of 1 g bd (1.5 g bd was permitted in African American/black patients) throughout the study; dose-equivalent twice daily (bid), three times daily (tds), or four times daily (qid) dosing with MMF was permitted if tolerability was a concern. Additionally, all patients received basiliximab induction therapy[*] and corticosteroid treatment[#]. Doses of these immunosuppressants were adjusted based on clinical evidence of efficacy, occurrence of adverse events and whole blood trough concentrations. Target whole blood tacrolimus concentrations were 7 to 16 ng/mL (Days 0 to 90) and 5 to 15 ng/mL thereafter (for both Prograf and MR4 treatment groups). Target whole blood cyclosporin concentrations were 125 to 400 ng/mL (Days 0 to 90) and 100 to 300 ng/mL thereafter. Patients were allowed to cross over to another treatment regimen to address adverse events or severe refractory rejection which led to discontinuation of the study drug; however, crossover to the MR4/MMF arm was not permitted. Patients who crossed over to another treatment regimen or discontinued primary study drug (but did not withdraw consent) were to be followed throughout the course of the study.

The study included patients who were recipients of a primary or retransplanted cadaveric or non-HLA-identical living kidney transplant, aged≥ 12 years and received the first oral dose of randomized study drug within 48 hours of transplant procedure. Overall, the inclusion/exclusion criteria were representative of the target patient population.

Efficacy endpoints and statistical considerations

The primary efficacy endpoint was 1-year efficacy failure rate, which was defined as any patient who died, experienced a graft failure (permanent return to dialysis [> 30 days] or retransplant), had a biopsy-confirmed (Banff Grade ≥ I) acute rejection (BCAR), or was lost to follow-up. Secondary efficacy assessments included 1-year patient and graft survival rates, incidence of biopsy-confirmed acute rejection (BCAR), anti-lymphocyte antibody treatment for acute rejection, clinically treated acute rejection episodes, Incidence of BCAR (Banff Grade≥ I) at 6 and 12 months, Time to first acute rejection episode, incidence of anti-lymphocyte antibody therapy for treatment of rejection, severity of acute rejection, number of patients experiencing multiple rejection episodes, treatment

[*] All patients were to receive antibody induction as basiliximab 20 mg intravenously on Day 0 (first dose could be administered before skin closure). A second dose was to be administered between days 3 to 5.

[#] The initial dose of methylprednisolone was to be a 500 to 1000 mg (or equivalent dose) intravenous bolus administered on Day 0. Patients were to receive 200 mg methylprednisolone (or equivalent dose) orally on Day 1. Oral prednisone was then tapered according to the followings schedule: By Day 14:- 20 to 30 mg, By Month 1:- 10 to 20 mg, By Month 2:- 10 to 15 mg and By Month 3 to 12:- 5 to 10 mg

failure (defined as discontinuation for any reason), crossover for treatment failure, and renal function (assessed by calculated creatinine clearance and serum creatinine). The efficacy endpoints were appropriate and complied with the European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP) guidelines for clinical investigation of immunosuppressants for solid organ transplantation.[7]

A patient whose outcome at one year was unknown was considered an efficacy failure, patient non-survivor, and graft loss. There was no other imputation of missing data.

Analyses for efficacy failure, patient and graft survival, and biopsy-confirmed acute rejection were based on the FAS; the cut-off for these endpoints was Day 365. Efficacy failure was additionally analysed for the Per Protocol (PP) Set. For patient and graft survival and biopsy-confirmed acute rejection, the results of Kaplan-Meier estimates with data censored at the time of last follow-up and analyses with lost-to-follow-up considered as a failure are presented. The incidence of biopsy-confirmed acute rejection is presented based on both local assessment (primary analysis) and central, blinded assessment. This was a non-inferiority trial comparing the efficacy failure of Prograf/MMF and MR4/MMF versus Neoral/MMF using a non-inferiority margin of 10% and a type I error rate of 0.05. Analyses for the primary endpoint were performed adjusting for the two primary treatment comparisons and additionally for the interim reviews of the data by the Drug Safety Monitoring Board. An analysis of patients who experienced efficacy failure was performed and the treatment groups were compared using a Cochran-Mantel-Haenszel test stratified by donor type; secondary efficacy endpoints were not adjusted; that is, using 95% confidence intervals (CI) for each pairwise comparison. A total of approximately 660 patients were planned for enrolment in a 1:1:1 ratio into one of the three treatment groups, resulting in 220 patients per treatment group. This sample size had at least 90% power to conclude non-inferiority using a margin of 10% and based on estimates of the 1-year efficacy failure rate for Neoral / MMF (30%) and Prograf / MMF (25%).

Patient disposition and baseline demographics

Of the 668 patients enrolled in the study, the FAS comprised 638 patients who received at least one dose of study drug. A total of 513 (80.4%) patients completed the 1-year study on randomised treatment; 179 of 212 patients (84.4%) in the Prograf/MMF group, 183 of 214 patients (85.5%) in the MR4/MMF group and 151 of 212 patients (71.2%) in the Neoral/MMF group. Overall, the number of patients in the Neoral/MMF group who discontinued due to an adverse event or rejection was approximately twice that of patients in either the Prograf/MMF or MR4/MMF group**.** There were almost twice as many males (404/638; 63.3%) than females (234/638; 36.7%) in the FAS. Approximately three-quarters of patients were white (475/638; 74.5%) and the majority (571/638; 89.5%) were < 65 years old (mean ± SD age, 48.03 ± 12.921 years). Although the protocol allowed for the enrolment of patients as young as 12 years old, the youngest patient in the study was 17 years old at baseline. The vast majority of patients (614/638; 96.2%) experienced a primary kidney transplant upon entry into the study, with approximately half receiving a kidney from a deceased donor and half receiving a kidney from a living donor. The majority of patients (491/638; 77.0%) had ≥ 3 HLA mismatches and underwent some type of dialysis (hemodialysis, peritoneal dialysis, or both) (539/638; 84.5%) prior to study entry, with the median duration of pre-study dialysis being 29 months. Overall, the treatment groups were balanced with regard to transplant recipient demographics and other baseline characteristics**.** There was a significant difference across treatment groups for donor sex (p-value = 0.0381; chi-square test). The treatment groups were well-matched for the other donor demographic parameters (race, age, and age group)**.** Numerically more

[7] CHMP/EWP/263148/06 Guideline On Clinical Investigation Of Immunosuppressants For Solid Organ Transplantation

males in the Prograf/MMF treatment group (85/136; 62.5%) received a kidney from a female donor than males in the MR4/MMF treatment group (68/138; 49.3%) or Neoral/MMF treatment group (73/130; 56.2%); this may be important due to the relative disparity in the size of the graft versus the size of the recipient (that is, a larger male recipient receiving a relatively smaller graft from a female).

Approximately 100% of patients in all 3 treatment groups received concomitant immunosuppressive medications, although numerically more patients in the Neoral/MMF treatment group were administered anti-thymocyte immunoglobulin, immunoglobulin human normal, and muromonab-CD3, and numerically fewer patients in the MR4/MMF were administered sirolimus in comparison to the other treatment groups**.**

Mean trough concentrations of study drug were generally at the middle to high end of the target range through the first month post transplant, regardless of treatment group. After Month 1, trough concentrations of study drug gradually declined and remained toward the lower end of the target range for all treatment groups. After Day 3, the proportion of patients with trough concentration levels of study drug within the target range were comparable across the three treatment groups, although the proportion of patients with trough concentration levels of study drug within the target range was always numerically lower in the MR4 group compared with Prograf and Neoral groups at all time points except Days 3 and 4 and Month 2**;** the implication of this finding in terms of treatment compliance or tacrolimus exposure following MR4 was not explored further.

Efficacy results

The incidence of efficacy failure was numerically lower for both Prograf/MMF (32/212; 15.1%) and MR4/MMF (30/214; 14.0%) when compared to Neoral/MMF (36/212; 17.0%). The CIs constructed for the incidence differences of Prograf/MMF minus Neoral/MMF and MR4/MMF minus Neoral/MMF had upper bounds that were less than the non-inferiority limit of 10%, indicating both Prograf/MMF and MR4/MMF were statistically non-inferior to Neoral/MMF for the primary endpoint. The efficacy failure rate was similar in the Prograf/MMF (15.1%) and MR4/MMF (14%) treatment groups (diff= -1.1%, 95% CI: -7.8%, 5.7%).

It is important to note that the slightly higher efficacy failure rate in the Neoral/MMF groups appears to be driven by higher incidence of BCAR (locally assessed) while the incidence of death and graft failure rates were higher in the Prograf/MMF group compared to both MR4/MMF and Neoral/MMF groups (Table 10).

However, robustness of the primary efficacy results were supported by similar results adjusting for donor type (living or deceased) and also in the PP population**.** Since this was primarily a non-inferiority study, the PP results would be most relevant and confirm non-inferiority of Prograf and MR4 compared with Neoral. Furthermore, assessment of efficacy failure rates through 1 year using results obtained from central blinded assessments of biopsies showed similar results (12.3%, 7.7% and 10.8% in Prograf/MMF, MR4/MMF and Neoral/MMF groups, respectively) and confirmed non-inferiority of tacrolimus compared to cyclosporin based therapy**.**

Table 10: Study 02-0-158

Summary of 1-Year Efficacy Failure Rate

	Treatment Group		
	Prograf/MMF (n = 212)	MR4/MMF (n = 214)	Neoral/MMF (n = 212)
Efficacy Failure †	32 (15.1%)	30 (14.0%)	36 (17.0%)
Death	9	3	5
Graft Failure	9	5	4
BCAR (local assessments)	16	22	29
Lost to Follow-up	4	3	1
Relative Risk	0.89	0.83	
Incidence Difference	-1.9%	-3.0%	
[97.6% CI]	[-9.9%, 6.2%]	[-10.9%, 4.9%]	
[95.2% CI]	[-8.9%, 5.2%]	[-9.9%, 4.0%]	

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Only events up to day 365 are included in the analyses. After day 365, two patients died (Patient Numbers 01812009 [Neoral/MMF] and 07502001 [Prograf/MMF]), one patient experienced a graft failure (Patient Number 00522012 [Neoral/MMF]), and two patients experienced their first BCAR (Patient Numbers 00422004 and 00522003 [both MR4/MMF]).
Lost to follow-up was defined as any patient who did not have at least 335 days of follow-up information.
Relative risk and incidence difference are relative to the Neoral/MMF treatment group.
† A patient was only counted once regardless of how many criteria were met.
Graft failure: Permanent return to dialysis (> 30 days) or retransplant.
BCAR: Biopsy-confirmed acute rejection. Biopsy results were from local assessments.
CI: Confidence interval.
MMF: Mycophenolate mofetil.
MR4: Tacrolimus modified-release formulation.

All 3 treatment groups showed similar incidence of patient survival, (93.9%, 97.2% and 97.2% in Prograf/MMF, MR4/MMF and Neoral/MMF groups, respectively) and graft survival (91.5%, 95.3% and 95.3%, respectively) suggesting non-inferiority of tacrolimus-based regimen compared to cyclosporin-based therapy**.** Kaplan-Meier estimates of 1-year patient and graft survival rates with data censored at the time of the last follow-up provided similar results**.**

The incidence of BCAR (locally assessed) at 6 months and 1 year was statistically significantly lower in the Prograf/MMF treatment group than the Neoral/MMF treatment group; MR4/MMF was statistically non-inferior to Neoral/MMF for BCAR at 6 months and 1 year, but incidence of BCAR in the MR4 group was twice that in the Prograf group **(**Table 11**).** However, central blinded review of biopsies showed numerically fewer BCARs in all 3 treatment groups and Prograf/MMF and MR4/MMF were statistically non-inferior to Neoral/MMF for BCAR when biopsies were assessed by central, blinded reviewers**.** When the biopsies were evaluated by central, blinded reviewers, the majority of BCARs were assessed to be Banff Grade IA, IB, or IIA, regardless of treatment group.

Significantly fewer patients in the Prograf/MMF treatment group (p-value = 0.009; chi-square test) had clinically-treated acute rejections compared with those in the Neoral/MMF treatment group. Furthermore, significant fewer patients in the Prograf/MMF treatment group (p-value = 0.012; chi-square test) and MR4/MMF treatment group (p-value= 0.040; chi-square test) received anti-lymphocyte therapy for the treatment of acute rejection compared with those in the Neoral/MMF treatment group**.**

Table 11: Study 02-0-158

Summary of Biopsy-Confirmed Acute Rejection Episodes (Local Assessments)

	Treatment Group			p-Values†	
	Prograf / MMF (n = 212)	MR4 / MMF (n = 214)	Neoral / MMF (n = 212)	Prograf/MMF versus Neoral/MMF	MR4/MMF versus Neoral/MMF
At 6 Months	8 (3.8%)	17 (7.9%)	25 (11.8%)	0.002	0.183
Relative Risk	0.32	0.67			
Incidence Diff.	-8.0%	-3.8%			
[95.0% CI]	[-13.1%, -3.0%]	[-9.5%, 1.8%]			
At 1 Year	16 (7.5%)	22 (10.3%)	29 (13.7%)	0.040	0.280
Relative Risk	0.55	0.75			
Incidence Diff.	-6.1%	-3.4%			
[95.0% CI]	[-12.0%, -0.3%]	[-9.6%, 2.8%]			
Maximum Grade of Acute Rejection					
I-A	8	11	14		
I-B	4	3	6		
II-A	3	6	6		
II-B	1	1	1		
III	0	1	2		

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
Only events up to day 365 are included in the analyses. Relative risk and incidence difference are relative to the Neoral treatment group.
† p-values obtained using chi-square test.
CI: Confidence interval. Incidence Diff.: Incidence difference. MMF: Mycophenolate mofetil.
MR4: Tacrolimus modified-release formulation.

There were no significant differences in the incidence of delayed graft function[*] between the tacrolimus groups (Prograf/MMF or MR4/MMF) compared to the Neoral/MMF treatment group**.**

Significantly fewer patients in the Prograf/MMF and MR4/MMF treatment groups discontinued their randomized study drug for any reason (treatment failure) compared with those in the Neoral/MMF treatment group (15.6%, 14.5% and 28.8% in Prograf, MR4 and Neoral groups, respectively; p-value <0.001; chi-square test). Furthermore, significantly fewer patients in the Prograf/MMF and MR4/MMF treatment groups crossed over to another treatment arm due to treatment failure compared with those in the Neoral/MMF treatment group (2.8%, 4.7% and 18.4%, respectively; p-value < 0.001; chi-square test). It was noted that the relative risk of treatment failure in the Prograf/MMF and MR4/MMF treatment groups compared to the Neoral/MMF treatment group was 0.54 and 0.50, respectively. Furthermore, the relative risk of crossover due to treatment failure in the Prograf/MMF and MR4/MMF treatment groups compared to the Neoral/MMF treatment group was 0.15 and 0.25, respectively**.**

There was a trend toward lower mean serum creatinine values for the tacrolimus treatment groups (Prograf/MMF and MR4/MMF); compared with Neoral/MMF group, there were significantly lower values in Prograf/ MMF group at 6 months and in MR4/MMF treatment group at 12 months**.** Numerically fewer patients who received MR4/MMF experienced a clinically significant increase (< 2.5 mg/dL at baseline increasing to≥ 2.5 mg/dL) in serum cr eatinine values during the study compared to those who received Prograf/MMF or Neoral/MMF, but numbers were too small to enable definitive conclusions**.**

[*] Delayed graft function was defined as at least one dialysis episode within the first 7 days after completion of the transplant procedure. Acute tubular necrosis requiring dialysis within the first week following transplant met the definition of delayed graft function.

Mean creatinine clearance values were significantly greater at Months 6 and 12 for the Prograf/MMF treatment group compared to the Neoral/MMF treatment group (p-value < 0.05; two-way ANOVA with treatment and centre as factors). Mean creatinine clearance values were significantly greater at Months 4, 6, 10, and 12 for the MR4/MMF treatment group compared to the Neoral/MMF treatment group**.** These results correspond with the lower serum creatinine values observed for the MR4/MMF treatment group as compared to the Neoral/MMF treatment group during the course of the study Numerically fewer patients who received MR4/MMF experienced clinically significant decreases (≥ 40 mL/min at baseline decreasing to < 40 mL/min) in creatinine clearance values during the study than those who received Prograf/MMF or Neoral/MMF**.** Although the number of dialysis episodes or the number of days on dialysis were numerically lower in the tacrolimus groups compared with Neoral/MMF the difference was not statistically significant**.**

Efficacy in subgroups

Numerically lower efficacy failure rates and incidence of BCAR were seen with the elderly (≥ 65 years of age) compared with non-elderly (< 65 years old) across all three treatment groups, but these results are not conclusive due to very small number of elderly patients**.**

A numerically higher efficacy failure rate was observed in females compared to males in the tacrolimus groups, especially MR4 (females versus males: 10.1% versus 21.1%), while it was similar in the Prograf (14% versus 17.1%) and Neoral (17.7% versus 15.9%) groups**.** However, incidence of BCAR was greater in females compared with males in MR4 (male versus female: 5.8% versus 18.4%) and Prograf (5.9% versus 10.5%), while the opposite was true in the Neoral group (15.4% versus 11%). In females, a treatment by race interaction was observed with respect to the incidence of BCAR; a higher incidence of BCAR was observed in black women (5/14; 35.7%) compared to black men (1/27; 3.7%) in the MR4/MMF treatment group, and in black men (7/22; 31.8%) compared to black women (1/14; 7.1%) in the Neoral/MMF treatment group. It should be noted that event rates for death and graft failure in the male and female subgroup were small; therefore, comparisons should be made with caution**.**

Efficacy failure rates and the incidence of BCAR were numerically higher for male patients who received a graft from a male donor in the Prograf/MMF treatment group than those who received grafts from female donors: the opposite was true for the Neoral/MMF treatment group. The efficacy failure rate was similar for both cohorts in the MR4/MMF treatment group, although the incidence of BCAR was numerically higher for male patients who received a graft from a female donor in the MR4/MMF treatment group. Efficacy failure rates were numerically higher for male patients who received a graft from a female donor in the Neoral/MMF treatment group than those in the Prograf/MMF and MR4/MMF treatment groups. The incidence of BCAR was significantly higher for male patients who received a graft from a female donor in the Neoral/MMF treatment group compared with those in the Prograf/MMF treatment group (p-value = 0.004; chi-square test)**.**

Black transplant recipients had a numerically higher efficacy failure rate and BCAR incidence than white transplant recipients across all three treatment groups. Additionally, black transplant recipients in the Prograf/MMF treatment group had a numerically higher graft failure rate than white transplant recipients. However, black patients who received Prograf/MMF or MR4/MMF had numerically lower efficacy failure rates and lower incidence of BCAR that those who received Neoral/MMF. This was also observed for white patients. However, these results should be interpreted with caution as the sample size of the black population was small, as were event rates for death and graft failure; therefore, comparisons should be made with caution**.**

There were no apparent clinically significant differences in efficacy failure or its components based on the presence of diabetes at baseline within the three treatment groups**.** Efficacy failure rates were numerically higher in patients who received grafts from deceased donors compared with those who received grafts from living donors in the Prograf/MMF and Neoral/MMF treatment groups; the efficacy failure rate was similar for both cohorts in the MR4/MMF treatment group. However, the

incidence of BCAR in patients with a deceased donor was significantly lower in the Prograf/MMF (7.5%) and MR4/MMF (9%) treatment groups compared with the Neoral/MMF (20.8%) treatment group**.**

Efficacy failure rates were numerically higher in Brazilian patients who received Prograf/MMF or MR4/MMF compared to patients in the US and Canada. The efficacy failure rate was similar for both cohorts in the Neoral/MMF treatment group. However, these results should be interpreted with caution as the number of Brazilian patients was much less than US/Canada patients**.**

Phase III studies (non-inferiority between Prograf and MR4 tacrolimus formulations)

Non-inferiority study in primary liver transplant patients

FG506E-11-03 was a multicentre, 1:1 randomized, double blind, two arm parallel group study to evaluate and compare the efficacy and safety of MR4 with that of Prograf in combination with steroids in 475 patients undergoing primary liver transplantation. 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 24 weeks, the study was unblinded and continued in an open design extension period until the last patient had completed their 12-month visit. The initial dose was 0.2mg/kg per day given as a single dose (MR4) or 2 doses (Prograf); subsequently, doses could be adjusted based on clinical evidence of efficacy, occurrence of adverse events and according to whole blood tacrolimus trough level measurements. The study lasted at least 12 months per patient.

The study included patients aged >18 years and receiving a primary, split liver or a whole liver graft from a cadaveric donor with compatible ABO blood type; patients must have received the first dose of tacrolimus and corticosteroids within 24 hours of skin closure and were expected to be maintained on tacrolimus throughout the study.

Efficacy endpoints and statistical considerations

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; severity of biopsy-proven acute rejection; and patient and graft survival within the first 24 weeks and 12 months following transplantation.

The primary endpoint, incidence of acute rejection proven by local biopsy within 24 weeks following transplantation, was analysed using Kaplan-Meier methods. The sample size had at least 80% power to confirm non-inferiority between treatment groups (at 2.5% level of significance based on one-sided t-test). The study report states that this was based on results of previous studies, which indicated that a reasonable assumption for the event rate of patients with biopsy-proven acute rejection was approximately 35% and a difference in this event rate of 15% between both treatment groups was considered as a clinically meaningful margin of non-inferiority. However, the sponsors have not provided adequate data to justify this non- inferiority margin. Efficacy analysis was done in both the FA and PP sets, but the primary analysis of efficacy data was based on the PP Set (PPS), which was appropriate for this non-inferiority study.

Patient disposition and baseline patient characteristics

Of the 475 patients randomized to treatment, 471 (99.2%) were in the FAS, 237 (99.2%) patients in the MR4 and 234 (99.2%) patients in the Prograf group. A total of 111 patients in the FAS were excluded from the PPS with similar number of exclusions in both treatment groups (56 and 55 in the MR4 and Prograf groups, respectively). The most common reason for exclusion from the PPS

was withdrawal of the patient before a biopsy-proven acute rejection episode (106 patients in total); however, the exact reasons for withdrawal before acute rejection episode were not provided in the study report. The PPS included 360 (75.8%) patients (182 and 178 patients in the MR4 and Prograf groups, respectively). The incidence of withdrawals was similar in both groups (36.7% and 33.3%, respectively) with approximately 25% in each group discontinuing due to AEs**.**

The treatment groups were well balanced with regard to basic demographics and primary diagnoses**.** There were no clinically relevant differences between MR4 and Prograf in terms of donor characteristics and donor/recipient mismatch; however, there were a slightly higher number of CMV negative recipients receiving CMV positive donor organs in the MR4 arm (Prograf versus MR4: 12.4% versus 17.4%)**.**

Prophylactic MMF administration was not permitted during the study and patients could only receive MMF in case of acute rejection or in case of renal impairment after 6 months of study participation. During the 12 months post-transplant, the administration of MMF was comparable in the MR4 (16.0%) and Prograf (14.5%) treatment groups. Antibody administration was only permitted as rejection therapy; during the 12 months post-transplant, administration of antibodies was comparable in the MR4 (3.8%) and Prograf (5.6%) treatment groups.

Efficacy results

In the PPS, the local biopsy-confirmed acute rejection event rates (Kaplan-Meier analysis) were 36.3% (MR4) and 33.7% (Prograf) with a difference of 2.6% (MR4 minus Prograf) and 95% CIs for the difference (-7.3%, 12.4%) were within the pre-defined non-inferiority margin of 15%. The results for the FAS were similar to the results of the PPS **(**Table 12**).** 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**.** Furthermore, robustness of primary efficacy results was confirmed by results of the central biopsy review**.** The incidence of local biopsy-confirmed acute rejection episodes and the incidence of biopsy-confirmed corticosteroid-resistant acute rejection were also similar in both MR4 and Prograf treatment groups for both the PP and the FASs. In the FAS, the 12-month patient survival rates (89.2% and 90.8%) and the graft survival rates (85.3% and 85.6%) were also comparable in the MR4 and Prograf groups. In the FAS the number of deaths was comparable for both MR4 and Prograf. 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 Prograf arm. In the PPS, there were more deaths reported in the MR4 arm compared to the Prograf arm (11 versus 6, p-value of < 0.05; Chi-square test)**.** However, patients who died prior to experiencing a biopsy-proven acute rejection were not included in the PPS by definition and details of reasons for withdrawal before rejection episode were not provided in the study report. Overall, graft loss was comparable between the MR4 and Prograf arms at 24 weeks and 12 months post-transplant. The majority of efficacy failures were due to local biopsy-proven acute rejection episodes in both treatment groups and for both analysis sets. The efficacy failure rates for MR4 and Prograf were comparable. The 12-month difference [95% CI] between MR4 and Prograf in the efficacy failure rate[*] was 0.8% [-9.2% to 10.8%] in the PPS and it was 1.0% [-10.0% to 8.0%] in the FAS**.**

[*] Efficacy failure, defined as any patient who had a biopsy-proven acute rejection, graft loss, death or whose outcome at the end of the considered analysis period was unknown, was analysed using Kaplan-Meier procedures and providing frequency tables.

Table 12: Study FG-506E-11-03

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†	2.6%	
95% confidence intervals	-7.3%, 12.4%	
p-value‡	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†	3.3%	
95% confidence intervals	-5.7%, 12.3%	
p-value§	0.354	

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

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

In the Phase III study FG-506E-11-03, MR4 was non-inferior to Prograf 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 Prograf. Patient, graft survival and efficacy failure rates were also comparable for MR4 and Prograf, and were consistent with previous experience. Overall, results from this study showed that MR4 was as efficacious as Prograf, when used as primary immunosuppressant in de novo liver transplantation.

Non-inferiority, Phase III study in primary renal transplant patients

FG-506E-12-03 was a multicentre, 1:1 randomized, double blind, two arm parallel group study to evaluate and compare the efficacy and safety of MR4 versus Prograf in combination with MMF (Cellcept) and steroids in patients undergoing kidney transplantation. The study was conducted from August 2004 to December, 2006. The study design was similar to study FG-506-11-03 described above with exception of differences in the main inclusion criteria, that is, this study included 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 Prograf-based immunosuppressive regimen after informed consent had been given. Efficacy endpoints were similar to the Phase III non-inferiority study discussed above with the exception that the non-inferiority margin was 10% instead of 15% in the liver transplant study. However, data to substantiate this non-inferiority margin were not provided in the study report.

Of the 699 patients randomized to treatment, 667 (95.4%) were in the FAS (331 and 336 patients in the MR4 and Prograf groups respectively). The PPS included 571 (81.7%) patients (280 and 291 patients, respectively). A total of 96 patients in the FAS were excluded from the PPS (51 in the MR4 group and 45 in the Prograf group). The most common reason for exclusion from the PPS was withdrawal of the patient before a biopsy-proven acute rejection episode (82 patients). Overall,

135/667 (20.2%) patients prematurely discontinued the study medication with a slightly higher withdrawal rate in the MR4 group (22.4%) compared with the Prograf group (18.2%). AEs were the most common cause of withdrawal with similar incidence in the MR4 (13.0%) and Prograf group (11.6%); incidence of death (Prograf versus MR4: 0.6% versus 1.2%) and violations of inclusion/ exclusion criteria (0.9% versus 1.8%) were slightly higher in the MR4 group**.** 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**.** The most common primary diagnoses were glomerulonephritis (Prograf versus MR4: 29.2% versus 37.5%), unknown cause (15.5% versus 11.4%), polycystic disease (16.2% versus 10.7%) and nephrosclerosis (11.7% versus 10.0%) with no relevant differences between the treatment groups in the pattern of primary diagnoses. There were no clinically relevant differences between MR4 and Prograf in terms of donor demographics**.** Numerically more cytomegalovirus (CMV) negative patients in the MR4 treatment group (17.5%) received an organ from a CMV positive donor than patients in the Prograf (12.1%) treatment group. Donor/recipient mismatch, donor type and cold ischemia time were comparable for both treatment groups, with the exception of HLA DR mismatch, which was significantly higher in the MR4 group compared to the Prograf group**.** For the PPS, the percentage of recipients/donors with zero DR mismatch was smaller and the proportion having two DR mismatches was higher in the MR4 group than in the Prograf group, contributing to the significantly higher mean DR mismatches observed in the MR4 group (p=0.017; Wilcoxon rank sum test). Similar findings were observed for the FAS**.**

The whole blood tacrolimus trough levels for MR4 and Prograf were generally comparable, although the mean whole blood tacrolimus trough levels were slightly lower for MR4 than Prograf by 2.4 ng/mL at Week 1. Corticosteroid and MMF administration as maintenance therapy was comparable throughout the study for both MR4 and Prograf groups, with steroid withdrawal being performed in a similar manner for both formulations. Antibody administration was only permitted as rejection therapy. During the 12 months post-transplant including the extension period, administration of antibodies was comparable in the MR4 (8.5%) and Prograf (6.3%) treatment groups. During the 12 months post-transplant including the extension period, more patients in the MR4 group (19 patients, 5.7%) received other immunosuppressive medication[*] compared to the Prograf group (seven patients, 2.1%), including administration of commercial tacrolimus, short-term application occurring by error and intentional change of maintenance regimen.

The frequency of overall acute rejections and of corticosteroid-resistant acute rejection was slightly higher in the MR4 group compared with the Prograf treatment group. This was the case for both the PP and the FA Sets **(**Table 13**).** At 24 weeks post transplant, the difference [95% CI] in the primary endpoint, event rate of local biopsy confirmed acute rejection, between MR4 and Prograf in the PPS was 4.5% [-1.8% to 10.9%] and the upper limit of the CI was just outside the pre defined non-inferiority margin of 10%. However, the criterion for non-inferiority was met in the FAS with treatment difference [95% CI] of 3.8% [-2.1% to 9.6%]. Similar results were observed for event rate of local biopsy-confirmed acute rejection at 12 months**.** Based on the central biopsy review of all available biopsies, the difference [95% CI] in the event rate of central biopsy-confirmed acute rejection at 24 weeks post-transplant between MR4 and Prograf was 7.9% [1.2% to 14.6%]. The upper limit of the CI was outside the pre-defined non-inferiority margin of 10%. The results for the FAS confirmed the PPS observation, with a difference [95% CI] of 6.4% [-0.1%, 12.8%]**.**

When all biopsies were centrally reviewed, more patients were identified to have a positive biopsy when compared to the local assessment. The interpretation of post-hoc diagnosis of acute rejection in patients free from clinically diagnosed acute rejection episodes is not clear

[*] other immunosuppressive treatment was defined as any immunosuppressant or adjunct other than MMF, tacrolimus, corticosteroids, or antibodies in the 12 months post-transplant including the extension period

in renal transplantation; nevertheless, the non-inferiority criteria in this analysis were not met.

Table 13: Study FG-506E-12-03

Frequency of Acute Rejection

	Per Protocol Set			
	FK506 (N=291)		MR4 (N=280)	
	Patients (%)	Episodes	Patients (%)	Episodes
Acute rejections	77 (26.5)	92	90 (32.1)	107
Spontaneously resolving†	7 (2.4)	8	4 (1.4)	4
Corticosteroid sensitive‡	53 (18.2)	62	64 (22.9)	69
Corticosteroid resistant§	20 (6.9)	20	28 (10.0)	31
Other	2 (0.7)	2	3 (1.1)	3
	Full Analysis Set			
	FK506 (N=336)		MR4 (N=331)	
	Patients (%)	Episodes	Patients (%)	Episodes
Acute rejections	82 (24.4)	98	94 (28.4)	113
Spontaneously resolving†	7 (2.1)	8	5 (1.5)	5
Corticosteroid sensitive‡	56 (16.7)	66	66 (19.9)	72
Corticosteroid resistant§	21 (6.3)	21	30 (9.1)	33
Other	3 (0.9)	3	3 (0.9)	3

† An acute rejection episode that was not treated with new or increasing corticosteroid medication, antibodies or any other medication and resolved, irrespective of any tacrolimus or MMF dose changes

‡ An acute rejection episode that was treated with new or increased corticosteroid medication only and resolved, irrespective of any tacrolimus or MMF dose changes

§ An acute rejection episode that did not resolve following treatment with corticosteroids only, or was not treated with corticosteroids first but only with antibodies, irrespective of any tacrolimus or MMF dose changes

The HLA DR mismatch was reported statistically significantly more frequently in the MR4 group compared to the Prograf group. As HLA mismatches are an established risk factor for the occurrence of acute rejection episodes following kidney transplantation, an additional analysis was performed to adjust for the HLA DR mismatch imbalance in the study. After 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] was 1.9% [-4.4% to 8.3%] in the PPS and 2.4%, [-3.5% to 8.4%] in the FAS**.** However, the actual incidence of acute rejection following this new analysis was not provided in the study report.

For the PPS, the Kaplan-Meier estimated patient survival rates were comparable at both 24 weeks post-transplant (100% for both MR4 and Prograf) and at 12 months post-transplant (MR4 versus Prograf: 98.9% versus 98.8%). In the FAS, eighteen patients died; ten patients in the MR4 group and eight patients in the Prograf group. For the PPS, the Kaplan-Meier estimated graft survival rates were comparable at both 24 weeks post-transplant (98.2% versus 99.0%) and at 12 months post-transplant (96.8% versus 97.5%) with similar results in the FAS. At 12-months, the difference [95% CI] between MR4 and Prograf in the efficacy failure rate was 3.3% [-3.4% to 10.0%] in the PPS and it was 4.7% [-2.0% to 11.3%] in the FAS.

Renal function was assessed based on delayed graft function[#], serum creatinine and creatinine clearance (Cockcroft & Gault formula). The incidence of initial renal dysfunction was comparable

[#] Delayed graft function was defined as the patient having dialysis for more than one day within the first seven days post-transplantation (Day 0 to Day 7).

between MR4 and Prograf groups, with similar incidence of delayed graft function in the PPS (15.0% and 16.2% in the MR4 and Prograf groups, respectively). Improvement in renal function throughout the 12 months post-transplant was also comparable with 12-month serum creatinine levels in completers of 130.68 µmol/L and 130.02 µmol/L for MR4 and Prograf, respectively; corresponding figures for creatinine clearance were 66.76 mL/min and 67.25 mL/min, respectively**.**

Overall, this large, randomized, double blind double dummy, multi-centre Phase III study compared the efficacy and safety of MR4 versus Prograf, both in combination with MMF and steroids, in adult kidney transplant patients. The primary hypothesis to demonstrate non-inferiority for the primary efficacy variable, event rate of biopsy confirmed acute rejection, was not met in the PP Analysis. Nevertheless, the study demonstrated non-inferiority of MR4 in the FAS. The imbalance in HLA-DR mismatch between the MR4 and Prograf groups may have 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 non-inferiority in the PP set was not met, the study in fact supports the concept of therapeutic equivalence of the two formulations.

It is important to note that biopsy-proven acute rejection, the primary endpoint in the two above Phase III non-inferiority studies was not appropriate; a composite endpoint such as efficacy failure rate used in the pivotal study 02-0-158 is recommended according to the CHMP guidelines. However, the sponsors did look at efficacy failure rate as a secondary endpoint and those results were similar to those observed for the primary endpoint of BCAR, that is, non-inferiority between MR4 and Prograf was shown in study FG506E-11-03 in liver transplantation, but it was not shown in the other study FG506E-12-03 in kidney transplantation. Hence, results from the two non-inferiority, Phase III studies can only be considered supportive.

Phase II supportive studies

Supportive efficacy data were provided by two Phase II, open-label, randomised pharmacokinetic studies comparing the efficacy and safety of MR4 to Prograf in kidney (**FG-506E-12-01**) and liver transplant **FG-506-11-01**) adult recipients. Both studies were multi-centre, open-label, prospective, 1:1 randomised studies primarily designed to compare the pharmacokinetics of tacrolimus administered as MR4 and Prograf on the first day of treatment and under steady state conditions over a 6-week period. Patients with malignancy or history of malignancy within the last 5 years, systemic infections requiring treatment, serum creatinine > 175µmol/L, or who had previously received or were receiving an organ transplant other than liver, were excluded from these studies. Pregnant women and nursing mothers were also excluded. Efficacy in terms of incidence of biopsy confirmed acute rejection episodes, acute rejection episodes, severity of biopsy-confirmed acute rejection, and patient and graft survival were also investigated.

The Phase II study **(FG-506E-12-01)** in 119 kidney transplant patients was conducted from January 2003 to January 2004. Following transplantation, patients received either MR4-based (0.20 mg/kg once daily) or Prograf-based (0.10 mg/kg twice daily) immunosuppression. Concomitant immunosuppression consisted of MMF and corticosteroids. Following completion of this study, patients who received MR4 were able to enter Study FG-506-14-02 in order to capture long-term efficacy and safety data for MR4 on an ongoing basis. The majority of the patients were male Caucasians with mean age of 44 years. Baseline demographics and disease characteristics were similar in both treatment groups with the exception of higher number of males in the Prograf group**.** Donor demographics and ischaemia times were also comparable for the MR4 and Prograf treatment groups**.** The total daily doses of both MR4 and Prograf were similar for the two treatment arms for the first 7 days post-transplant. Thereafter, the total daily dose of MR4 was slightly higher than the corresponding doses of Prograf**.** During Week 1, the mean whole blood tacrolimus trough levels were 12.0 and 14.4 ng/mL in the MR4 and Prograf groups, respectively. After this time, the

maximum mean whole blood tacrolimus trough concentrations were 13.9 and 13.6ng/mL in the MR4 and Prograf groups, respectively. Corticosteroids as rejection therapy were administered to slightly more MR4 patients (12/60, 20.0%) compared with Prograf patients (10/59, 16.9%), The majority of rejection therapy was administered in the first 3 weeks post-transplant and doses of steroids ranged from 40 to 1250 mg in the MR4 group and 100 to 1250 mg in the Prograf group.

The overall frequencies of acute rejection (Prograf versus MR4: 16.9% versus 20%) and of biopsy-proven acute rejection (15.3% versus 13.3%) were comparable for Prograf and MR4. There were no marked differences in the classification or histological severity of the acute rejections reported (Table 14).

Table 14: Study FG-506E-12-01

: Overall Frequency of Acute Rejection

	Prograf (N=59)			MR4 (N=60)		
	Patients	(%)	Events	Patients	(%)	Events
Acute rejections†	10	(16.9)	10	12	(20.0)	12
Spontaneously resolving	0		0	0		0
Corticosteroid sensitive	7	(11.9)	7	10	(16.7)	10
Corticosteroid resistant	3	(5.1)	3	2	(3.3)	2
Suspected acute rejection‡	1	(1.7)	1	4	(6.7)	4

Full Analysis Set
† For definition see Section 5.5.3.1; ‡ Acute rejection not confirmed by biopsy
N = Total number of patients

Overall Frequency of Biopsy-Proven Acute Rejection

	Prograf (N=59)			MR4 (N=60)		
	Patients	(%)	Events	Patients	(%)	Events
Acute rejections†	9	(15.3)	9	8	(13.3)	8
Spontaneously resolving	0		0	0		0
Corticosteroid sensitive	6	(10.2)	6	6	(10.0)	6
Corticosteroid resistant	3	(5.1)	3	2	(3.3)	2

Full Analysis Set
† For definition see Section 5.5.3.1
N = Total number of patients

The Kaplan-Meier estimates for freedom from biopsy-proven acute rejections at Week 6 of the study were comparable for both MR4 (86.2%) and Prograf (83.1%). There was no evidence of an increase in early post-transplant acute rejections in the MR4-treated patients. There was also no episode of acute rejection beyond Week 2 in the MR4 group. Renal function, evaluated by return to long term dialysis or ongoing dialysis, incidence of delayed graft function and never functioning graft, serum creatinine levels and creatinine clearance were comparable for MR4 and Prograf during this 6-week study, with the exception of slightly lower serum creatinine values for MR4-treated patients at Week 6. Incidences of graft loss were infrequent, with Kaplan-Meier estimated graft survival rates at Week 6 of 98.3% and 93.1% for MR4 and Prograf, respectively. There were no deaths during the study.

The Phase II study **FG-506-11-01** involving 129 adult patients undergoing primary liver or split liver transplantation was conducted from January 2003 to January 2004. The majority of the patients were male Caucasians with mean age of 50-52 years; baseline demographics/ disease

characteristics and donor characteristics were similar in the Prograf and MR4 groups. Apart from the first dose (Day 1), the mean total daily dose of MR4 was higher than that of Prograf throughout the study**.** Whole blood tacrolimus trough levels in the early transplant period were higher for Prograf-treated patients than MR4-treated patients; however, by Day 7 the trough levels were comparable for the two groups. Corticosteroids as rejection therapy were administered to slightly more MR4 patients (15/67, 22.4%) compared with the Prograf patients (10/62, 16.1%). The majority of rejection therapy was administered in the first 2 weeks post-transplant and steroid doses ranged from 67.5 to 1250 mg in the MR4 group and 500 to 1250 mg in the Prograf group.

The overall frequencies of acute rejection, and of biopsy-proven acute rejection were comparable for Prograf (29%) and MR4 (28.4%) (Table 15). There were no marked differences in the classification or histological severity of the reported acute rejections**.** The Kaplan-Meier estimates for freedom from biopsy-proven acute rejections at Week 6 of the study were comparable for both MR4 and Prograf, with respective values of 70.1% and 68.8%. There was no evidence of an increase in early post-transplant acute rejections in the MR4-treated patients**.** The Kaplan-Meier estimated graft survival rate at Week 6 of the study was also comparable (96.9% and 93.3% for MR4 and Prograf groups, respectively). There was no graft loss beyond Week 1 for the MR4-treated patients, and no graft loss beyond Week 3 for the Prograf-treated patients. Two patients died during the study, one each in the MR4 and Prograf groups, and both deaths occurred in the early post-transplant period.

Overall, results from the above two Phase II studies provided supportive evidence for efficacy of tacrolimus (both Prograf and new prolonged release MR4 formulations) with no significant differences between the two groups in terms of biopsy confirmed acute rejection episodes, acute rejection episodes, severity of biopsy-confirmed acute rejection, and patient and graft survival. However, it is important to note that these studies were not controlled and patient and graft survival data should be interpreted with caution due to short duration of treatment (only 6 weeks).

Table 15: Study FG-506E-11-01

Overall Frequency of Acute Rejection

	Prograf (N=62)			MR4 (N=67)		
	Patients	(%)	Events	Patients	(%)	Events
Acute rejections†	18	(29.0)	19	19	(28.4)	20
Spontaneously resolving	4	(6.5)	4	4	(6.0)	4
Corticosteroid sensitive	8	(12.9)	8	10	(14.9)	10
Corticosteroid resistant	5	(8.1)	5	6	(9.0)	6
Other acute rejection‡	2	(3.2)	2	0		0
Suspected acute rejection§	1	(1.6)	1	1	(1.5)	1

Full Analysis Set
† For definition see Section 5.5.3.1; ‡ Rejection not otherwise classifiable; § Acute rejection not confirmed by biopsy
N = Total number of patients

Overall Frequency of Biopsy-Proven Acute Rejection

	Prograf (N=62)			MR4 (N=67)		
	Patients	(%)	Events	Patients	(%)	Events
Acute rejections†	17	(27.4)	18	18	(26.9)	19
Spontaneously resolving	4	(6.5)	4	4	(6.0)	4
Corticosteroid sensitive	7	(11.3)	7	9	(13.4)	9
Corticosteroid resistant	5	(8.1)	5	6	(9.0)	6
Other acute rejection‡	2	(3.2)	2	0		0

Full Analysis Set
† For definition see Section 5.5.3.1; ‡ Rejection not otherwise classifiable
N = Total number of patients

Conversion studies

Pharmacokinetic data from studies which have investigated the use of MR4 in stable kidney, liver and heart transplant recipients converted from Prograf capsules to MR4 capsules (1mg:1 mg) have been discussed. Although not in direct support of efficacy, patient and graft survival data were evaluated in these studies and the results are summarised in the following section. However, it is important to note that the primary objective in all 6 of these studies was to compare the tacrolimus pharmacokinetics following conversion from Prograf to the proposed MR4 formulation.

MR4 studies in kidney transplant patients

No efficacy endpoints were analysed in the 8-week study period in the open-label, multi-centre, single-sequence, 4-period crossover study **FG-506E-12-02** (from April to December 2003) involving 69 stable, adult kidney transplant recipients (at least 6 months post-transplant) although incidences of acute rejection, patient and graft survival were assessed as safety parameters. No incidences of acute rejection, patient or graft losses were reported during this study.

In the Phase II, open-label, multicentre, conversion study **(02-0-131)** involving 68 stable, adult kidney transplant recipients, efficacy was not assessed during the 5-week treatment period.

However, there were no graft losses, patient deaths, or episodes of acute rejection during the pharmacokinetic treatment period.

In the Phase II, open-label, multicentre, one-way conversion study **(FJ-506E-KT01),** 37 Japanese kidney transplant patients were treated with Prograf for 1 week followed by 12 weeks treatment after conversion to MR4-based immunosuppression. No notable safety findings were observed after conversion to MR4 compared to Prograf. No rejection episode, renal impairment, or graft loss was observed after conversion to MR4

MR4 studies in liver transplant patients

In the Phase II, open-label, single sequence, four period crossover, multi-centre conversion study **(02-0-152),** 70 stable, adult liver transplant recipients entered the study on their stable dose of Prograf, administered twice daily, at a dose level designed to maintain a tacrolimus trough concentration of 5 to 20 ng/mL. After 14 days of Prograf treatment (Period 1), patients were converted to an equivalent (mg:mg), once daily dosing of MR4; after 14 days of MR4 (Period 2), patients were converted back to Prograf for 14 days (Period 3) and subsequently converted back to MR4 for 14 days (Period 4). Treatment was for 56 days (8 weeks), with a long-term extension period until commercial availability of MR4.

There were no graft losses or patient deaths during the pharmacokinetic treatment period. One patient had a biopsy performed on Day 53 which resulted in the diagnosis of acute grade III severe rejection. This patient subsequently discontinued the study on Day 60. The second patient had a biopsy performed on Day 43 which diagnosed chronic cholestasis, and another biopsy on Day 55 which diagnosed severe cholestasis. There was no evidence of acute or chronic organ rejection for this patient, and the patient subsequently discontinued the study on Day 64.

There were no acute rejection episodes, instances of liver dysfunction, graft losses, or deaths during the 2-week pharmacokinetic treatment period in the Phase II open-label multi-centre conversion study **(03-0-160)** in 19 stable paediatric liver transplant recipients.

MR4 studies in heart transplant patients

FG-506-15-02 was an open-label, multi-centre, prospective, single arm study performed in 85 stable, adult heart transplant recipients (at least 6 months post-transplant), who were receiving Prograf-based treatment at the time of screening. There was an initial 2-week screening period, during which time patients received a stable dose of Prograf twice daily, designed to maintain a tacrolimus trough concentration of 5 to 15 ng/mL. On Day 1, patients continued to receive Prograf, as study medication, twice daily for 1 week. On Day 8, the treatment was converted to a once daily MR4 regimen on a 1:1 (mg:mg) basis for 4 weeks. Following completion of this study, patients who received MR4 were able to enter Study **FG-506-14-02** in order to capture efficacy and safety data for MR4 on an ongoing basis. There were no graft losses, patient deaths, or episodes of acute rejection during the 5-week pharmacokinetic treatment period.

Long-term efficacy

The Phase III, multicentre, open, prospective, single-arm study (**FG-506-14-02**) assessed long-term efficacy and safety in transplant recipients who had previously participated in one of the Phase II MR4 pharmacokinetic studies and had received at least one dose of MR4. This 1-year interim analysis provides data on MR4 patients from Phase II conversion studies in kidney (**FG-506E-12-02**; N=67) and heart transplantation (**FG-506-15-02**; N=79), and from Phase II *de novo* studies in kidney (**FG-506E-12-01**; N=47) and liver transplantation (FG-506-11-01; N=47). The primary endpoints were patient and graft survival. Graft loss was defined as re-transplantation or death; for kidney transplantation it was also defined as nephrectomy or return to long-term dialysis. The secondary endpoint for efficacy was the incidence of and time to first biopsy-proven acute rejection episode.

Graft loss was reported for 5/240 (2.1%) patients during this 1-year interim analysis**.** The Kaplan-Meier estimated graft survival rate was above 95% at all times, for patients of all previous studies**.** The Kaplan-Meier estimated patient survival rate at Months 10 to 12 of the study was above 95% for all transplant indications**.** The highest numbers of acute rejections were seen in the *de novo* study patients and these were all classed as corticosteroid sensitive acute rejection episodes. These acute rejection episodes were the first reported in this study, but may not necessarily represent the first acute rejection episodes for these patients after transplantation. In the heart conversion patients, 1/4 episodes were classed as corticosteroid resistant since the episode was ongoing at the end of this 1-year interim analysis period. No episode was assessed as severe and there were there were no acute rejection episodes in kidney conversion patients**.** All patients previously from conversion kidney transplant study FG-506E-12-02 remained free from acute rejection. The Kaplan-Meier survival estimates for freedom from biopsy- proven acute rejections were above 93% at all measured time periods for patients from the other 3 studies. Overall, efficacy appeared to be maintained in terms of patient and graft survival and prevention of biopsy-confirmed acute rejection up to 2 years post-conversion from twice daily Prograf to once daily MR4. However, there were no controlled studies evaluating long-term efficacy of MR4.

Prograf as Rescue therapy for treatment of graft rejection resistant to other immunosuppressive treatment

The sponsors have submitted reports of a few studies (including published reports) supporting the use of Prograf as rescue therapy for treatment of graft rejection resistant to other immunosuppressive treatment**.** However, there have been no studies performed with MR4 to investigate the treatment of rejection in transplant recipients and the claim for this indication for MR4 is based on the same active substance (tacrolimus) in both Prograf and MR4 (Prograf XL).

Prograf Rescue therapy in kidney transplant patients

FG-506-02-23 was an open, multi-centre, randomised, parallel group study to compare the efficacy and safety of a tacrolimus-based immunosuppressive regimen with that of a cyclosporin-microemulsion based regimen in 119 adult renal allograft recipients who experience a first acute rejection episode. The study was conducted from 1996 to 1999. The baseline demographics and disease characteristics were similar in the 2 treatment groups with the exception of a higher number of patients with corticosteroid-resistant first acute rejection in the cyclosporin group compared with the tacrolimus group (25.9% versus 6.6%)**.** The first acute rejection episode resolved in a higher percentage of patients who were switched to tacrolimus (57/61 patients; 93.4%) compared with those who continued cyclosporin-microemulsion (44/58 patients; 75.9%) and the discrepancy in distribution of corticosteroid-resistant rejections may have affected this. However, of the patients whose first acute rejection had resolved, fewer patients had a second acute rejection in the tacrolimus group (8.8%) compared with the cyclosporin-microemulsion group (34.1%). The 3-month survival estimates for patients free from a second biopsy-proven acute rejection were significantly higher in the tacrolimus group compared with the cyclosporin group (89.1% versus 61.4%, p=0.0021, Wilcoxon-Gehan test). Most of the second acute rejections occurred during the first 2 weeks of the study. Overall, results from this study provided evidence that treatment with tacrolimus was effective for kidney transplant patients who develop first episode of acute rejection following cyclosporin therapy.

FJ-0004 was a Phase III, multi-centre, open-label, non-controlled study in 104 patients with on-going kidney transplant rejection switching to tacrolimus treatment. Patients were treated for 12 weeks, or longer if the outcome was promising and maintenance therapy was required; the longest duration of treatment was 20 months. No primary endpoints were defined for this study. Of the 84 patients converted to tacrolimus because of previous rejection while on another therapy, 20 (23.8%) experienced a subsequent rejection episode. A patient survival rate of 95.2% (80/84) and graft survival rate of 79.8% (67/84) were observed.

Prograf Rescue therapy in liver transplant patients

Study **FPC-FK506-9** aimed to evaluate the safety and efficacy of tacrolimus in the rescue of liver allografts in patients undergoing refractory rejection during treatment with conventional immunosuppressant agents (the study was conducted in 1993). This was an open-label, multi-centre, 1-year study in adult and paediatric liver transplant patients who had experienced drug resistant immune rejection. Study **91-0039** aimed to provide long-term safety and efficacy data (over 3 years) for tacrolimus in liver transplant patients who had participated in the FPC-FK506-9 study. In the initial study FPC-FK506-9, 386 patients were enrolled (intent-to-treat); 86 patients were ≤ 12 years old (mean: 3.9 years) and 300 were > 12 years old (mean: 43.3 years); the long-term study 91-0039 involved 26 patients. Overall, the results at 1-year and 3-years provided some evidence of efficacy of tacrolimus plus steroids as rescue treatment for patients with rejection following liver transplantation**.** However, this study only used historical controls (from 3 earlier studies with patients receiving cyclosporin before tacrolimus was available).

GHBA-157 was a multi-centre, open-label, randomised, parallel-group study, lasting 12 months, followed by an open-label extension for a further 24 months. This study evaluated 18 adult patients who were withdrawn from the cyclosporin group due to intractable graft rejection and were subsequently switched to tacrolimus as rescue treatment. Tacrolimus was able to reverse refractory rejection occurring under cyclosporin-based immunosuppression after liver transplantation in approximately two-thirds of the cases (66% patient and graft survival after 12 months).

GHBA-159-1 was a Phase II, multi-centre, open-label study in which 77 adult and paediatric patients with intractable primary liver allograft rejection received oral or intravenous tacrolimus; treatment was for 36 months. The primary endpoints were graft and patient survival and allograft rejection. The majority of the patients were free from acute rejection (98.7%, 86.2% and 80.8% at 1, 12 and 36 months, respectively) and patient and graft survival was >50% at 1 year. Overall, results suggest that tacrolimus provided some benefits in patients with a diagnosis of intractable primary liver allograft rejection**.**

91-0036 was an open-label, non-comparative, multi-centre rescue therapy study in 667 adult and paediatric (132 were < 12 years old) liver transplant patients who had experienced acute, chronic or humoral rejection or unacceptable intolerance of their current immunosuppressive treatment. All patients were switched to tacrolimus and compassionate use was continued until commercial availability of the drug. The majority of the patients were free from biopsy-confirmed acute rejection at 1 year (60.1%) and 2 years (53.5%). Overall, results from this study suggested that tacrolimus, in combination with corticosteroids, was a safe and effective therapy in adult and paediatric liver transplant patients with refractory rejection or who showed unacceptable intolerance or toxicity to conventional immunosuppressive treatments.

Prograf Rescue therapy in heart transplant patients

HRa was an open-label, single centre investigator-initiated study to evaluate the efficacy and safety of tacrolimus in combination with low dose corticosteroids as primary immunosuppression in 10 adult patients undergoing heart transplantation. Of the 10 patients, 8 remained on a regimen of corticosteroids but at considerably lower doses; the average prednisone dose was 20 mg/day before rescue and 7.5 mg/day after rescue. The average maintenance dose of tacrolimus was 0.12 mg/kg per day, 7 patients were rejection free following conversion.

The retrospective data collection summarised in Report **FG95-506-10** aimed to obtain updated information on the use of tacrolimus for treatment of rejection in heart transplant recipients from the Pittsburgh centre; data of 55 rescue patients were entered into the transplant data base. Kaplan-Meier analyses of patient survival were based on 38 evaluable patients; for adults (n = 24 patients > 23 years) it was 90.9% and 85.2% at 6 and 12 months respectively, children (n = 14 patients) survival was 100% and 88.9% at 6 and 12 months respectively and all patients (covering adults and

children) it was 93.7% and 85.9% respectively. The 10 adult rescue patients in Study HRa were also included in this retrospective rescue analysis.

In Report **FG94-506-09** compassionate-use experience with tacrolimus as rejection therapy for heart transplant recipients in Europe prior to its first availability on the market in the UK (1994) was collected. The Kaplan-Meier estimate of cumulative patient survival in 10 patients with available data was 80% at 9 months. One patient died of chronic rejection which was already present at the time of switch. Another patient died of multi-organ failure. Overall, 6 patients remained free of recurrent rejection following the switch.

Patients with solid organ allografts transplants that could not be sustained by cyclosporin-based immunosuppressive therapy or patients who had unacceptable intolerance to cyclosporin were enrolled into an open-label non-comparative rescue study with tacrolimus (93-0-003). As part of this multi-centre study, Mentzer et al (1998) published the results with tacrolimus used as a rescue immunosuppressant in 12 heart transplant patients with acute cellular rejection and 1 patient with humoral rejection.[8] The analysis additionally included 3 patients rescued for intolerance of cyclosporin. Patient and graft survival were 100% with a follow-up ranging from 82 to 332 days. Overall, 6 patients experienced no or only one rejection episode following conversion.

In study **FG-506-05-02**, 16 patients were transferred from cyclosporin to tacrolimus treatment, 14 for treatment of heart allograft rejection; 12 patients (75%) survived and completed the study on tacrolimus. The data from the early Pittsburgh experience as well as from other U.S. and European centres demonstrated the efficacy of tacrolimus in the treatment of cardiac rejection by either reducing the grade of rejection or completely clearing rejection. Tacrolimus was generally well tolerated and allowed a dose reduction of concomitant corticosteroid therapy.

Published results of mostly retrospective single centre studies each including at least 10 adult patients treated for rejection episodes were summarised**.** In most cases, conversion from cyclosporin to tacrolimus appeared to be a successful treatment for ongoing acute rejection by either reducing the grade of rejection or completely clearing the rejection, thus resulting in excellent patient and graft survival. The reduced need for concomitant therapy with corticosteroids following conversion to tacrolimus is consistent with reports of conversion for various other indications, particularly kidney transplantation rescue studies.

Prograf Rescue therapy in other organ transplantation

93-0-003 was an open-label, multi-centre, open-ended, rescue therapy study to evaluate the efficacy and safety of tacrolimus in 146 adult and paediatric solid organ allograft transplant patients whose engraftment could not be sustained by conventional immunosuppressive treatment or who had unacceptable intolerance to conventional immunosuppressive treatment. Transplants included kidney (96 patients), heart (16 patients), lung (15 patients), pancreas (12 patients), liver (2 patients) and multi-organ (5 patients) Tacrolimus was safe and effective in the treatment of persistent allograft rejection in kidney transplant patients unresponsive to other immunosuppressive therapies. Although the patient populations for the other solid organ transplants were small, tacrolimus appeared to be of benefit in the treatment of persistent allograft rejection in heart, lung, pancreas and multi-organ transplant recipients unresponsive to other immunosuppressive therapies**.**

A large multicentre, intercontinental, retrospective study on the conversion from cyclosporin to tacrolimus in lung transplant recipients involved 244 patients from 13 centres worldwide (Sarahrudi

[8] Mentzer, Jahania M, Lasley RD. Tacrolimus as a rescue immunosuppressant after heart and lung transplantation. Transplant 1998; 65: 109-113.

et al., 2004).[9] Indications for conversion were recurrent ongoing rejection (n = 110) and stage 1 to 3 BOS* (n = 134). The incidence of acute rejection decreased significantly within 3 months 'after' versus 'before conversion' from cyclosporin to tacrolimus ($p < 0.01$). For patients with recurrent, ongoing rejection, the forced expiratory volume in 1 second (FEV_1) decreased by 1.96% of predicted value per month ($p = 0.08$ versus zero slope) before and increased by 0.34% of predicted value per month ($p = 0.32$ versus zero slope) after conversion ($p < 0.06$). Results from studies performed in 12 centres not participating in the intercontinental multicentre study showed similar results**.**

There was some evidence of efficacy of tacrolimus as rescue therapy in patients with pancreas transplantation, although the number of patients evaluated was small (Gruesner, 1997).[10] Further evidence for the safety of tacrolimus in pancreas transplanted patients was shown in some investigator-initiated studies where tacrolimus was used as conversion therapy due to intolerance of cyclosporin (Hariharan et al. 1997), including 1 paediatric case report (Kaufmann et al. 1995).[11,12]

Approximately 140 intestinal transplants are performed per year world-wide. The Intestinal Transplant Registry reports that none of the adult patients world-wide with functioning intestinal grafts, and only 4 paediatric patients, are presently receiving maintenance treatment with cyclosporin. Virtually all surviving intestinal transplant patients (176 adults and 220 children) are receiving maintenance therapy with tacrolimus (ITR Intestinal Transplant Registry: http://www.intestinaltransplant.org/). Investigators from the University of Pittsburgh (n = 257 comprising 168 patients up to June 2001 plus 89 patients from July 2001 onwards). Apart from data of the University of Pittsburgh, 8 other centres published single centre experience with tacrolimus in at least 10 patients which showed similar results.

Only 18 patients were reported in the literature to have received a single or double hand or hand-forearm transplants world-wide from September 1998 to March 2004. An additional patient received a thumb transplant. All cases were treated with a tacrolimus-based regimen from the start (Dubernard et al. 2004).[13] Literature on the conversion of cyclosporin to tacrolimus following limb transplantation is not available.

Efficacy Conclusions

Efficacy data from Phase III, pivotal study 02-0-158 demonstrated evidence for efficacy of MR4-based immunosuppression for prophylaxis in 668 patients undergoing de novo kidney transplantation. Both Prograf and MR4 used in combination with MMF were non-inferior to Neoral/MMF treatment in terms of the composite endpoint of efficacy failure rate (15.1%, 14% and 17% in Prograf, MR4 and Neoral groups, respectively).

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[9] Sarahrudi, Estenne M, Corris P et al. International experience with conversion from cyclosporin to tacrolimus for acute and chronic lung allograft rejection. J Thorac Cardiovasc Surg 2004; 127(4): 1126-1132.

* Bronchiolitis obliterans syndrome or BOS is the clinical manifestation of chronic rejection in a lung graft

[10] Gruessner: Tacrolimus in pancreas transplantation: a multicenter analysis. Clin Transplant 1997; 11(4): 299-312.

[11] Hariharn S, Peddi VR, Munda R et al. Long-term renal and pancreas function with tacrolimus rescue therapy following kidney/pancreas transplantation. Transplant Proc 1997; 29(1/2): 652-653.

[12] Kaufman DB, Kaplan B, Kanwar YS et al. The successful use of tacrolimus (FK506) in a pancreas/kidney transplant recipient with recurrent cyclosporin-associated haemolytic uremic syndrome. ransplantation 1995; 59(12): 1737-1738.

[13] Dubernard JM, Owen E, Herzberg G et al. Human hand allograft: report on first 6 months. Lancet 1999; 353(9161): 1315-1320.

Supportive evidence was provided by two Phase III non-inferiority (MR4 versus Prograf) studies (FG506E-11-03 and FG506E-12-03) and two Phase II studies (FG-506E-12-01 and FG-506-11-01) in patients undergoing primary renal and liver transplantation.

Furthermore, pharmacokinetic and patient/graft survival data from 6 Phase II studies in which patients were converted from Prograf to MR4 support that the same total daily dose, target trough concentrations, therapeutic monitoring and maintenance strategies currently used for Prograf can be used for MR4.

There is no evidence that daily dosing recommendations for MR4 in kidney and liver transplant recipients would differ from those for Prograf based on age, race, sex, presence of diabetes at baseline or donor type.

Safety

Tacrolimus belongs to the class of calcineurin inhibitors, and the mode of action is similar to that of cyclosporin, the first substance of this class introduced to the market. However, it should be noted that tacrolimus is a macrolide lactone produced by *Streptomyces tsukubaensis* and bears no structural relationship to cyclosporin, which is a cyclic polypeptide consisting of 11 amino acids. Cyclosporin has been marketed for approximately 20 years and tacrolimus for approximately 10 years. The safety profiles of both drugs are very well established.

In the initial submission for Prograf, the analysis of safety was based on data from 10 clinical studies involving 2678 patients treated with Prograf (1631 kidney-transplanted patients [61%] and 1047 liver-transplanted patients [39%]). The exposure to Prograf has been extensive, both through exposure of the marketed product and through clinical studies; for example in the period of the most recent Periodic Safety Update Report (PSUR) 8, April 2004 to March 2005, the worldwide exposure to tacrolimus was estimated as 210,000 patient years.

Safety of prolonged release tacrolimus (Prograf XL or MR4) was assessed in 4 main studies: a pivotal, Phase III, 12-month study **(02-0-158),** two Phase II, 6-week studies **(FG-506E-12-01, FG-506-11-01)** and a long-term, 1-year interim safety analysis **(FG506-14-02)** (Table 16). Assessment of safety was based on incidence of treatment-emergent adverse events, results of clinical laboratory tests and findings from vital sign measurements. Furthermore, known calcineurin inhibitor class-specific adverse reactions such as infections, malignancies, renal dysfunction, glucose metabolism disorders, neurological disorders and hypertension were also evaluated.

Table 16: Overview of Safety Studies

Overview of MR4 Studies Used for Safety Evaluation

Study	Phase	Location	MR4 Patients	Duration	Dosing Regimen
***De novo* kidney transplant recipients**					
02-0-158	III	Brazil, Canada, USA	214	12 months	Basiliximab induction; MR4+MMF+CS or Prograf+MMF+CS or Neoral+MMF+CS
FG-506E-12-01	II	Australia, Europe	60	6 weeks	MR4+MMF+CS or Prograf+MMF+CS
***De novo* liver transplant recipients**					
FG-506-11-01	II	Australia, Canada, Europe	67	6 weeks	MR4+CS or Prograf+CS
Long-term follow-up					
FG-506-14-02	III	Australia, Canada, Europe, South Africa, USA	240‡	1-year interim analysis	MR4+CS (also + Aza/MMF depending on previous study)

Aza = azathioprine; CS = corticosteroids; MMF = mycophenolate mofetil; MR4 = tacrolimus modified-release formulation

‡ MR4 patients included from Studies FG-506E-12-01, FG-506-11-01, FG-506E-12-02 (kidney) and FG-506-15-02 (heart)

A total of 341 patients undergoing *de novo* kidney and liver transplantation received MR4-based immunosuppression. A further 348 patients (including 19 paediatric patients) were converted from Prograf-based immunosuppression to MR4-based immunosuppression (kidney, liver and heart transplantation); 242 healthy volunteers received MR4 during Phase I studies.

Additional 1-year safety data are presented for Study FG-506-14-02 which included patients who received MR4 in the *de novo* studies FG-506E-12-01 and FG-506-11-01 together with patients from the conversion studies who received MR4 in study **FG-506E-12-02** involving stable kidney transplant recipients, and study **FG-506-15-02** involving stable heart transplant recipients.

Studies performed in stable adult kidney, liver and heart transplant recipients and paediatric liver transplant recipients converted from Prograf-based immunosuppression to MR4-based immunosuppression were primarily designed to compare the pharmacokinetics of tacrolimus administered as MR4 and Prograf. Furthermore, the 2 Phase III, non-inferiority studies **FG506E-11-03** (in 475 primary liver transplant patients) and **FG-506E-12-03** (in 667 kidney transplant patients) provided additional safety data comparing Prograf with the new prolonged release MR4 formulation (Prograf-XL).

As expected, the number of reported adverse events (AEs) was high in all treatment groups across all in *de novo* transplantation studies when compared to conversion studies.

Safety in pivotal study 02-0-158 in kidney transplant patients

Study drug exposure

Study **02-0-158** was a 1-year Phase III comparative study designed to evaluate and compare the efficacy and safety of MR4 and Prograf versus Neoral in 668 primary kidney transplant recipients (all patients were also receiving MMF). The total daily doses of both MR4 and Prograf were generally stable throughout the first month post-transplant and gradually decreased thereafter. The gradual reduction of immunosuppressive load following transplantation is an established clinical practice [Kirk et al. 2005].[14] The mean whole blood tacrolimus trough levels were slightly higher in the Prograf arm compared to the MR4 arm in the first 14 days post-transplant and were generally comparable thereafter.

AEs

All patients in the MR4 and Prograf groups, and 99.1% of patients in the Neoral group, experienced adverse events. Greater than 85% of patients in each treatment group experienced a gastrointestinal disorder; furthermore, > 50% of patients in each treatment group experienced an AE listed under the following the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs): injury, poisoning, and procedural complications; metabolism and nutrition disorders; infections and infestations; general disorders and administration site conditions; nervous system disorders; investigations. The incidence of diarrhoea, tremor and peripheral oedema was significantly higher in both the tacrolimus (Prograf and MR4) groups compared with the Neoral group. The incidence of hydronephrosis (0.9%, 0.5% and 4.2% in Prograf, MR4 and cyclosporin groups, respectively, $p = 0.0112$; Fisher's exact test), toxic nephropathy (0.5%, 1.4% and 3.8%, respectively; $p = 0.0435$) and hirsutism (0%, 0% and 8.5%, respectively, $p \leq 0.001$) was significantly higher in the Neoral (cyclosporin) group compared to both the tacrolimus groups (Table 17). However, gastroenteritis, sinusitis, diabetes mellitus, orthostatic hypotension and alopecia were significantly higher in the MR4 group compared to Neoral. Compared with Prograf, gastroenteritis, lower abdominal pain and paraesthesia were significantly ($p<0.05$) more common in the MR4 group (Table 18). Overall, the incidence of treatment-emergent AEs considered by the investigator to be related to both primary study drug and MMF was similar among the three treatment groups and any differences in the incidence of treatment-related AEs (for example, diarrhoea, tremor) were not unexpected (Table 19).

[14] Kirk A, Mannon R, Swanson J et al. Strategies for minimizing immunosuppression in kidney transplantation. Transplant Int 2005; 18: 2-14.

Table 17: Study 02-0-158

Study 02-0-158: Summary of Most Frequently Reported and/or Statistically Significant Treatment-Emergent Adverse Events Regardless of Relationship to Study Drug

MedDRA System Organ Class Preferred Term	Treatment Group		
	Prograf/MMF (n = 212)	MR4/MMF (n = 214)	Neoral/MMF (n = 212)
All Systems			
Any Adverse Event	212 (100.0%)	214 (100.0%)	210 (99.1%)
Gastrointestinal Disorders			
Diarrhoea	94 (44.3%)***	97 (45.3%)***	54 (25.5%)
Nausea	82 (38.7%)	90 (42.1%)	99 (46.7%)
Constipation	76 (35.8%)	89 (41.6%)	87 (41.0%)
Vomiting	54 (25.5%)	56 (26.2%)	52 (24.5%)
Dyspepsia	38 (17.9%)	32 (15.0%)	32 (15.1%)
Abdominal Pain	27 (12.7%)	29 (13.6%)	38 (17.9%)
Loose Stools	15 (7.1%)*	11 (5.1%)	4 (1.9%)
Gingival Hyperplasia	0**	1 (0.5%)**	10 (4.7%)
Injury, Poisoning, and Procedural Complications			
Post Procedural Pain	61 (28.8%)	63 (29.4%)	58 (27.4%)
Incision Site Complication	60 (28.3%)	44 (20.6%)	49 (23.1%)
Graft Dysfunction	50 (23.6%)	39 (18.2%)	37 (17.5%)
Arteriovenous Fistula Thrombosis	1 (0.5%)	0*	5 (2.4%)
Metabolism and Nutrition Disorders			
Hypomagnesaemia	60 (28.3%)	55 (25.7%)	47 (22.2%)
Hypophosphataemia	59 (27.8%)	51 (23.8%)	45 (21.2%)
Hyperkalaemia	54 (25.5%)	47 (22.0%)	41 (19.3%)
Hyperglycaemia	45 (21.2%)	41 (19.2%)	32 (15.1%)
Hyperlipidaemia	37 (17.5%)	35 (16.4%)*	52 (24.5%)
Hypokalaemia	34 (16.0%)	34 (15.9%)	37 (17.5%)
Diabetes Mellitus	24 (11.3%)	30 (14.0%)*	14 (6.6%)
Hyponatraemia	2 (0.9%)*	6 (2.8%)	10 (4.7%)
Infections and Infestations			
Urinary Tract Infection	54 (25.5%)	34 (15.9%)	47 (22.2%)
Sinusitis	7 (3.3%)	15 (7.0%)*	5 (2.4%)
Gastroenteritis	1 (0.5%)	14 (6.5%)*	4 (1.9%)
General Disorders and Administration Site Conditions			
Oedema Peripheral	74 (34.9%)*	76 (35.5%)*	97 (45.8%)
Pyrexia	25 (11.8%)	24 (11.2%)	35 (16.5%)
Fatigue	23 (10.8%)	34 (15.9%)	26 (12.3%)
Nervous System Disorders			
Tremor	73 (34.4%)**	75 (35.0%)***	42 (19.8%)
Headache	51 (24.1%)	46 (21.5%)	52 (24.5%)
Paraesthesia	3 (1.4%)*	12 (5.6%)	13 (6.1%)
Investigations			
Blood Creatinine Increased	49 (23.1%)	40 (18.7%)	48 (22.6%)

Table continued on next page

Table 17 (cont.): Study 02-0-158

MedDRA System Organ Class Preferred Term	Treatment Group		
	Prograf/MMF (n = 212)	MR4/MMF (n = 214)	Neoral/MMF (n = 212)
Blood and Lymphatic System Disorders			
Anaemia	64 (30.2%)	72 (33.6%)	59 (27.8%)
Leukopenia	33 (15.6%)	35 (16.4%)	25 (11.8%)
Vascular Disorders			
Hypertension	68 (32.1%)	64 (29.9%)	74 (34.9%)
Orthostatic Hypotension	10 (4.7%)	15 (7.0%)*	5 (2.4%)
Lymphocele	2 (0.9%)	1 (0.5%)*	7 (3.3%)
Musculoskeletal and Connective Tissue Disorders			
Back Pain	27 (12.7%)	32 (15.0%)	30 (14.2%)
Psychiatric Disorders			
Insomnia	64 (30.2%)*	55 (25.7%)	45 (21.2%)
Skin and Subcutaneous Tissue Disorders			
Alopecia	15 (7.1%)*	14 (6.5%)*	4 (1.9%)
Hypertrichosis	0*	0**	7 (3.3%)
Renal and Urinary Disorders			
Hydronephrosis	2 (0.9%)	1 (0.5%)*	9 (4.2%)
Nephropathy Toxic	1 (0.5%)*	3 (1.4%)	8 (3.8%)
Reproductive System and Breast Disorders			
Benign Prostatic Hyperplasia	4 (1.9%)	1 (0.5%)*	7 (3.3%)
Endocrine Disorders			
Hirsutism	0***	0***	18 (8.5%)
Eye Disorders			
Visual Acuity Reduced	0*	2 (0.9%)	6 (2.8%)

Patient base: Full Analysis Set; all randomised patients who received at least one dose of study drug. Within a MedDRA system organ class, patients may have experienced more than one adverse event. The sum of the terms may exceed 100%. Most frequent = ≥ 15% of patients in any treatment group. Statistical significance determined using Fisher's exact test (2-tailed) versus Neoral/MMF.

*Statistical significance at 0.05; **Statistical significance at 0.01; ***Statistical significance at 0.001.

MMF = mycophenolate mofetil; MR4 = tacrolimus modified-release formulation.

Table 18: Study 02-0-158

Study 02-0-158: Summary of Treatment-Emergent Adverse Events with a Difference in Incidence ≥ 5%, or Statistically Significant Difference, Between Prograf and MR4 Treatment Groups

MedDRA (v. 6.1) System Organ Class Preferred Term	Treatment Group		
	Prograf/MMF (n = 212)	MR4/MMF (n = 214)	p-value†
All Systems			
Any adverse event	212 (100.0%)	214 (100.0%)	
Gastrointestinal Disorders			
Constipation	76 (35.8%)	89 (41.6%)	NA
Abdominal Pain Lower	2 (0.9%)	10 (4.7%)	0.0359*
Injury, Poisoning, and Procedural Complications			
Incision Site Complication	60 (28.3%)	44 (20.6%)	NA
Graft Dysfunction	50 (23.6%)	39 (18.2%)	NA
Infections and Infestations			
Urinary Tract Infection	54 (25.5%)	34 (15.9%)	0.0166*
Gastroenteritis	1 (0.5%)	14 (6.5%)	0.0008***
General Disorders and Administration Site Conditions			
Fatigue	23 (10.8%)	34 (15.9%)	NA
Nervous System Disorders			
Paraesthesia	3 (1.4%)	12 (5.6%)	0.0320*
Respiratory, Thoracic, and Mediastinal Disorders			
Cough	27 (12.7%)	16 (7.5%)	NA

Patient base: Full Analysis Set; all randomised patients who received at least one dose of study drug. Within a MedDRA system organ class, patients may have experienced more than one adverse event. The sum of the terms may exceed 100%.

† p-value from Fisher's exact test (2-tailed); *Statistical significance at 0.05; ***Statistical significance at 0.001.

MMF = mycophenolate mofetil; MR4 = tacrolimus modified-release formulation; NA = not applicable

Table 19: Study 02-0-158

Study 02-0-158: Summary of Most Frequently Reported Treatment-Emergent Adverse Events Related to Both Primary Study Drug and MMF

MedDRA System Organ Class Preferred Term	Treatment Group		
	Prograf/MMF (n = 212)	MR4/MMF (n = 214)	Neoral/MMF (n = 212)
All Systems			
Any Adverse Event	111 (52.4%)	126 (58.9%)	107 (50.5%)
Infections and Infestations			
Urinary Tract Infection	14 (6.6%)	13 (6.1%)	14 (6.6%)
Gastrointestinal Disorders			
Diarrhoea	29 (13.7%)	32 (15.0%)	13 (6.1%)
Nausea	14 (6.6%)	21 (9.8%)	21 (9.9%)
Vomiting	10 (4.7%)	13 (6.1%)	11 (5.2%)
Nervous System Disorders			
Tremor	12 (5.7%)	20 (9.3%)	6 (2.8%)

Patient base: Full Analysis Set; all randomised patients who received at least one dose of study drug. Within a MedDRA system organ class, patients may have experienced more than one adverse event. The sum of the terms may exceed 100%. All systems: Shows the number of patients with any adverse event. Related: Considered by the investigator to have a possible, probable, or definite relationship to study drug. Most frequent = ≥ 5% of patients in any treatment group.

MMF = mycophenolate mofetil; MR4 = tacrolimus modified-release formulation

Deaths, SAEs and discontinuations due to AEs

A total of 20 patients died during the course of the study; one patient (Neoral) died but had never received study drug (this patient was not included in the FAS).

Two patients died while receiving randomised therapy (Neoral) and the primary cause of death did not appear to be related to study drug or MMF. The remaining 17 patients died after discontinuing primary randomised therapy (3, 10 and 4 patients in MR4, Prograf and cyclosporin groups, respectively) The majority of patient deaths in this study were attributed to cardiac/vascular disorders (for example, myocardial infarction, pulmonary embolism) or infections (for example, sepsis, tuberculosis)**.**

The incidence of SAEs was slightly lower in the MR4 group (45.3%) compared with the Prograf (51.4%) and Neoral (51.9%) groups. With the exception of cytomegalovirus infection, urinary tract infection, and increased blood creatinine, the SAEs observed in this study were experienced by < 10 patients in any treatment group. Overall, the incidence of individual SAEs was similar in all 3 treatment groups**.** Approximately 21% to 23% of the patients in each treatment group experienced a treatment-emergent SAE considered by the investigator to be related to the primary study drug. The overall incidence of SAEs was similar among the three treatment groups, and was consistent with the established safety profile of tacrolimus and cyclosporin**.**

The incidence of treatment-emergent AEs leading to discontinuation of randomised treatment was statistically significantly greater in the Neoral group than the MR4 group (17.5% versus 8.9%, p = 0.010) and numerically greater than the Prograf group (10.8%). The majority of AEs leading to discontinuation were considered by the investigator to be related (possible, probable, definite) to study drug overall (primary study drug only, or the combination of primary study drug and MMF)**.** The majority of AEs leading to discontinuation were experienced by only a single patient within any treatment group. The most common treatment-emergent AEs leading to discontinuation were toxic nephropathy (4/212; 1.9% Neoral group only), gingival hyperplasia (4/212; 1.9% Neoral group only), drug toxicity (3/212; 1.4% Neoral group only), and graft dysfunction (Neoral: 3/212; 1.4%; MR4: 2/214, 0.9%).

Other significant AEs

Infections, malignancies, renal dysfunction, hepatic dysfunction, glucose metabolism disorders, dyslipidaemia and hypertension have been reported in association with calcineurin inhibitor treatment alone (either Prograf or cyclosporin), or in combination with corticosteroids and azathioprine.

The overall incidence of selected renal AEs was comparable across the three treatment groups. The Neoral group had a significantly higher incidence of toxic nephropathy (p = 0.037) than the Prograf group and also a numerically higher incidence than the MR4 group (0.5%, 1.4% and 3.8% in Prograf, MR4 and Neoral groups, respectively). No other significant differences in the incidence of selected renal adverse events were observed**.**

There were no significant differences in treatment-emergent hepatic AEs across the three treatment groups**.**

Overall, the Neoral group had a significantly higher incidence of lipid-related AEs (p = 0.035) than the Prograf group and a numerically higher incidence than the MR4 group (25.5%, 28.0% and 35.4% in Prograf, MR4 and Neoral groups, respectively). Furthermore, the Neoral group had a significantly higher incidence of hyperlipidaemia (p = 0.041) than the MR4 group and a numerically higher incidence than the Prograf group (17.5%, 16.4% and 24.5%, respectively)**.**

There were no significant differences in treatment-emergent AEs related to hypertension**.**

An analysis for a composite endpoint of glucose intolerance was performed (using fasting glucose ≥ 126 mg/dL, HbA1C ≥ 6%, insulin use ≥ 30 days, or oral hypoglycaemic use from Days 0 to 30 or at any time during the study) in the at-risk population (patients who did not present with diabetes at baseline). There were no significant differences in the composite endpoint of glucose intolerance from Days 0 to 30 for the at-risk population, although the incidence of oral hypoglycaemic use was greater in the tacrolimus groups compared to the Neoral group, but only Prograf was statistically significantly (p = 0.0357) greater (4.7%, 2.5% and 0.7% in the Prograf, MR4 and Neoral groups, respectively). When the analysis was expanded to include any time during the study, no significant difference in glucose intolerance (as a composite endpoint) or incidence of fasting plasma glucose ≥ 126 mg/dL was observed between the MR4 and Neoral groups, although the incidence was significantly higher in the Prograf group compared to the Neoral group (p = 0.0137 for composite endpoint and p = 0.0481 for incidence of fasting plasma glucose ≥ 126 mg/dL). Compared to the Neoral group, both the Prograf and MR4 groups had a significantly higher incidence of HbA1C ≥ 6% (p < 0.0001) and oral hypoglycaemic use (p = 0.0212 for Prograf versus Neoral and p = 0.0006 for MR4 versus Neoral). There was no significant difference in insulin use ≥ 30 days at any time during the study, and no clinically meaningful differences in mean HbA1C values among the three groups were observed. Mean HbA1C values were < 6.7% for all three treatment groups at most time points (Table 20).

Table 20: Study 02-0-158

Study 02-0-158: Summary of Glucose Intolerance

Parameter	Treatment Group		
	Prograf/MMF (N=150)	MR4/MMF (N=163)	Neoral/MMF (N=152)
Days 0 to 30			
Glucose Intolerance – Composite†	89 (59.3%)	82 (50.3%)	78 (51.3%)
Fasting Plasma Glucose ≥ 126 mg/dL	88 (58.7%)	81 49.7%)	78 (51.3%)
$HbA_{1C} \geq 6\%$	0	0	0
Insulin Use ≥ 30 days	3 (2.0%)	1 (0.6%)	1 (0.7%)
Oral hypoglycaemic Use	7 (4.7%)*	4 (2.5%)	1 (0.7%)
Any time during study			
Glucose Intolerance – Composite†	112 (74.7%)*	113 (69.3%)	93 (61.2%)
Fasting Plasma Glucose ≥ 126 mg/dL	96 (64.0%)*	92 (56.4%)	80 (52.6%)
$HbA_{1C} \geq 6\%$	59 (39.3%)***	66 (40.5%)***	28 (18.4%)
Insulin Use ≥ 30 days	9 (6.0%)	9 (5.5%)	4 (2.6%)
Oral hypoglycaemic Use	15 (10.0%)*	23 (14.1%)***	5 (3.3%)

Patient base: Full analysis set; all randomised patients who received at least one dose of study drug. Only patients in the at-risk population (patients with no history of diabetes at baseline) were considered in the analyses.

† A patient was only counted once regardless of how many glucose intolerance criteria were met. The sum of the terms may exceed 100%; *Statistical significance at 0.05; ***Statistical significance at 0.001.

MMF = mycophenolate mofetil; MR4 = tacrolimus modified-release formulation

Overall, the composite glucose intolerance endpoint was not significantly different between treatment groups, although incidence of HbA1C>6% and oral hypoglycaemic use was significantly greater in the tacrolimus groups (Prograf and MR4) compared with cyclosporin.

The overall incidence of infections was numerically lower in the Neoral group (123/212; 58.0%) than either the Prograf (146/212; 68.9%) or MR4 (148/214; 69.2%) groups. There was a significant

difference in the incidence of urinary tract infection among treatment groups (p = 0.0467), with more infections observed in the Prograf and Neoral groups than in the MR4 group. There was also a significant difference in the incidence of skin infection among treatment groups (p = 0.0239), with more events occurring in the Prograf group. The incidence of sinusitis was significantly greater in the MR4 group compared with the Neoral group (p = 0.0368)**.**

The overall incidence of gastrointestinal-related AEs was comparable among the three treatment groups and a total of 27/638 (4.2%) patients experienced some type of gastroenteritis (MedDRA referred terms of gastroenteritis, gastroenteritis salmonella, gastroenteritis staphylococcal or gastroenteritis viral) during the course of the study. The incidence of diarrhoea in the MR4 and Prograf groups was significantly higher than in the Neoral group (p < 0.001 for both comparisons)**.** Although the occurrence of gastroenteritis in the MR4 group was much higher (0.5%, 6.5% and 1.9% in Prograf, MR4 and Neoral groups, respectively), the vast majority of these adverse events were not treatment-limiting. Additionally, all patients recovered from the gastroenteritis with no residual effects, with the exception of 2 patients, who still had gastroenteritis at the time of death. There were more changes in MMF doses for patients who experienced gastroenteritis than for MR4; only 1 patient had a dose change of MR4 (discontinued therapy) as a result of gastroenteritis**.**

Laboratory parameters, vital signs

Generally, the clinical laboratory findings in *de novo* kidney transplant recipients were consistent with the clinical laboratory findings observed in transplant recipients administered Prograf. At Month 12, serum creatinine values were similar for the MR4 and Prograf groups and were significantly lower in the MR4 group compared with the Neoral group (p = 0.047; two-way ANOVA). Mean creatinine clearance values were significantly greater at Months 4, 6, 10 and 12 for the MR4 group compared to the Neoral group. These results correspond with the lower serum creatinine values observed for the MR4 group as compared to the Neoral group during the course of the study. Mean creatinine clearance values were also significantly greater at Months 6 and 12 for the Prograf group compared to the Neoral group.

The incidence of potentially clinically significant changes in LDL cholesterol (≥ 200 mg/dL) in the at-risk population (patients whose LDL cholesterol was < 200 mg/dL at baseline) was significantly higher in the Neoral group compared to the Prograf group (p-value = 0.029) and numerically higher than the MR4 group. None of the other laboratory parameters or vital signs showed clinically relevant difference between the treatment groups.

QTc prolongation with or without torsades de pointes or proarrhythmia effects is an extremely rare occurrence in transplant recipients receiving Prograf. Risk factors such as long QT syndrome or hypokalaemia were frequently present in these rare instances. The co-administration of Prograf with known QT prolonging drugs showed that QT prolongation occurred in only a few isolated cases. The European Prograf Summary of Product Characteristics (SPC) and proposed MR4 PI appropriately list electrocardiogram (ECG) investigations abnormal, ventricular arrhythmias and cardiac arrest, supraventricular arrhythmias, palpitations, heart rate/ pulse/ ECG investigations abnormal, QT prolongation and torsades de pointes as “uncommon cardiac disorders.

ADRs not listed in the approved Prograf SPC

Adverse drug reactions (ADRs) observed in Study 02-0-158 which are not listed in the Prograf SPC (version 4.0) were: cardiac murmur (1 patient; 0.5%); immunosuppressant drug level increased (1 patient; 0.5%); drug level below therapeutic (1 patient; 0.5%); lacrimation increased (1 patient; 0.5%); osteopenia (1 patient; 0.5%); spinal osteoarthritis (1 patient; 0.5%); abdominal hernia (1 patient; 0.5%); menopausal syndrome (1 patient; 0.5%); and prostatism (1 patient; 0.5%). ADRs which were observed in Study 02-0-158 with an incidence outside the range of incidences in the Prograf global core company safety information (G-CCSI) version 4.0 were: electrolyte imbalance (1 patient; 0.5%); amnesia (2 patients, 0.9%); intermittent claudication (1 patient; 0.5%); atrial

flutter (1 patient; 0.5%); musculoskeletal stiffness (1 patient; 0.5%); and rigors (1 patient; 0.5%). In comparison to the number of patients evaluated in the Prograf G-CCSI version 4.0 (N=2,678) the patient number in Study 02-0-158 (N=214) is relatively small. The frequency of the reported ADRs may easily exceed the frequency of rarely reported ADRs or ADRs only reported in isolated cases in the Prograf G-CCSI version 4.0.

Safety in supportive Phase II studies

Phase II study in kidney transplant patients

Drug exposure

In Phase II study **506E-12-01**, the total daily doses of both MR4 and Prograf were generally stable throughout the 6-week study, and were similar for the two treatment arms for the first 7 days post-transplant. Thereafter, the total daily dose of MR4 was slightly higher than the corresponding doses of Prograf. The mean whole blood tacrolimus trough levels in the two treatment arms were comparable.

AEs

A total of 93.3% and 98.3% of patients in the MR4 and Prograf groups, respectively, experienced adverse events. The four most frequently reported AEs were anaemia, hypertension, graft dysfunction and diarrhoea.

There were no significant differences in the incidence of AEs between the MR4 and Prograf-treated patients, although hypertension was reported in more than twice as many Prograf-treated patients than MR4-treated patients (Table 21). The most frequently reported (≥ 6 patients) treatment-related AEs were tremor, urinary tract infection, hypertension, hyperglycaemia and liver function test abnormal with no significant differences between the Prograf and MR4 tacrolimus formulations**.**

Deaths, SAEs, discontinuations due to AEs

There were no deaths during the 6-week study. The incidence of SAEs was slightly higher in the MR4 group (28.3%) compared with the Prograf group (18.6%); wound infection was the most frequently reported SAE in 3/60 (5.0%) patients in the MR4-treated group (and no patients in the Prograf-treated group). None of the individual SAEs showed a significant difference ($p>0.05$) between Prograf and MR4 groups. The most frequently reported SAE regardless of relationship to study drug was non-site specific procedural complications, which included graft dysfunction, graft thrombosis, intraoperative haemorrhage and procedural complication**.** The incidence of treatment-related SAEs was similar in the Prograf and MR4 groups; the most frequently reported treatment-related SAE was wound infection in 2 patients in the MR4-treated group, with the remaining SAEs being single incidences**.**

There were 3 discontinuations due to AEs. Two patients in the MR4 group were withdrawn due to AEs (one patient had unrelated Candida infection on Day 4 and was consequently withdrawn on Day 5; another patient had a treatment-related graft vein thrombosis on Day 10 and was consequently withdrawn from the study). One patient in the Prograf group was withdrawn due to unrelated renal artery thrombosis on Day 3. Three additional patients in the Prograf group were withdrawn under “other AEs” (all 3 withdrawn on Day 1 due to myocardial infarction, renal tubular necrosis and graft failure).

Laboratory parameters

In both MR4 and Prograf-treated patients, serum creatinine and creatinine clearance gradually improved during the study as the kidney grafts stabilised, and by Week 6 of the study both parameters were approaching values that reflected good renal allograft function after kidney transplantation. There were no marked differences between the MR4 and Prograf-treated patients,

with the exception of the Week 6 serum creatinine values which were lower in the MR4 group (p=0.016, Wilcoxon rank sum test).

Table 21: Study FG506E-12-01

Study FG-506E-12-01: Most Frequently Reported Adverse Events Regardless of Relationship to Study Medication

MedDRA High Level Term *MedDRA Preferred Term*	Prograf (N=59)			MR4 (N=60)		
	Patients	(%)	Events	Patients	(%)	Events
Potassium imbalance	12	(20.3)	15	10	(16.7)	10
Hyperkalaemia	8	(13.6)	9	5	(8.3)	5
Hypokalaemia	6	(10.2)	6	5	(8.3)	5
Hyperglycaemic conditions NEC	6	(10.2)	6	3	(5.0)	3
Anaemias NEC	18	(30.5)	18	19	(31.7)	20
Anaemia NOS	15	(25.4)	15	16	(26.7)	17
Diarrhoea (excl infective)	9	(15.3)	9	6	(10.0)	6
Diarrhoea NOS	9	(15.3)	9	6	(10.0)	6
Gastrointestinal atonic and hypomotility disorders NEC	4	(6.8)	5	7	(11.7)	7
Constipation	4	(6.8)	4	7	(11.7)	7
Renal failure and impairment	8	(13.6)	9	6	(10.0)	6
Renal impairment NOS	8	(13.6)	8	6	(10.0)	6
Renal vascular and ischaemic conditions	6	(10.2)	6	5	(8.3)	5
Bladder and urethral symptoms	6	(10.2)	6	2	(3.3)	2
Urinary tract infections	7	(11.9)	7	7	(11.7)	7
Urinary tract infection NOS	7	(11.9)	7	6	(10.0)	6
Non-site specific procedural complications	16	(27.1)	19	13	(21.7)	15
Graft dysfunction	9	(15.3)	9	8	(13.3)	9
Liver function analyses	8	(13.6)	8	10	(16.7)	11
Liver function test abnormal	6	(10.2)	6	7	(11.7)	7
Vascular hypertensive disorders NEC	13	(22.0)	13	6	(10.0)	6
Hypertension NOS	13	(22.0)	13	6	(10.0)	6

Full Analysis Set

MR4 = tacrolimus modified-release formulation; N = total number of patients; NEC = not elsewhere classified; NOS = not otherwise specified

Note: Incidence rate for high level term of at least 10.2% of patients in either treatment group

ADRs not listed in the approved Prograf SPC

Only one ADR was observed in Study FG-506E-12-01 which is not listed in the Prograf SPC version 4.0 (impaired healing in 1 patient; 1.7%). It is known that immunosuppressive agents may lead to an impaired healing of the wound, mostly due to infections. In the Prograf G-CCSI version 4.0 the various symptoms of impaired healing are listed. ADRs which were observed in Study FG-506E-12-01 with an incidence outside the range of incidences in the Prograf G-CCSI version 4.0 were: acidosis NOS (2 patients; 3.3%); and hepatic disorder NOS (1 patient; 1.7%). In comparison

to the number of patients evaluated in the Prograf G-CCSI version 4.0 (N=2,678) the patient number in Study FG-506E-12-01 (N=60) is small, thus limiting interpretation of data.

Phase II study in liver transplant patients

Study drug exposure

In Phase II study **506-11-01**, the mean total daily dose of MR4 was higher than that of Prograf throughout the study. By Day 7 post-transplant, the trough levels were comparable for both MR4 and Prograf.

AEs

A total of 95.5% and 100% of patients in the MR4 and Prograf groups, respectively, experienced AEs. The most frequently reported AEs were hyperglycaemia, anaemia, renal failure, diarrhoea and insomnia. There were no marked differences in the incidence of adverse events between the MR4 and Prograf-treated patients, with the exception of abnormal abdominal findings (mainly ascites) and infections, which were reported more frequently in the MR4 patients (Table 22). Ascites was reported for 15/67 (22.4%) patients who received MR4 compared with 1/62 (1.6%) patients who received Prograf ($p < 0.001$; Fisher's exact test). A possible causal relationship to the study drug (assessed by the investigator) was given for three of the ascites events in the MR4 group. Of the 15 patients in the MR4 group, 8 had pre-existing ascites at the time of transplant. The ascites resolved during the study period in 6 of the 15 patients, whilst the remaining ascites events were ongoing at the end-of-study visit. The four most frequently reported treatment-related AEs were renal failure, insulin-dependent diabetes mellitus, hypertension and hyperglycaemia with no significant ($p>0.05$) difference between the Prograf and MR4 groups**.**

Deaths, SAEs, discontinuations due to AEs

Two patients died during the study; 1 patient receiving MR4 died on Day 3 of the study due to cardiac arrest which was considered by the investigator to be unlikely to be related to administration of MR4. Another patient, who was administered Prograf, died on Day 19 of the study due to pneumonia which began on Day 14 and was considered by the investigator to be possibly related to administration of Prograf.

The incidence of SAEs was slightly higher in the MR4 group (47.8%) compared with the Prograf group (35.5%). The most frequently reported SAEs (at least 4 patients) were bile duct stenosis, renal failure NOS and post-procedural bile leak. There were no significant differences in the nature and incidence of SAEs between the MR4 and Prograf-treated patients, although the incidence of bile duct stenosis and respiratory failure was numerically higher in the MR4 group compared with the Prograf group. The most frequently reported treatment-related SAEs (in at least 2 patients) were renal failure, epilepsy, hydrothorax, acute renal failure and respiratory failure with no significant difference between the Prograf and MR4 groups**.**

There were very few AEs that led to discontinuation of patients from the study, with no apparent difference between MR4 and Prograf. The AEs responsible for discontinuation of patients were consistent with the known safety profile of tacrolimus in liver transplantation.

Laboratory parameters

The hepatic function parameters were above the upper limit of normal for the majority of the study participants, which was not unexpected in the early phase following liver transplantation. MR4 and Prograf-treated patients were comparable throughout the study with regards to hepatic function tests**.** Renal function, as determined by serum creatinine levels and creatinine clearance, was comparable for MR4 and Prograf during the study. There was a slight deterioration in mean renal function from baseline.

ADRs not listed in the approved Prograf SPC

ADRs observed in Study FG-506-11-01 which are not listed in the Prograf SPC/G-CCSI version 4.0 were: drug level below therapeutic (1 patient; 1.5%); systemic inflammatory response syndrome (1 patient; 1.5%). Drug level below therapeutic is not an ADR but depends on the mode

Table 22: Study FG506E-11-01

Study FG-506-11-01: Most Frequently Reported Adverse Events Regardless of Relationship to Study Medication

MedDRA High Level Term *MedDRA Preferred Term*	Prograf (N=62)			MR4 (N=67)		
	Patients	(%)	Events	Patients	(%)	Events
Hyperglycaemic conditions NEC	21	(33.9)	21	17	(25.4)	17
Hyperglycaemia NOS	20	(32.3)	20	17	(25.4)	17
Diabetes mellitus (incl subtypes)	17	(27.4)	19	15	(22.4)	17
Diabetes mellitus insulin-dependent	14	(22.6)	14	11	(16.4)	12
Potassium imbalance	11	(17.7)	12	9	(13.4)	10
Protein metabolism disorders NEC	11	(17.7)	11	9	(13.4)	9
· *Hypoalbuminaemia*	11	(17.7)	11	9	(13.4)	9
Magnesium metabolism disorders NEC	11	(17.7)	13	5	(7.5)	5
Hypomagnesaemia	11	(17.7)	13	5	(7.5)	5
Nausea and vomiting symptoms	13	(21.0)	17	12	(17.9)	17
Diarrhoea (excel infective)	11	(17.7)	11	16	(23.9)	18
Diarrhoea NOS	11	(17.7)	11	16	(23.9)	18
Gastrointestinal and abdominal pains (excl oral and throat)	6	(9.7)	6	11	(16.4)	11
Abdominal findings abnormal	1	(1.6)	1	15*	(22.4)	15
Ascites	1	(1.6)	1	15*	(22.4)	15
Anaemias NEC	25	(40.3)	25	24	(35.8)	25
Anaemia NOS	21	(33.9)	21	16	(23.9)	17
Infections NEC	5	(8.1)	5	14*	(20.9)	16
Non-site specific procedural complications	21	(33.9)	26	16	(23.9)	19
Non-site specific injuries NEC	13	(21.0)	13	11	(16.4)	11
Necrotic preservation injury of graft	11	(17.7)	11	10	(14.9)	10
Pneumothorax and pleural effusions	14	(22.6)	15	19	(28.4)	21
Pleural effusion	11	(17.7)	11	12	(17.9)	13
Disturbances in initiating and maintaining sleep	12	(19.4)	12	15	(22.4)	15
Insomnia	12	(19.4)	12	15	(22.4)	15
Renal failure and impairment	25	(40.3)	27	27	(40.3)	34
Renal failure NOS	16	(25.8)	16	17	(25.4)	18

Cholestasis and jaundice	14	(22.6)	15	16	(23.9)	17
Vascular hypertensive disorders NEC	13	(21.0)	13	20	(29.9)	21
Hypertension	8	(12.9)	8	18	(26.9)	19
Pain and discomfort NEC	12	(19.4)	12	13	(19.4)	13
Pain	10	(16.1)	10	11	(16.4)	11
Musculoskeletal and connective tissue signs and symptoms NEC	11	(17.7)	13	11	(16.4)	11

Full Analysis Set

* $p < 0.05$ (Fisher's exact test)

MR4 = tacrolimus modified-release formulation; N = total number of patients; NEC = not elsewhere classified; NOS = not otherwise specified

Note: Incidence rate for high level term of at least 16.4% of patients in either treatment group

of administration and the individual rate of absorption. A systemic inflammatory response syndrome is characterised by the classical signs of pain, heat, redness, swelling and impaired function; histologically a dilatation of arterioles, capillaries and venules can be seen. It is related to an increased permeability of the small vessels with exudation of fluids and leukocytic migration. The signs of an inflammatory response syndrome are all listed in the Prograf G-CCSI version 4.0.

ADRs which were observed in Study FG-506-11-01 with an incidence outside the range of incidences in the Prograf G-CCSI version 4.0 were: brachial plexus lesion (1 patient; 1.5%); biopsy liver (1 patient; 1.5%); renal failure NOS (14 patients; 20.9%); epistaxis (1 patient; 1.5%); decubitus ulcer (1 patient; 1.5%); and sinus bradycardia (1 patient; 1.5%).

Long term safety

Study drug exposure

FG-506-14-02 is an ongoing Phase III study to evaluate long-term efficacy and safety data in patients receiving MR4. Any patient who received MR4 during one of the European Phase II pharmacokinetic studies was eligible to continue to receive MR4 in this study until MR4 becomes commercially available. Safety data from a 1-year interim analysis for Study FG-506-14-02 (defined as 1-year following entry to this study), included data from patients who received MR4 in *de novo* studies: FG-506E-12-01 (kidney transplant recipients) and FG-506-11-01 (liver transplant recipients) and in conversion studies: FG-506E-12-02 (kidney transplant recipients) and FG-506-15-02 (heart transplant recipients). Mean daily doses and corresponding tacrolimus trough levels for conversion study patients were maintained throughout the 1-year interim analysis period. In accordance with standard clinical practice, immunosuppressive therapy was tapered from Months 1 to 3 to Months 10 to 12 in patients of *de novo* studies**.** The whole blood tacrolimus trough levels reflected the trends observed in MR4 dosing, with a slight decrease throughout the study for liver and kidney *de novo* patients. This reflects the dosing recommendations in the Prograf SPC and the proposed MR4 SPC, and is consistent with previous experience with Prograf. For kidney conversion patients and heart conversion patients, who were at least 6 months post-transplant and were therefore in the maintenance phase, the whole blood tacrolimus trough levels were generally stable. The majority of the patients were Caucasian males aged between 21-65 years.

AEs

The incidence of AEs decreased with time after transplantation. Fewer AEs were reported for former conversion study patients compared with those from *de novo* studies. This was expected as the patients from the conversion studies were clinically stable and at least 6 months post-transplant at the time of entering the study.

The most common AEs were anaemia, diarrhoea, ascites, abdominal pain, tremor, headache, hyperglycaemia and infections and were expected AEs in this patient population (Table 23). For the

6/47 (12.8%) liver *de novo* patients who suffered ascites, 4 of these cases resolved in the first 3 months and the remaining 2 resolved on Day 174 and Day 275 respectively.

There were more AEs considered to be related to MR4 administration in patients from the *de novo* kidney and liver studies than in patients from the conversion kidney and heart studies, which was also expected since most post-transplantation adverse events occur early after transplantation, and patients in the conversion studies were clinically stable at the time of entry into this study. However, the AE profile was not unexpected for the patient population evaluated**.**

Table 23: Study FG506E-14-02

Study FG-506-14-02: Most Frequently Reported Adverse Events Regardless of Relationship to MR4

	***De novo* studies**		**Conversion studies**	
MedDRA High Level Term *MedDRA Preferred Term*	**FG-11-01 (Liver) N = 47** **n (%)**	**FG-12-01 (Kidney) N = 47** **n (%)**	**FG-12-02 (Kidney) N = 67** **n (%)**	**FG-15-02 (Heart) N = 79** **n (%)**
Anaemias NEC	12 (25.5)	10 (21.3)	0	1 (1.3)
Anaemia	8 (17.0)	7 (14.9)	0	1 (1.3)
Leukopenias NEC	9 (19.1)	4 (8.5)	0	1 (1.3)
Leukopenia	9 (19.1)	4 (8.5)	0	1 (1.3)
Abdominal findings abnormal	6 (12.8)	0	0	1 (1.3)
Ascites	6 (12.8)	0	0	0
Diarrhoea (excl. infective)	10 (21.3)	9 (19.1)	4 (6.0)	13 (16.5)
Diarrhoea	10 (21.3)	9 (19.1)	4 (6.0)	13 (16.5)
Gastrointestinal and abdominal pains (excl. oral and throat)	9 (19.1)	2 (4.3)	1 (1.5)	3 (3.8)
Abdominal pain	6 (12.8)	0	0	0
Nausea and vomiting symptoms	5 (10.6)	0	1 (1.5)	9 (11.4)
Nausea	5 (10.6)	0	1 (1.5)	9 (11.4)
Oedema NEC	5 (10.6)	7 (14.9)	7 (10.4)	3 (3.8)
Oedema peripheral	4 (8.5)	6 (12.8)	7 (10.4)	0
Cholestasis and jaundice	6 (12.8)	0	0	0
Cholestasis	6 (12.8)	0	0	0
Structural and other bile duct disorders	5 (10.6)	0	0	0
Bile duct stenosis	5 (10.6)	0	0	0
Cytomegaloviral infections	6 (12.8)	10 (21.3)	0	0
Cytomegalovirus infection	5 (10.6)	9 (19.1)	0	0
Infections NEC	7 (14.9)	0	1 (1.5)	1 (1.3)
Upper respiratory tract infections – pathogen class unspecified	8 (17.0)	20 (42.6)	6 (9.0)	11 (13.9)
Nasopharyngitis	7 (14.9)	10 (21.3)	1 (1.5)	5 (6.3)
Upper respiratory tract infection	0	7 (14.9)	3 (4.5)	3 (3.8)
Urinary tract infections	2 (4.3)	19 (40.4)	3 (4.5)	2 (2.5)
Urinary tract infection	2 (4.3)	18 (38.3)	3 (4.5)	2 (2.5)

Table 23 (cont.): Study FG506E-14-02

MedDRA High Level Term *MedDRA Preferred Term*	*De novo* studies		Conversion studies	
	FG-11-01 (Liver) N = 47	FG-12-01 (Kidney) N = 47	FG-12-02 (Kidney) N = 67	FG-15-02 (Heart) N = 79
	n (%)	n (%)	n (%)	n (%)
Liver function analyses	6 (12.8)	8 (17.0)	2 (3.0)	3 (3.8)
Hepatic enzyme increased	5 (10.6)	4 (8.5)	1 (1.5)	2 (2.5)
Renal function analyses	3 (6.4)	10 (21.3)	2 (3.0)	1 (1.3)
Blood creatinine increased	3 (6.4)	9 (19.1)	2 (3.0)	1 (1.3)
Virus identification and serology	7 (14.9)	0	0	1 (1.3)
Hepatitis C virus	7 (14.9)	0	0	0
Amino acid metabolism disorders NEC	0	6 (12.8)	0	0
Hyperhomocysteinaemia	0	6 (12.8)	0	0
Diabetes mellitus (incl. subtypes)	13 (27.7)	10 (21.3)	0	3 (3.8)
Diabetes mellitus	3 (6.4)	5 (10.6)	0	2 (2.5)
Diabetes mellitus insulin-dependent	8 (17.0)	2 (4.3)	0	1 (1.3)
Elevated cholesterol	0	5 (10.6)	1 (1.5)	0
Hypercholesterolaemia	0	5 (10.6)	1 (1.5)	0
Hyperglycaemic conditions NEC	10 (21.3)	5 (10.6)	0	1 (1.3)
Hyperglycaemia	10 (21.3)	5 (10.6)	0	1 (1.3)
Potassium imbalance	7 (14.9)	5 (10.6)	0	1 (1.3)
Hyperkalaemia	6 (12.8)	1 (2.1)	0	0
Purine metabolism disorders NEC	3 (6.4)	7 (14.9)	2 (3.0)	3 (3.8)
Hyperuricaemia	2 (4.3)	7 (14.9)	0	0
Musculoskeletal and connective tissue signs and symptoms NEC	7 (14.9)	5 (10.6)	3 (4.5)	14 (17.7)
Back pain	5 (10.6)	1 (2.1)	2 (3.0)	8 (10.1)
Headaches NEC	10 (21.3)	1 (2.1)	1 (1.5)	6 (7.6)
Headache	10 (21.3)	1 (2.1)	1 (1.5)	6 (7.6)
Tremor (excl. congenital)	11 (23.4)	12 (25.5)	1 (1.5)	2 (2.5)
Tremor	11 (23.4)	12 (25.5)	1 (1.5)	2 (2.5)
Renal failure and impairment	17 (36.2)	2 (4.3)	0	6 (7.6)
Renal insufficiency	12 (25.5)	0	0	2 (2.5)
Pneumothorax and pleural effusions NEC	7 (14.9)	1 (2.1)	0	0
Pleural effusion	7 (14.9)	1 (2.1)	0	0
Vascular hypertensive disorders NEC	15 (31.9)	9 (19.1)	7 (10.4)	4 (5.1)
Hypertension	11 (23.4)	9 (19.1)	7 (10.4)	4 (5.1)

Note: Incidence rate of at least 10% of patients in any one study

N = study population (Full Analysis Set); n = number of patients; NEC = not elsewhere classified

Deaths, SAEs, discontinuations due to AEs

In Study FG-506-14-02, a total of 4 patients died during the 1-year interim analysis period and 1 patient died following withdrawal from the study. Two patients died in the liver *de novo* study due to acute respiratory failure on Day 9 (assessed by the investigator as possibly related to study drug) and abnormal hepatic function due to recurrence of hepatitis C on Day 224 (assessed by the investigator as highly probably related to study drug). One patient from the kidney conversion study died on Day 60 resulting from Pseudomonal sepsis (patient had previously been withdrawn on Day 42) and another patient from the kidney conversion study died on Day 127 resulting from an unrelated cerebrovascular accident. There was one death in the heart conversion study (patient died on Day 285 as a result of a B-cell unclassifiable lymphoma, assessed by the investigator as probably related to study drug).

The frequency and nature of SAEs reported were consistent with the known safety profile for tacrolimus. The most frequently reported SAE was urinary tract infections in the *de novo* kidney study and abdominal and gastrointestinal SAEs in the *de novo* liver study. The majority of SAEs assessed by the investigator as causally-related to MR4 were infections, which is consistent with administration of an immunosuppressant such as tacrolimus; urinary tract infections were most common in the de novo kidney study.

Ten patients discontinued due to AEs during the study and no AE was responsible for more than one discontinuation. Another 3 patients were withdrawn due to having their immunosuppressive medication switched, 1 was lost to follow up, 2 patients were withdrawn because they had approved participation for a 1-year period only and 5 patients withdrew their consent. Patients previously in study FG-506-15-02 had the highest rate of discontinuation of all the studies.

Other significant AEs

Dyslipidaemia events were rare in liver *de novo*, kidney conversion and heart conversion patients. For kidney *de novo* patients, there were more events of dyslipidaemia, most of which were hypercholesterolemia.

Hypertension was seen across all study groups in Study FG-506-14-02 with the highest incidence observed in the liver *de novo* patients (11/47; 23.4%) and kidney *de novo* group (9/47; 19.1%); the incidence of hypertension was lower in the kidney conversion group (7/67; 10.4%) and the heart conversion group (4/79; 5.1%).

The higher incidence of glucose metabolism disorders in *de novo* studies is consistent with the known safety profile of tacrolimus. The conversion studies showed a comparatively low incidence of glucose metabolism disorders and there were no events in the kidney conversion group.

Neurological events occurred most frequently in the liver *de novo* patients and least frequently in the kidney conversion patients. The most frequent neurological events were tremor and headache, and were mainly reported in *de novo* patients.

Infections were seen across all patient groups, with a higher incidence of infections observed in the *de novo* study patients. Most infections were viral in nature, with the exception of the urinary tract infection in renal transplant patients. The highest occurrence of infections was in the kidney *de novo* patients with 72.3% of patients experiencing infection, mostly urinary tract infections which are more common in this indication.

Malignant neoplasms were observed in 1 patient in each *de novo* study; 2 and 3 patients in the kidney conversion and heart conversion groups, respectively had malignant neoplasms. This incidence is consistent with incidences reported in transplant registry reports [Taylor et al. 2005].[15]

[15] Taylor DO, Edwards LB, Boucek MM et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-second Official Adult Heart Transplant Report - 2005. J Heart Lung Transplant 2005; 24(8): 945-955.

Laboratory parameters, vital signs

As can be expected for kidney transplant recipients (seen previously in Study FG-506E-12-01 and Study FG-506E-12-02), the serum creatinine levels were higher and creatinine clearance rates were lower than normal for patients in these two study groups (these patients have only one functioning kidney allograft). However, levels of serum creatinine and creatinine clearance remained stable for the period analysed.

The hepatic function parameters were above the upper limit of normal for most of the study, which can be expected in the early phase following liver transplantation. By the end of this interim analysis period, values were either within or approaching the normal range.

There were no new safety concerns regarding vital signs, physical findings; hypertension was most commonly reported.

Safety in Phase III non-inferiority studies

FG506E-11-03 was a multicentre, 1:1 randomized, double blind, two arm parallel group study to evaluate and compare the efficacy and safety of MR4 with that of Prograf in combination with steroids in 475 patients undergoing primary liver transplantation. Prograf was administered for at least 1 year as a dual regimen in combination with steroids in both treatment arms.

The most frequently reported AEs were consistent with the established safety profile for systemic tacrolimus with hypertension, anaemia, renal insufficiency, diarrhoea and hyperglycaemia being the most frequently reported AEs. There were a number of AEs with a significant difference (p-value < 0.05, Fisher's exact test) in incidence between MR4 and Prograf; diarrhoea (Prograf versus MR4: 18.4% versus 25.3%) and scar pain (0% versus 2.5%) reported more frequently following administration of MR4; staphylococcal infections, intra-abdominal haemorrhage, hepatocellular damage and hepatitis were more frequently reported following administration of Prograf (Table 24). The most frequently reported treatment-related AEs were also consistent with the established safety profile for systemic tacrolimus and were generally comparable between the MR4 and Prograf arms, with the exception of hyperglycaemia (Prograf versus MR4: 15% versus 8.4%), confusion and disorientation (5.1% versus 1.7%) which were significantly higher in the Prograf arm compared to the MR4 arm.

The overall incidence of infections was comparable between the MR4 (64.6%) and Prograf (65.4%) groups. The most frequently reported infections were bacterial and cytomegalovirus infections in both treatment groups. Opportunistic or severe infections were either rare or balanced between MR4 and Prograf. The overall incidence of renal and urinary disorders (Prograf versus MR4: 47.9% versus 50.2%)**,** neurological (38.5% versus 33.8%) and vascular disorders was similar in the Prograf and MR4 treatment groups. There were no clinically relevant or statistically significant differences between MR4 and Prograf in the incidence of glucose metabolism disorders, either overall or in patients without pre-existing glucose metabolism disorder. The incidence and pattern of glucose metabolism disorders was consistent with the established safety profile for systemic tacrolimus. The incidence of neoplasms, and malignant neoplasms, was comparable for MR4 and Prograf in the first 12 months post-transplant. A number of malignancies, particularly the metastases to lung and the metastatic malignant melanoma, were most likely present prior to study enrolment but were only discovered during the course of the study. In the extension period, there were an additional three neoplasms reported; one in the MR4 arm (lymphoproliferative disorder) and two in the Prograf arm (Kaposi's sarcoma and hepatic neoplasm malignant).

Overall, 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 Prograf 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 Prograf arm. The incidence of the most frequently reported SAEs was generally comparable between Prograf and MR4 (22.6% versus 24.1%). There was a significantly higher incidence of gastrointestinal SAEs in the Prograf group compared to the MR4 group (2.1% versus 0%, p = 0.030), while SAEs of renal failure/ impairment were significantly higher in the MR4 group (6% versus 12.2%, p = 0.024). There were no significant differences between MR4 and Prograf in the incidence of the most frequently reported AEs leading to discontinuation from the study and the most common AEs leading to discontinuation were renal, neurological and hepatobiliary AEs**.**

There were no clinically relevant differences in any haematology, biochemistry parameters, vital signs or ECG parameters and the incidence of hypertension, hyperlipidaemia and diabetes was also similar in both treatment groups.

Table 24: Study FG506E-11-03

Incidence of Most Frequently Reported Adverse Events Regardless of Relationship to Study Medication

MedDRA SOC MedDRA High Level Term *MedDRA Preferred Term*	FK506 (N=234) Patients (%)	MR4 (N=237) Patients (%)
Metabolism and nutrition disorders	**157 (67.1)**	**158 (66.7)**
Diabetes mellitus (incl. subtypes)	63 (26.9)	56 (23.6)
Diabetes mellitus insulin-dependent	32 (13.7)	35 (14.8)
Hyperglycaemic conditions NEC	55 (23.5)	47 (19.8)
Hyperglycaemia	53 (22.6)	44 (18.6)
Potassium imbalance	51 (21.8)	43 (18.1)
Hyperkalaemia	35 (15.0)	26 (11.0)
Infections and infestations	**153 (65.4)**	**153 (64.6)**
Bacterial infections NEC	50 (21.4)	44 (18.6)
Cytomegaloviral infections	22 (9.4)	29 (12.2)
Hepatitis viral infections	29 (12.4)	20 (8.4)
Hepatitis C	29 (12.4)	19 (8.0)
Staphylococcal infections†	12 (5.1)	3 (1.3)
Gastrointestinal disorders	**141 (60.3)**	**138 (58.2)**
Diarrhoea (excl. infective)	43 (18.4)	60 (25.3)
Diarrhoea	43 (18.4)	59 (24.9)
Nausea and vomiting symptoms	49 (20.9)	41 (17.3)
Nausea	33 (14.1)	32 (13.5)
Gastrointestinal and abdominal pains (excl. oral and throat)	37 (15.8)	40 (16.9)
Abdominal pain	33 (14.1)	28 (11.8)
Abdominal findings abnormal	31 (13.2)	31 (13.1)
Ascites	31 (13.2)	31 (13.1)
Gastrointestinal atonic and hypomotility disorders NEC	30 (12.8)	22 (9.3)
Constipation	28 (12.0)	19 (8.0)
Gastrointestinal disorders NEC†	12 (5.1)	4 (1.7)
Intra-abdominal haemorrhage†	7 (3.0)	1 (0.4)
Blood and lymphatic system disorders	**122 (52.1)**	**130 (54.9)**
Anaemias NEC	84 (35.9)	92 (38.8)
Anaemia	72 (30.8)	74 (31.2)
Thrombocytopenias	39 (16.7)	36 (15.2)
Thrombocytopenia	38 (16.2)	36 (15.2)
Leukopenias NEC	27 (11.5)	31 (13.1)
Leukopenia	27 (11.5)	31 (13.1)
Renal and urinary disorders	**112 (47.9)**	**119 (50.2)**
Renal failure and impairment	109 (46.6)	107 (45.1)
Renal insufficiency	54 (23.1)	58 (24.5)
Renal impairment	38 (16.2)	32 (13.5)
Hepatobiliary disorders	**111 (47.4)**	**98 (41.4)**
Cholestasis and jaundice	49 (20.9)	49 (20.7)
Cholestasis	35 (15.0)	30 (12.7)
Hepatocellular damage and hepatitis NEC†	37 (15.8)	20 (8.4)
Hepatitis†	7 (3.0)	1 (0.4)

Table continued on next page

Table 24 (cont.): Study FG506E-11-03

MedDRA SOC MedDRA High Level Term *MedDRA Preferred Term*	**FK506 (N=234) Patients (%)**	**MR4 (N=237) Patients (%)**
Hepatic and hepatobiliary disorders NEC	6 (2.6)	4 (1.7)
Biloma†	5 (2.1)	0
General disorders and administration site conditions	**102 (43.6)**	**100 (42.2)**
Febrile disorders	41 (17.5)	41 (17.3)
Pyrexia	41 (17.5)	41 (17.3)
Oedema NEC	35 (15.0)	32 (13.5)
Oedema peripheral	29 (12.4)	25 (10.5)
Pain and discomfort NEC	29 (12.4)	28 (11.8)
Vascular disorders	**103 (44.0)**	**98 (41.4)**
Vascular hypertensive disorders NEC	76 (32.5)	73 (30.8)
Hypertension	76 (32.5)	73 (30.8)
Investigations	**91 (38.9)**	**101 (42.6)**
Liver function analyses	56 (23.9)	56 (23.6)
Hepatic enzyme increased	41 (17.5)	35 (14.8)
Therapeutic drug monitoring analyses†	1 (0.4)	9 (3.8)
Injury, poisoning and procedural complications	**86 (36.8)**	**91 (38.4)**
Non-site specific procedural complications	55 (23.5)	58 (24.5)
Non-site specific injuries NEC	30 (12.8)	23 (9.7)
Respiratory, thoracic and mediastinal disorders	**90 (38.5)**	**81 (34.2)**
Pneumothorax and pleural effusions NEC	51 (21.8)	43 (18.1)
Pleural effusion	42 (17.9)	36 (15.2)
Nervous system disorders	**90 (38.5)**	**80 (33.8)**
Tremor (excl congenital)	43 (18.4)	34 (14.3)
Tremor	43 (18.4)	34 (14.3)
Headaches NEC	32 (13.7)	34 (14.3)
Headache	32 (13.7)	34 (14.3)
Psychiatric disorders	**82 (35.0)**	**85 (35.9)**
Disturbances in initiating and maintaining sleep	31 (13.2)	29 (12.2)
Insomnia	31 (13.2)	29 (12.2)
Musculoskeletal and connective tissue disorders	**63 (26.9)**	**62 (26.2)**
Musculoskeletal and connective tissue signs and symptoms NEC	43 (18.4)	33 (13.9)
Back pain	29 (12.4)	26 (11.0)
Skin and subcutaneous tissue disorders	**48 (20.5)**	**48 (20.3)**
Dermal and epidermal conditions NEC†	0	8 (3.4)
Scar pain†	0	6 (2.5)
Cardiac disorders	**34 (14.5)**	**44 (18.6)**

Full Analysis Set

Adverse events coded using MedDRA 6.1; Most frequently reported defined as incidence rate of at least 12% in either treatment group and those with a difference in incidence between FK506 and MR4 associated with $p < 0.05$ (†; Fisher's exact test)

NEC = Not elsewhere classified

FG-506E-12-03 was a multicentre, 1:1 randomized, double blind, two arm parallel group study to evaluate and compare the efficacy and safety of modified release tacrolimus (MR4) versus Prograf in combination with MMF and steroids in 667 patients undergoing kidney transplantation.

The most frequently reported AEs were consistent with the established safety profile for systemic tacrolimus; however, pharyngitis, cytomegaloviral infections, gastroenteritis, polyomavirus infections, gastrointestinal disorders, nephrogenic anaemia, urinary tract procedural complications, haemorrhages, joint related signs and symptoms, testicular disorder and dysmenorrhoea were all reported more frequently following administration of MR4 (Table 25). The most frequently reported treatment-related AEs were also consistent with the established safety profile for systemic tacrolimus and were generally comparable between the MR4 and Prograf arms, with the exception of bacterial infections (Prograf versus MR4: 22.6% versus 16.0%) which were significantly higher in the Prograf arm compared to the MR4 arm.

The overall incidence of infections was comparable between the MR4 (37.8%) and Prograf (37.8%) groups. The most frequently reported infections were bacterial and cytomegalovirus infections in both treatment groups. Opportunistic or severe infections were either rare or balanced between MR4 and Prograf. There were no significant differences in incidence of bacterial, fungal and protozoal infections between Prograf and MR4 treatment groups. However, there were significantly more cytomegalovirus and polyomavirus infections in the MR4 group compared to the Prograf group ($p=0.043$ and $p=0.037$; Fisher's exact test). Post transplantation, cytomegalovirus infections were reported in 21 patients in the Prograf group and 36 patients in the MR4 group. Of the 57 patients, 52 patients recovered, three patients had evidence of ongoing infection at the final examination (all in the Prograf group) and one patient in each group recovered with residual effects. The incidence of neoplasms, and malignant neoplasms, was slightly higher in the Prograf group (5.7%) compared with MR4 (3.3%) in the first 12 months post-transplant. A number of malignancies were most likely present prior to study enrolment but were only discovered during the course of the study.

The overall incidence of renal and urinary disorders, glucose metabolism disorders**,** neurological and vascular/ hypertensive disorders were similar in the Prograf and MR4 treatment groups.

Overall, 18 patients died during the study period of 12 months. Of the 18 patients, six patients died during the 12 months post-transplant and twelve patients following discontinuation from the study. Causality of death was not assessed in 9 patients; deaths were considered probably related to study treatment in 4 cases (septic shock and viral pneumonia in MR 4 patients).

Table 25: Study FG506E-12-03

Incidence of Most Frequently Reported Adverse Events Regardless of Relationship to Study Medication

MedDRA SOC MedDRA High Level Term *MedDRA Preferred Term*	**FK506 (N=336) Patients (%)**	**MR4 (N=331) Patients (%)**
Metabolism and nutrition disorders	**231 (68.8)**	**236 (71.3)**
Potassium imbalance	79 (23.5)	91 (27.5)
Hyperkalaemia	49 (14.6)	50 (15.1)
Hypokalaemia	36 (10.7)	48 (14.5)
Diabetes mellitus (incl. subtypes)	69 (20.5)	68 (20.5)
Hyperglycaemic conditions NEC	70 (20.8)	67 (20.2)
Hyperglycaemia	65 (19.35)	61 (18.4)
Infections and infestations	**216 (64.3)**	**228 (68.9)**
Bacterial Infections	123 (36.6)	105 (31.7)
Urinary tract infection bacterial	102 (30.4)	86 (26.0)
Upper respiratory tract infections – pathogen class unspecified	47 (14.0)	49 (14.8)
Pharyngitis†	4 (1.2)	12 (3.6)
Cytomegaloviral infections †	21 (6.3)	36 (10.9)
Cytomegaloviral infection †	19 (5.7)	33 (10.0)
Abdominal and gastrointestinal infections	21 (6.3)	21 (6.3)
Gastroenteritis †	3 (0.9)	11 (3.3)
Polyomavirus infections †	1 (0.3)	7 (2.1)
Tinea infections †	0	5 (1.5)
Gastrointestinal disorders	**223 (66.4)**	**203 (61.3)**
Diarrhoea (excl. infective)	103 (30.7)	88 (26.6)
Diarrhoea	103 (30.7)	88 (26.6)
Nausea and vomiting symptoms	79 (23.5)	81 (24.5)
Nausea	42 (12.5)	51 (15.4)
Vomiting	43 (12.8)	42 (12.7)
Gastrointestinal atonic and hypomotility disorders NEC	64 (19.0)	47 (14.2)
Constipation	60 (17.9)	45 (13.6)
Gastrointestinal and abdominal pains (excl. oral and throat)	47 (14.0)	49 (14.8)
Abdominal pain	28 (8.3)	39 (11.8)
Gastrointestinal disorders NEC †	3 (0.9)	11 (3.3)
Renal and urinary disorders	**160 (47.6)**	**156 (47.1)**
Renal vascular and ischaemic conditions	52 (15.5)	45 (13.6)
Renal tubular necrosis	38 (11.3)	35 (10.6)
Bladder and urethral symptoms	43 (12.8)	43 (13.0)
Renal failure and impairment	40 (11.9)	29 (8.8)
Urinary abnormalities	32 (9.5)	34 (10.3)
Blood and lymphatic system disorders	**146 (43.5)**	**167 (50.5)**
Anaemias NEC	88 (26.2)	105 (31.7)
Anaemia	87 (25.9)	102 (30.8)
Leukopenias NEC	39 (11.6)	53 (16.0)
Leukopenia	37 (11.0)	51 (15.4)
Anaemias due to chronic disorders †	2 (0.6)	9 (2.7)
Nephrogenic anaemia †	2 (0.6)	9 (2.7)
Injury, poisoning and procedural complications	**150 (44.6)**	**140 (42.3)**
Non-site specific procedural complications	121 (36.0)	111 (33.5)
Graft dysfunction	56 (16.7)	57 (17.2)
Urinary tract procedural complications †	1 (0.3)	7 (2.1)
Urinary anastomotic leak †	0	6 (1.8)

Table 25 (cont.): Study FG506E-12-03

MedDRA SOC MedDRA High Level Term *MedDRA Preferred Term*	FK506 (N=336) Patients (%)	MR4 (N=331) Patients (%)
Vascular disorders	**123 (36.6)**	**135 (40.8)**
Vascular hypertensive disorders NEC	76 (22.6)	80 (24.2)
Hypertension	76 (22.6)	80 (24.2)
Haemorrhages NEC †	10 (3.0)	22 (6.6)
Haematoma †	5 (1.5)	14 (4.2)
Investigations	**130 (38.7)**	**114 (34.4)**
Renal function analyses	66 (19.6)	57 (17.2)
Blood creatinine increased	63 (18.8)	54 (16.3)
Liver function analyses	47 (14.0)	35 (10.6)
General disorders and administration site conditions	**119 (35.4)**	**110 (33.2)**
Oedema NEC	68 (20.2)	54 (16.3)
Oedema peripheral	48 (14.3)	38 (11.5)
Pain and discomfort NEC	41 (12.2)	38 (11.5)
Nervous system disorders	**102 (30.4)**	**108 (32.6)**
Tremor (excl. congenital)	58 (17.3)	58 (17.5)
Tremor	58 (17.3)	58 (17.5)
Headaches NEC	33 (9.8)	40 (12.1)
Headache	33 (9.8)	39 (11.8)
Musculoskeletal and connective tissue disorders	**73 (21.7)**	**79 (23.9)**
Musculoskeletal and connective tissue signs and symptoms NEC	43 (12.8)	40 (12.1)
Joint related signs and symptoms †	17 (5.1)	30 (9.1)
Athralgia †	13 (3.9)	29 (8.8)
Respiratory, thoracic and mediastinal disorders	**83 (24.7)**	**70 (21.1)**
Psychiatric disorders	**71 (21.1)**	**64 (19.3)**
Disturbances in initiating and maintaining sleep	34 (10.1)	29 (8.8)
Insomnia	34 (10.1)	29 (8.8)
Skin and subcutaneous tissue disorders	**68 (20.2)**	**57 (17.2)**
Apocrine and eccrine gland disorders †	10 (3.0)	1 (0.3)
Night sweats †	9 (2.7)	0
Cardiac disorders	**44 (13.1)**	**42 (12.7)**
Reproductive system and breast disorders	**36 (10.7)**	**39 (11.8)**
Testicular and epididymal disorders	4 (1.2)	8 (2.4)
Testicular disorder †	0	5 (1.5)
Menstruation and uterine bleeding NEC	3 (0.9)	7 (2.1)
Dysmenorrhoea †	0	5 (1.5)

Full Analysis Set

Adverse events coded using MedDRA 6.1. Most frequently reported defined as incidence rate of ≥ 10% in either treatment group together with events with an incidence difference associated with a p-value < 0.05

MedDRA = Medical Dictionary for Drug Regulatory affairs; NEC = Not Elsewhere Classified; SOC = System Organ Class

† p = < 0.05 (Fisher's exact test)

There were no clinically relevant differences in the cause of death between the treatment groups and there was no clear pattern regarding the causes of death during the study and following withdrawal. The incidence of the most frequently reported SAEs was generally comparable between Prograf and MR4 with exception of significantly higher incidence of bacterial pyelonephritis[*] in the MR4 group (Prograf versus MR4: 0.9% versus 3.6%, p = 0.019)**.** The incidence of withdrawal due to an AE was

[*] Bacterial pyelonephritis was reported in three patients in the tacrolimus group and twelve patients in the MR4 group. Bacterial pyelonephritis of five patients (one in tacrolimus and four in the MR4 group) was considered related to study medication; there was no statistical significant difference.

similar in the MR4 (13%) and Prograf (11.6%) groups; renal and gastrointestinal AEs were most common AEs leading to discontinuations.

There were no clinically relevant differences in any haematology, biochemistry parameters, vital signs or ECG parameters and incidence of hypertension, hyperlipidaemia and diabetes was also similar in both treatment groups. Renal function was comparable through out the 12 months of the study in both arms with similar creatinine values in the MR4 and Prograf group (130.68 μmol/L and 130.02 μmol/L, respectively); corresponding figures for creatinine clearance were 66.76 mL/min and 67.25 mL/min, respectively.

Safety in Phase II, PK conversion studies

Safety was also evaluated in the PK conversion studies involving 348 patients who had undergone kidney, liver or heart transplantation; patients were converted from a Prograf-based immunosuppressive regimen to a MR4- based treatment regimen. The incidence of AEs in these studies was less than that observed in the *de novo* transplantation studies as the patients in the conversion studies were at least 6 months post-transplant and more likely to be clinically stable.

In the Phase II conversion study **(02-0-131)** involving 67 adult kidney transplant patients, the AE profile of MR4 was consistent with that of Prograf. There were no deaths that occurred and no patients discontinued the study due to an adverse event during the pharmacokinetic treatment period. There was no occurrence of graft loss or any acute rejection episodes during the pharmacokinetic treatment period, and the changes in mean serum creatine values were not clinically significant. There were no newly diagnosed cases of post-transplant diabetes mellitus during the pharmacokinetic treatment period, and changes in mean glucose values were not clinically significant. Laboratory results indicate renal function remained stable with the exception of one patient diagnosed with a human polyomavirus infection. There were no clinically significant changes in liver function tests that could be attributed to the study drug. There was no clinical indication of over- or under-immunosuppression after patients were converted to MR4. There were no clinically significant changes in concomitant medication use during the pharmacokinetic treatment period.

In the Phase II, 4-period, crossover study **FG-506E-12-02**, involving 69 adult kidney transplant patients, there were no incidences of acute rejection, deaths or graft losses during the study. The number of AEs reported was low and comparable for Prograf and MR4 administration**;** there was a single SAE of abdominal discomfort (reported during Prograf dosing) which was considered by the investigator to be not related to study drug. The most frequently reported AE was headache, experienced by 3 (4.3%) patients following Prograf administration and by 5 (7.4%) patients following MR4 administration. There were no exceptional findings in any of the clinical laboratory parameters assessed. Mean values for serum creatinine and creatinine clearance were stable throughout the study, as were plasma glucose levels.

In the Phase II conversion study **(FJ-506E-KT01)** involving 35 kidney transplant patients, AEs were observed in 27.0% (10/37) of patients during Prograf capsule administration and in 48.6% (17/35) of patients during MR4 capsule administration with the main difference in incidence of infection which was experienced by 5.4% (2/37) of patients during Prograf administration and by 25.7% (9/35) of patients during MR4 capsule administration**.** A higher incidence of AEs, especially infection, during MR4 capsule administration was considered to be due to a shorter treatment period for Prograf (from Week -1 to Day -1) compared with MR4 (from Day 1 to Week 12).

In the phase II, open label, single-sequence, four period crossover, multi-centre conversion study **(02-0-152)** involving 65 stable, adult liver transplant recipients being treated with Prograf-based immunosuppression, the incidence of AEs was similar in the Prograf and MR4 treatment periods. There was only one biopsy-confirmed acute rejection episode during the pharmacokinetic treatment period. There was no incidence of graft loss during the pharmacokinetic treatment period. There

were no newly diagnosed cases of post-transplant diabetes mellitus or clinically significant changes in mean glucose values. Overall, there was no indication of over- or under-immunosuppression while patients were taking MR4. There were no changes in concomitant medications use within the pharmacokinetic evaluable set during the pharmacokinetic treatment period, including immunosuppressants. Approximately, 80% of patients who received MR4 did not require any dose adjustments during the pharmacokinetic treatment period.

In the Phase II, open-label study **(FG-506-15-02)** involving 45 stable heart transplant patients converted from a Prograf-based to a MR4-based immunosuppression regimen, there were no incidences of acute rejection, deaths or graft losses during the study. The number of adverse events reported was low. There were more adverse events reported during MR4 administration (26.8%) than during Prograf (3.5%); however, this was to be expected as the MR4 treatment duration was 4 weeks compared to 1 week for Prograf. All of the adverse events observed were consistent with the known safety profile of tacrolimus.

The phase II, open-label, multicentre conversion study **(03-0-160)** involved 18 stable paediatric liver transplant recipients being treated with Prograf-based immunosuppression. The duration of the pharmacokinetic treatment period was 2 weeks; 1 week of Prograf administration, followed by 1 week of MR4 administration. Patients who completed the 2-week pharmacokinetic treatment period were eligible to continue receiving MR4 as part of the MR4 extension treatment period of the study. Overall, the adverse event profile of MR4 was consistent with that of Prograf with very few AEs during the 2-week pharmacokinetic treatment period. There were no clinically significant changes in laboratory values, renal and hepatic function appeared to remain stable. There were no deaths, rejections, graft losses, or discontinuations due to AEs. There were no changes in the use of concomitant immunosuppressive medications during the pharmacokinetic treatment period and no study drug dose changes due to adverse events.

An exploratory analysis of consolidated data from four transplant trials (three liver and one kidney) [Kershner and Fitzsimmons, 1996] examined the relationship between tacrolimus blood concentrations and clinical findings.[16] Toxicity was clearly correlated with tacrolimus blood concentration in both kidney and liver transplant patients. Trough levels of tacrolimus > 20 ng/mL for an extended duration was associated with increased risk of these adverse events. In addition to tacrolimus exposure, other factors such as concomitant corticosteroid dosage, and baseline age and weight were also significant explanatory variables.

The relationship between rejection and tacrolimus blood concentrations was demonstrated for kidney transplantation only. There is evidence to suggest that the risk of acute rejection is higher with low systemic exposure to tacrolimus in renal and heart transplant recipients in the early post-transplant period [Undre et al. 1999b; Undre et al. 2002].[17,18]

Safety in special patient populations

Safety in paediatric and elderly populations

The only available data for MR4 in a paediatric population are for stable paediatric liver transplant recipients converted from Prograf-based immunosuppression to MR4-based immunosuppression **(Study 03-0-160),** which showed similar safety results**.** There is no clinical evidence in any of the

[16] Kerschner Rp, Fitzsimmons WE. Relationship of FK506 whole blood concentrations and efficacy and toxicity after liver and kidney transplantation. Transplantation. 1996; 62(7): 920-926.

[17] Undre NA, van Hooff J, Christiaans M et al. Low systemic exposure to tacrolimus correlates with acute rejection. Transplant Proc 1999; 31(1-2): 296-298.

[18] Undre NA, Stevenson PJ for the European Tacrolimus Heart Study Group. Pharmacokinetics of tacrolimus in heart transplantation. Transplant Proc 2002; 34: 1836.1838.

studies performed to date with Prograf, or in clinical usage, to suggest that the ADR profile in the elderly population is substantially different to that in younger adult patients. Special studies to evaluate safety in the elderly population have not been performed with either Prograf or MR4.

Effect of gender and race on safety of MR4

There is no clinical evidence in any of the studies performed to date to suggest that the ADR profile of Prograf or MR4 differs based on gender or race.

Safety in patients with hepatic or renal impairment

In patients with severe liver impairment, it may be necessary to reduce tacrolimus doses in order to maintain the whole blood tacrolimus trough levels within the recommended target range. This is reflected in the proposed PI. The pharmacokinetics of tacrolimus are not affected by renal function, therefore no dose adjustment should be required in patients with impaired renal function. However, due to the nephrotoxic potential of tacrolimus, careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

Use in pregnancy, Abuse potential, withdrawal/ rebound and use while driving or operating machinery

The mechanism of action of tacrolimus, together with the pharmacological classification, suggest no potential for abuse, withdrawal or rebound effects, which is supported by the available non-clinical and clinical data. Tacrolimus may cause visual and neurological disturbances with subsequent effects on driving (as indicated in the Prograf PI and the proposed PI). This effect may be enhanced if MR4 is administered in association with alcohol.

There is no experience with the administration of MR4 during pregnancy, and the experience with systemic use of tacrolimus in pregnancy remains limited; a firm conclusion about its mutagenicity or teratogenicity in humans has not been reached. The present knowledge is based on the outcomes of 211 pregnancies (systemic use of tacrolimus) in 179 women, of whom 149 were transplant patients and one was an autoimmune patient; 29 women had partners who were transplant patients.

The results are in accordance with published experience on the use of other immunosuppressive substances in pregnancy following organ transplantation. Approximately 47% of the children were born premature; however, the available data show that the majority of the newborns had normal birth weight for their gestational age. The rate of malformations (approximately 3%) was similar to that seen in patients treated with cyclosporin after organ transplantation [Lamarque et al. 1997].[19] No consistent pattern in the malformations was observed. A precautionary statement in the product information is still necessary. If a patient wishes to plan or to continue a pregnancy while taking tacrolimus, the decision should be made on an individual basis, carefully weighing all potential risks and benefits to the mother and the child. Tacrolimus crosses the placenta and is excreted in milk; hence, breast feeding should be avoided during tacrolimus treatment.

To date, there has been one case of overdose with MR4 during clinical development. In Study 02-0-131 (kidney transplant recipients) a patient was inadvertently converted from a total daily dose of 4 mg of Prograf to 20 mg of MR4. The patient experienced mild hypomagnesaemia (1.1 mg/dL) from Day 22 to Day 183, which was considered by the investigator to be possibly related to study drug and which was treated with medication. The patient recovered with no residual effects. The experience with tacrolimus overdose following administration of Prograf is also limited; the clinical signs and symptoms observed in the presented cases are in line with previous experience with, or

[19] Lamarque V, LeLeu MF, Monka C et al. Analysis of 629 pregnancy outcomes in transplant recipients treated with Sandimmun. Transplant Proc 1997; 29: 2480.

expected effects of, elevated tacrolimus levels (tremor, headache, nausea and vomiting, infections, urticaria, lethargy, increased blood urea nitrogen, elevated serum creatinine concentrations and increases in alanine aminotransferase levels); some patients were asymptomatic. No specific antidote to tacrolimus exists. In the majority of cases, patients recovered from the overdose and/or tacrolimus toxicity following a reduction in dose or treatment interruption. Furthermore, tacrolimus therapy was continued in most cases, with only a small number of patients experiencing sequelae. Symptoms of tacrolimus overdose and recommendations for the management of overdose are described adequately in the proposed PI.

Summary of safety

Safety was evaluated in a total of 341 patients undergoing de novo kidney and liver transplantation who received MR4-based immunosuppression for 12 months. A further 348 patients (including 19 paediatric patients) were converted from Prograf-based immunosuppression to MR4-based immunosuppression (kidney, liver and heart transplantation) in shorter duration studies (6 to 12 weeks); 242 healthy volunteers received MR4 during Phase I studies.

Safety results from the pivotal Phase III study (02-0-158) in kidney transplant patients showed that gastrointestinal AEs were most commonly associated with MR4 treatment. The incidence and safety profile of MR4 was generally similar to that of Prograf, although the incidence of gastroenteritis, lower abdominal pain and paraesthesia was significantly ($p<0.05$) higher in the MR4 group (compared with Prograf). Overall, the most common AEs in both tacrolimus groups (Prograf and MR4) were diarrhoea, infections, tremor, oedema and hyperglycaemia (associated with increased use of oral hypoglycaemics).

A summary of other Phase III non-inferiority studies between Prograf and Prograf XL showed similar results in primary kidney (FG-506E-12-03) and liver (FG506E-11-03) transplant patients. Supportive 6-week, Phase II studies in kidney (506E-12-01) and liver (506-11-01) transplant patients showed similar safety profiles for both tacrolimus formulations. The six Phase II pharmacokinetic conversion studies showed that the safety profile of tacrolimus was generally similar following conversion from Prograf to Prograf XL; however, the duration of these conversion studies was only 6 to 12 weeks.

Long term safety was evaluated in the ongoing, open-label study (FG 506-14-02) involving 240 patients followed up for 1 year. The incidence of new onset adverse events associated with Prograf treatment appears to decrease over time, with the majority of adverse events occurring in the first months post-transplantation. The prevalence of malignancies cumulatively increases over time, which is not unexpected when patients are exposed to long-term immunosuppressive therapy; however, the incidence of malignancies following administration of Prograf appears to be consistent with that seen in transplant registry reports. The incidence of AEs decreased with time after transplantation. Fewer AEs were reported for former conversion study patients compared with those from de novo studies, which was expected as the patients from the conversion studies were clinically stable and at least 6 months post-transplant at the time of entering the study. The most common AEs were anaemia, diarrhoea, ascites, abdominal pain, tremor, headache, hyperglycaemia and infections and were expected AEs in this patient population

Clinical Summary and Conclusions

Tacrolimus is a well established immunosuppressive agent for the prophylaxis and treatment of allograft rejection. It has been well studied and fully evaluated for more than a decade. The risks of tacrolimus administration in terms of the incidence of adverse events and adverse drug reactions have been thoroughly assessed. Non-compliance with immunosuppressive regimens in the maintenance phase following transplantation has been shown to be a significant variable for late graft rejection and loss [Schweizer et al. 1990; Bunzel and Laederach-Hofmann, 2000; Weng et al.

2005].[20,21,22] Improved adherence to immunosuppressive regimens with once daily compared to twice daily dosing has been demonstrated in adult kidney transplant recipients [Weng et al. 2005].[17]

The tacrolimus prolonged-release formulation (MR4) has been developed with the aim of enabling once daily administration of tacrolimus, and may therefore improve compliance and decrease the risk of late graft rejection and loss.

Systemic exposure (AUC) is a significant explanatory variable for the efficacy and safety of tacrolimus. As the systemic exposure for Prograf and MR4 has been shown to be similar at equivalent doses, therapeutic equivalence of the two formulations can be concluded. Conversion studies in three different indications - kidney, liver and heart transplantation - have shown that conversion from Prograf to MR4 at the same daily dose resulted in equivalent systemic exposure to tacrolimus. The efficacy profile was maintained and no new safety concerns were identified. However, it is important to note that across all conversion studies, systemic exposure to tacrolimus following MR4 was 5% to 11% lower than that following administration of Prograf and this was more evident (up to 30% lower) in the initial few days. This may be important as patients may not be exposed to adequate tacrolimus when treated with once-daily MR4 (Prograf XL) in the immediate post-transplant period. Since efficacy (incidence of graft rejection) has been linked to systemic exposure to tacrolimus, it is recommended that following conversion from Prograf to MR4, tacrolimus exposure should be monitored and where necessary dose adjustments made to ensure that adequate systemic exposure is maintained. In addition, therapeutic equivalence at 1-year post-transplant has been demonstrated in large, Phase III comparative, non-inferiority studies in *de novo* kidney and liver transplant recipients.

All *de novo* studies but FG-506E-11-03 study performed with MR4 have used the same recommended initial oral daily dose as for Prograf; with the same target whole blood tacrolimus trough concentrations. Comparative *de novo* studies performed in kidney and liver transplant recipients have demonstrated comparably low incidences of acute rejection episodes for MR4 and Prograf and have shown a comparable safety profile. In all three *de novo* studies, a good correlation of AUC and whole blood trough levels was evident for both MR4 and Prograf, enabling use of established therapeutic drug monitoring approaches for MR4.

Across all studies with MR4 the identified safety profile was comparable with that for Prograf. A comparison of adverse drug reactions reported for MR4 in the *de novo* transplantation studies with the established safety profile for Prograf revealed no additional risks or safety concerns for MR4 as an alternative formulation of tacrolimus. Throughout development, the mean doses of MR4 and Prograf followed a similar pattern over time indicating that the individualisation and adaptation of tacrolimus therapy was comparable for MR4 and Prograf. There is no evidence of dose dumping or immediate release of the entire tacrolimus dose from any of the studies performed with once daily MR4. As tacrolimus is a low clearance drug, missing of a single day's tacrolimus administration for either formulation is unlikely to result in a clinically significantly decreased exposure to tacrolimus.

Overall, the benefit risk assessment for MR4 appears to be positive and Prograf can be substituted with MR4 in each of the claimed indications: (1) Prophylaxis of transplant rejection (primary immunosuppression and maintenance therapy) in adult kidney or liver allograft recipients, (2) Conversion from Prograf capsules taken twice daily to Prograf MR prolonged-release capsules

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[20] Schweizer RT, Rovelli M, Palmeri D et al. Noncompliance in organ transplant recipients. Transplantation 1990; 49: 374-377.

[21] Bunzell B, Laederach-Hofmann K. Solid organ transplantation: are there predictors for post transplant noncompliance? A literature overview. Transplantation 2000; 70: 711-716.

[22] Weng FL, Israni AK, Joffe MM et al. Race and electronically measured adherence to immunosuppressive medications after deceased donor renal transplantation. J Am Soc Nephrol 2005; 16: 1839.1848.

taken once daily in adult allograft recipients and (3) Treatment of allograft rejection resistant to treatment with other immunosuppressive drugs in adult patients.

Recommendation

The evaluator recommended that Prograf XL 0.5 mg, 1 mg and 5 mg prolonged-release capsules be approved as adjunct treatment (with other immunosuppressants) for kidney, liver, heart and lung transplantation in adults and children. However, approval is subject to incorporation of suggested changes to the proposed PI.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no objections to registration in respect of chemistry, manufacturing and controls. Tacrolimus is practically insoluble in water but is dissolved in ethanol during manufacture of the drug product. Tacrolimus is mixed with ethylcellulose, hypromellose and lactose to form intermediate sustained release granules. The sustained release character of the granules is imparted by the ethylcellulose, which controls the rate of permeation of water into the granules.

Twelve bioavailability studies were submitted with the application. Study FG-506-04-25, a multidose study of 4mg tacrolimus daily was considered the most definitive study. At Day 10 the modified release formulation and the current formulation were within equivalence criteria for AUC (AUC_{0-24} 93%; 90% CI: 87, 99) and C_{min} (C_{24} 87%; 90% CI: 81, 94), with 26% lower C_{max} for the modified release formulation. Two food effect studies showed that food caused moderate reduction in the rate and extent of absorption. Modified release capsules are recommended to be taken on an empty stomach, or at least 1 hour before or 2-3 hours after a meal. The inconsistent results in various bioavailability studies are of some concern. The sponsor attributed this to large inter- and intra-subject variability in tacrolimus pharmacokinetics, although there were clear cut differences in results between some studies.

Nonclinical

On the basis of bioequivalence for exposure of the current immediate release and the proposed modified release formulations and the lower C_{max} for the modified release formulation, no remarkable alterations in toxicity profile or animal:human safety margins are expected. There were no non-clinical objections of Prograf-XL, subject to the confirmation of bioequivalence of the two formulations. Several changes have been recommended to the *Interactions with other Medicines* section of product information.

Clinical

Pharmacokinetics

Pharmacokinetics (PK) were presented from 41 studies, although not all studies involved the modified release formulation. The submission included 7 studies conducted in 292 healthy subjects. There were 8 studies in 766 kidney transplant recipients, 6 studies in 230 liver transplant recipients, 4 studies in 107 heart transplant recipients and 2 studies in 12 patients with liver dysfunction.

Tacrolimus whole blood concentrations were determined using a validated LC/MS/MS method.

Pharmacokinetics in renal transplant recipients were compared with MR4 or Prograf in **Study FG-506E-12-01**. The first daily oral dose of tacrolimus was 0.20 mg/kg. Dose modifications were made according to clinical signs and by monitoring of whole blood concentrations. Following maintenance for 14 days the dose was reduced to 1/g day in clinically stable patients. The PK data set comprised 66 adult patients (34 MR4, 32 Prograf). Mean total daily doses generally remained stable and were similar for the two treatment arms for the first 7 days. In the PK evaluable population, mean daily doses of MR4 were 0.189 mg/kg at Day 1 and 0.175 mg/kg at Week 6. Mean daily doses of Prograf were 0.185 mg/kg on Day 1 and 0.164 mg/kg at Week 6. Systemic exposure (AUC_{0-24}) to tacrolimus on Day 1 was approximately 32% lower for MR4 on Day 1. The ratio of lnAUC at Day 14 was 107% and at Week 6 was 89.1%. Confidence limits for the Day 14 result were within the 80% to 125% equivalence criteria whereas the 6 week results were slightly outside the equivalence range. There was good correlation between AUC_{0-24} and C_{min} for both MR4 and Prograf, with similar correlation values.

Three studies assessed pharmacokinetic parameters in stable kidney transplant patients who were converted from Prograf-based immunosuppression to MR4 based regimens. **Study FG-506E-12-02** had a 4 period cross over design over 56 days. A total of 60 subjects were evaluable for PK. The tacrolimus AUC_{0-24} was comparable for Prograf and MR4 (92.9%, 90% CI: 89.8, 96) and within the equivalence criteria. C_{min} ratios were within equivalence criteria (90.9%; 90% CI: 87.3, 94.6) whereas C_{max} ratios were lower (73.2%; 90% CI: 67.7, 78.7). Inter- and intra-subject variability was similar for MR4 and Prograf. **Study 02-2-131** enrolled kidney transplant patients stable on Prograf-based regimens. Prograf was continued to Day 7. Subjects converted to MR4 (1:1 mg:mg daily dose) on Day 8 and had PK analyses over 4 weeks of MR4 treatment after which there was an MR4 extension phase. 70 subjects were entered and 66 subjects were included in the PK analysis. The mean dose of MR4 increased from 5.8 mg at Day 7 to 5.9 mg on Day 14 and 6.1 mg on Day 21. 30% of subjects required dose adjustment after converting. The tacrolimus AUC_{0-24} was comparable for Prograf and MR4 (ratio 94.4%, 90% CI; 90.34, 98.54) as were log calculated parameters. Dose adjusted parameters showed similar results. As seen in the previous study, C_{min} ratios were within equivalence criteria whereas C_{max} ratios were lower. **Study FJ-506E-KT01** evaluated PK in 35 adult kidney transplant patients who were stable on Prograf regimens and converted to MR4 with the same daily dose. After conversion, dose adjustment was not necessary in 85.7% through 12 weeks of MR4 administration. The tacrolimus AUC_{0-24} was comparable for MR4 and Prograf (ratio 0.95%, 90% CI; 0.88, 1.03)as were $lnAUC_{0-24}$ values. Lower C_{max} and later t_{max} were observed for MR4.

Study FG-506E-12-03 is a Phase III, randomised, double blind study of MR4 versus Prograf after kidney transplantation. PK parameters were assessed in the first two weeks in a subgroup of 34 patients. The initial post-operative dose was 0.2 mg/kg once daily for MR4 and 0.1 mg bd for Prograf. Target C_{min} was 10-15 ng/mL in the initial two weeks. Day 1 AUC_{0-24} was lower for MR4 than Prograf 16% lower in log analysis, with log ratio at Day 3 of 87.9%, at Day 7 of 116% and at Day 14 of 84.3%.

Pharmacokinetics of MR4 were assessed in 2 studies after primary liver transplantation and in 1 conversion study in stable liver transplant patients. **Study FG-506E-11-01** is a Phase II, open, randomised comparison of MR4 versus Prograf in patients undergoing primary liver transplantation. PK parameters were assessed at Day 1, Day 14 and Week 6 after transplantation. A total of 133 subjects were randomised with a PK evaluable set of 77 patients. The first daily oral dose was in the range 0.1-0.15 mg/kg for both MR4 and Prograf. On Day 1 tacrolimus AUC_{0-24} was approximately 50% lower for MR than Prograf. On Day 14 and at 6 weeks AUC_{0-24} were 113% (90% CI: 98.6, 127.4) and 121% (90% CI: 109, 132) respectively. Mean daily dose of MR4 was approximately 25% higher than Prograf, however. **Study FG-506E-11-03** is a Phase III

randomised, double blind study of MR4 versus Prograf after primary liver allograft transplantation. The initial post-operative dose was 0.2 mg/kg once daily for MR4 and 0.05 mg/kg bd for Prograf. Dose was adjusted to maintain blood concentration between 10-20 ng/mL. Steroids were coadministered. PK analysis was undertaken in 25 patients to Day 14. Systemic exposure to tacrolimus [ln(AUC_{0-24})] was 58% higher for MR4 than Prograf although the mean daily dose was approximately double. On Days 3, 7 and 14 the ln(AUC_{0-24}) for MR4 was 57%, 41% and 25% higher than for Prograf, although MR4 doses were higher. There were lower dose normalised exposures [ln(AUC_{0-24})] of -23%, -12% and -16% for MR4 at Days 1, 3 and 14, respectively.

Study 02-0-152 included evaluation of PK in adult liver transplant patients who were stable on Prograf regimens and converted to MR4 with the same daily dose. There was a 4 period cross over design over 56 days with patients receiving Prograf from Days 1-14 and Days 29-42. Patients received MR4 on Days 15-28 and Days 43-56. Other immunosuppressants were maintained at constant doses. 62 patients were included in the PK data set. Mean daily MR4 and Prograf doses were consistent through to Day 56. For the primary measure of exposure [ln(AUC_{0-24})] the MR4/Prograf ratio of steady state exposures was 88.79% (90% CI: 85.42, 92.29) and was similar in dose adjusted analysis. Lower C_{max} at steady state was observed for MR4 . C_{min} at steady state was lower for MR4 although analysis including all trough days reported 90% confidence limits within criteria for equivalence.

Study 03-0-160 included evaluation of PK in stable paediatric liver transplant patients converted from Prograf to MR4. 18 subjects aged between 5 to 13 years were included in the PK analysis following one week of Prograf administration and 1 week of MR4 administration. For the primary measure of exposure [ln(AUC_{0-24})] 90% CI were within the equivalence range. Mean C_{max} was higher for Prograf than MR4. C_{min} ratio was within equivalence criteria. Correlation coefficients for AUC_{0-24} and C_{min} correlated strongly during both Prograf and MR4 treatment periods.

One study assessed pharmacokinetic parameters in stable heart transplant patients who were converted from a Prograf-based immunosuppression regimen to a MR4 based regimen. **Study FG-506-15-02** enrolled 85 adult patients of whom 45 were included in a PK evaluable set. There was an approximately 2 week screening during which a stable Prograf dose was maintained followed by one week of Prograf study medication and 4 weeks of MR4. During MR4 administration 30% of patients had dose adjustment (increase in dose in 17/18 patients). Ln(AUC_{0-24}) was 90.5% for MR4 compared to Prograf, with 90% confidence intervals within equivalence criteria. There was good correlation between $AUC0_{-24}$ and C_{24} for Prograf and MR4.

In comparison to Prograf, MR4 showed an extended oral absorption profile. Across studies in kidney, liver and heart transplantation, where adults were converted from twice daily Prograf to MR4, mean systemic exposure of tacrolimus was between 5% and 11% lower but 90% confidence intervals were within the equivalence limits of 80% and 125%.

Pharmacodynamics

Phase II studies of modified release tacrolimus were undertaken in patients undergoing kidney transplantation and liver transplantation.

Study FG-506E-12-01 was conducted in patients undergoing kidney transplantation to compare acute rejection rates with MR4 or Prograf. Patients also received corticosteroids and mycophenolate mofetil for immunosuppression. This was a multicentre, open label, prospective, randomised study. 60 MR4 and 59 Prograf subjects were included in the full analysis.

Biopsy proven acute rejection rates over 6 weeks were comparable in MR4 (13.3%) and Prograf (15.3%) groups. Kaplan-Meier estimates for freedom from acute rejection were also comparable. Renal function measures were comparable for MR4 and Prograf during the 6 week study. There were no deaths and a graft survival rates were 96.9% for MR4 and 93.3% for Prograf groups.

Study FG-506E-11-1 was conducted in patients undergoing primary liver transplantation to compare acute rejection rates with MR4 or Prograf-based immunosuppressant regimens. This was a multicentre, open label, prospective, randomised study. 67 MR4 and 62 Prograf subjects were included in the full analysis.

Biopsy proven acute rejection rates over 6 weeks were comparable in MR4 (26.9%) and Prograf (27.4%) groups. Kaplan-Meier estimates for freedom from acute rejection were also comparable. Renal function measures were comparable for MR4 and Prograf during the 6 week study. There was a single patient death in each group and graft survival rates were 98.3% versus 93.1% for MR4 and Prograf groups, respectively.

Study 02-0-152 assessed stable liver transplant patients who were converted from a Prograf based regimen to the modified release regimen. 70 stable liver transplant patients received Prograf bd on Days 1-14 and 29-42. Patients received MR4 on a 1:1 (mg:mg) basis once daily on Days 15-28 and 43-56. Other immunosuppressants were maintained at constant doses during the 56 day treatment period. There were 3 instances of liver dysfunction in 2 patients during the MR4 treatment period.

There were other Phase II studies undertaken in liver transplantation (GHBA-157) and heart transplantation ((FG506-05-06) with the immediate release formulation. In a dose finding study in orthotopic heart transplantation tacrolimus (Prograf) was initiated at 0.075 mg/kg/day or 0.15 mg/kg/day. AUC was measured after first oral dose. A higher incidence of rejection was associated with lower AUC values of tacrolimus. The mean AUC of tacrolimus was significantly lower in patients who experienced rejection than in those who remained rejection free (76 versus 168 ng.h/mL, p=0.017).

Efficacy

Three Phase III studies assessed efficacy of MR4 in *de novo* renal or liver transplantation, supported by efficacy analyses in Phase II studies of *de novo* renal or liver transplantation. Six phase II studies were submitted to support efficacy in conversion from Prograf capsules twice daily to tacrolimus modified release once daily in adult allograft recipients.

Study 02-0-158 is a Phase III, randomised, open-label, comparative study to evaluate Prograf-based immunosuppression and MR4 based immunosuppression compared to cyclosporin based immunosuppression in *de novo* kidney transplant patients. All regimens included MMF, corticosteroids and basiliximab induction. Prograf was initially administered at a dose of 0.075 to 0.1 mg/kg twice daily, MR4 was initially administered at 0.15 to 0.2 mg/kg once daily and cyclosporin was administered at 4 to 5 mg/kg twice daily. Doses were adjusted based on clinical evidence of efficacy, adverse effects and blood concentrations. Dosing regimens were reflective of standard of care in USA. Enrolled patients were recipients of cadaveric or non-HLA identical living kidney transplants, aged $\geq$ 12 years and received the first dose of study drug within 48 hours of transplantation procedure.

The primary efficacy endpoint was 1 year efficacy failure rate, defined as any patient who died, experienced graft failure (permanent return to dialysis or re-transplant), had biopsy confirmed acute rejection Banff Grade $\geq$ 1, or was lost to follow-up. Secondary efficacy objectives included 1 year patient and graft survival rates, incidence of biopsy confirmed acute rejection, anti-lymphocyte antibody therapy for acute rejection, clinically treated acute rejection episodes, time to first acute rejection episode, severity of acute rejection, number of patients experiencing multiple rejection episodes, treatment failure, cross-over for treatment failure , and renal function.

In the full analysis population, the primary endpoint (1 year efficacy failure) was reported in 15.1% of Prograf, 14% of MR4 and 17% of Neoral groups. The confidence intervals of difference for primary endpoint between both tacrolimus groups and the cyclosporin group was with a non-inferiority criterion of -10%. Efficacy failure results were similar when adjusted by donor type

(living or deceased) and in Per Protocol analysis. BCAR was locally assessed and BCAR had a lower incidence in the Prograf group than MR4 or Neoral groups whereas death and graft failure incidences were higher in the Prograf group than other groups. A central blinded assessment of BCAR was associated with efficacy failure rates of 12.3% in Prograf, 7.7% in MR4 and 10.8% in Neoral groups. Confidence intervals of the difference for both tacrolimus groups from Neoral were within non-inferiority criteria in this analysis.

The incidence of patient survival at one year was 93.9%, 97.2% and 97.2 % for Prograf, MR4 and Neoral groups with confidence intervals of differences within non-inferiority criteria. The incidence of graft survival at one year was 91.5%, 95.3% and 95.3% for respective groups with confidence intervals of differences again within non-inferiority criteria.

The incidence of BCAR (locally assessed) at 6 months and 1 year was statistically significantly lower in the Prograf group than the Neoral group, and with the incidence of BCAR in the MR4 group twice than in the Prograf group. BCAR at 12 months when centrally assessed was reported in 4%, 4.8% and 7% for Prograf, MR4 and Neoral groups with both tacrolimus groups demonstrated to be non-inferior to cyclosporin group.

Clinically treated acute rejections and use of anti-lymphocyte antibody had lower incidences in the Prograf group than in the Neoral group. The MR4 group also had a lower use of anti-lymphocyte antibody than the Neoral group.

The incidence of treatment failure (discontinuation of randomised therapy) was lower in Prograf and MR4 groups than in the Neoral group, with incidences of 15.6%, 14.5% and 28.8% groups respectively. Crossover due to treatment failure also had a lower incidence in Prograf and MR4 groups compared to Neoral (2.8%, 4.7% and 18.4%). Mean creatinine values were lower in the Prograf group at 6 months and in the MR4 group at 12 months compared to the Neoral group.

Subgroup analysis suggested that black subjects had higher 1 year efficacy failure rates than white subjects for each of the treatment groups, but that black subjects who received Prograf or MR4 had numerically lower 1 years efficacy failure rates than black subjects who received Neoral.

1 year efficacy failure rates were lower for living donor organs than from deceased donors across all treatment groups. Subjects from Brazil had numerically higher 1 year efficacy failure rates than subjects from US/Canada, although with relatively small numbers of Brazilian subjects.

Study FG-506E-11-03 is a randomised, double blind, study to evaluate MR4 compared with Prograf, in combination with corticosteroids, in patients undergoing primary liver transplantation. During the first 24 weeks a double blind, double dummy design was maintained. After 24 weeks the study was unblinded and continued as an open extension. Initial tacrolimus dose was 0.2 mg/kg per day given as a single dose (MR4) or 0.1 mg/kg per day given as two doses (Prograf).

The primary efficacy variable was the rate of biopsy proven acute rejection within the first 24 weeks following transplantation, analysed by Kaplan-Meier methods in the Per Protocol data set. Treatment groups were well balanced with regard to demographics and baseline disease characteristics. Donor/recipient characteristics were reasonably matched in treatment groups except for recipient negative/donor positive CMV status, which was more frequent in the MR4 group (17.4% versus 12.4%).

The rate of local biopsy confirmed acute rejection in the first 24 weeks in PP set was 36.3% (MR4) and 33.7% (Prograf) with a difference of 2.6% (95% CI for difference: -7.3, 12.4). The confidence intervals were within the predefined non-inferiority margin of -15%. Results for the Full Analysis set were similar. The 12 month results (PP set) were 35.4% (Prograf) and 37.9% (MR4) with a difference of 2.5% (95% CI: -7.4, 12.5). Results for the primary efficacy endpoint were consistent with results for central biopsy reviewed acute rejection which reported event rates of 31.6% (Prograf) and 34.1% (MR4) with a difference of 2.5% (95% CI: -7.2, 12.3) in first 24 weeks in PP

set. The frequencies of biopsy confirmed corticosteroid resistant acute rejection were similar in treatment groups. 12 month patient survival rates in the FAS were 89.2% (MR4) and 90.8% (Prograf). 12 month graft survival rates in FAS were 85.3% (MR4) and 85.6% (Prograf). Efficacy failure at 12 months in the PP set was reported in 37.6% (Prograf) and 38.5% (MR4) with a difference of 0.8% (95% CI: -9.2, 10.8). In the FAS efficacy failure at 12 months was reported in 45.3% (Prograf) and 43.9% (MR4). The majority of efficacy failure was due to local biopsy confirmed acute rejection. In the FAS the frequency of graft loss and death was comparable between treatment groups.

FG-506E-12-03 is a randomised, double blind, parallel group study to evaluate modified release tacrolimus (MR4) and Prograf, in combination with MMF and steroids, in patients undergoing kidney transplantation. Patients were aged between 18-65 years with end stage kidney disease who were suitable for transplantation or re-transplantation.

The primary efficacy variable was the rate of biopsy proven acute rejection within the first 24 weeks following transplantation, analysed by Kaplan-Meier methods in the Per Protocol data set. Non-inferiority margin was 10% in this study. Treatment groups were well balanced with regard to demographic and baseline disease characteristics. Donor/recipient characteristics were reasonably matched in treatment groups except for HLA DR mismatch which was significantly higher in the MR4 group and recipient negative/donor positive CMV status, which was numerically higher in the MR4 group.

For the primary efficacy endpoint local biopsy proven acute rejection at Week 24 in the PP set the difference between MR4 and Prograf groups was 4.5% (95% CI: 1.8, 10.9).The upper confidence interval was just outside the criterion for non-inferiority. In the FAS the treatment difference was 3.8% (95% CI: -2.1, 9.6). Local biopsy confirmed acute rejection rates at 12 months showed similar differences between treatment groups. When biopsies were centrally reviewed the event rate for acute rejection at 24 weeks in the PP set was 17.5% (Prograf) and 25.4% (MR4) with a treatment difference of 7.9% (95% CI: 1.2, 14.6). Non-inferiority criteria in this analysis were not met.

An additional analysis was performed to adjust for HLA DR mismatch imbalance. The treatment difference was 1.9% (95% CI: -4.4, 8.3) after adjustment in the Per Protocol set and the treatment difference was 2.4% (95% CI: -3.5, 8.4) in the FAS. However, the actual incidence of acute rejection following the new analysis was not provided.

Patient survival rates were comparable in treatment groups. At 12 months in the PP set survival rates were 98.9% (MR4) and 98.8% (Prograf). At 12 months in the FAS survival rates were 97.5% (Prograf) and 96.9% (MR4). Graft survival rates were comparable in treatments groups. At 12 months in the PP set graft survival rates were 97.6% (Prograf) and 96.8% (MR4) and in the FAS graft survival rates were 92.8% (Prograf) and 91.5% (MR4). At 12 months the difference between treatment groups in efficacy failure was 3.3% (95% CI: -3.4, 10) in the PP set and 4.7% (95% CI: -2, 11.3) in the FAS.

Efficacy conclusions by the evaluator were as follows:

- Efficacy data from Phase III, pivotal study 02-0-158 demonstrated evidence for efficacy of MR4-based immunosuppression for prophylaxis in 668 patients undergoing de novo kidney transplantation. Both Prograf and MR4 used in combination with MMF were non-inferior to Neoral/MMF treatment in terms of the composite endpoint of efficacy failure rate (15.1%, 14% and 17% in Prograf, MR4 and Neoral groups, respectively).
- Supportive evidence was provided by two Phase III non-inferiority (MR4 versus Prograf) studies (FG506E-11-03 and FG506E-12-03) and two Phase II studies (FG-506E-12-01 and FG-506E-11-01) in patients undergoing primary renal and liver transplantation.

- Furthermore, pharmacokinetic and patient/graft survival data from six Phase II studies in which patients were converted from Prograf to MR4 support that the same total daily dose, target trough concentrations, therapeutic monitoring and maintenance strategies currently used for Prograf can be used for MR4.
- There is no evidence that daily dosing recommendations for MR4 in kidney and liver transplant recipients would differ from those for Prograf based on age, race, sex, presence of diabetes at baseline or donor type

Safety

Safety of prolonged release tacrolimus was assessed in 4 main studies, the pivotal Phase III study 02-0-158, two phase II 6 week studies (FG-506E-12-01 & FG-506E-11-01 and a 1 year interim safety analysis (FG506-14-02).

In Study 02-0-158, the incidence of diarrhoea, tremor, peripheral oedema and alopecia was significantly higher in both tacrolimus groups than the cyclosporin group. The incidence of hydronephrosis, toxic nephropathy and hirsutism was significantly higher in the cyclosporin group. Compared with Prograf, gastroenteritis, lower abdominal pain and paraesthesia were more common in the MR4 group.

Three deaths occurred in the MR4 group, 10 deaths in the Prograf group and 6 deaths in the Neoral group. The majority of deaths were attributed to cardiac/vascular disorders or infections. The incidence of treatment emergent SAEs was 45.3% in the MR4 group compared to 51.4% in Prograf group and 51.9% in Neoral group. The incidence of treatment emergent AEs leading to discontinuation was 10.8% in the Prograf/MMF group, 8.9% in the MR4/MMF group and 17.5% in the Neoral/MMF group. The most frequent treatment emergent AEs leading to discontinuation were toxic nephropathy, gingival hyperplasia, drug toxicity and graft dysfunction. Of other significant AE, a composite glucose intolerance endpoint was not significantly different between treatment groups, although HbA1c >6% and oral hypoglycaemic use were greater in tacrolimus groups compared with cyclosporin.

In study FG-506E-12-01 in kidney transplant patients through 6 weeks, there were no significant differences in incidence of AEs between MR4 and Prograf. There were no deaths and no difference in SAE incidence between treatment groups.

In study FG-506E-11-01 in liver transplant patients through 6 weeks, there were no marked differences between treatment in incidences of AEs except ascites and infections which were more frequent in the MR4 group. One death considered possibly related to Prograf was reported (pneumonia on Day 19). Incidence of SAEs was 47.8% in the MR4 group and 35.5% in the Prograf group, with bile duct stenosis and respiratory failure numerically higher in the MR4 group.

Study FG-506-14-02 is an ongoing study. A 1 year interim analysis of 240 patients who had received MR4 in extension after phase II pharmacokinetic studies was submitted. MR4 dose and mean tacrolimus trough levels decreased over time in patients enrolled from *de novo* studies.

The incidence of AEs decreased with time. Fewer AEs reported in conversion studies than the *de novo* studies. The AE profile was not unexpected for the patient population. The frequency and types of SAEs and adverse events leading to discontinuation are consistent with the known safety profile of tacrolimus.

A summary of safety was presented by the evaluator as follows:

- Safety was evaluated in a total of 341 patients undergoing de novo kidney and liver transplantation who received MR4-based immunosuppression for 12 months. A further 348 patients (including 19 paediatric patients) were converted from Prograf-based immunosuppression to MR4-based immunosuppression (kidney, liver and heart

transplantation) in shorter duration studies (6 to 12 weeks); 242 healthy volunteers received MR4 during Phase I studies.

- Safety results from the pivotal Phase III study (02-0-158) in kidney transplant patients showed that gastrointestinal AEs were most commonly associated with MR4 treatment. The incidence and safety profile of MR4 was generally similar to that of Prograf, although the incidence of gastroenteritis, lower abdominal pain and paraesthesia was significantly ($p<0.05$) higher in the MR4 group (compared with Prograf). Overall, the most common AEs in both tacrolimus groups (Prograf and MR4) were diarrhoea, infections, tremor, oedema and hyperglycaemia (associated with increased use of oral hypoglycaemics).
- Summary of other Phase III non-inferiority studies between Prograf and Prograf XL showed similar results in primary kidney (FG-506E-12-03) and liver (FG506E-11-03) transplant patients. Supportive 6-week, Phase II studies in kidney (506E-12-01) and liver (506-11-01) transplant patients showed similar safety profile for both tacrolimus formulations. The six Phase II pharmacokinetic conversion studies showed that the safety profile of tacrolimus was generally similar following conversion from Prograf to Prograf XL; however, the duration of these conversion studies was only 6 to 12 weeks.
- Long term safety was evaluated in the ongoing, open-label study (FG 506-14-02) involving 240 patients followed up for 1 year. The incidence of new onset adverse events associated with Prograf treatment appears to decrease over time, with the majority of adverse events occurring in the first months post-transplantation. The prevalence of malignancies cumulatively increases over time, which is not unexpected when patients are exposed to long-term immunosuppressive therapy; however, the incidence of malignancies following administration of Prograf appears to be consistent with that seen in transplant registry reports. The incidence of AEs decreased with time after transplantation. Fewer AEs were reported for former conversion study patients compared with those from de novo studies, which was expected as the patients from the conversion studies were clinically stable and at least 6 months post-transplant at the time of entering the study. The most common AEs were anaemia, diarrhoea, ascites, abdominal pain, tremor, headache, hyperglycaemia and infections and were expected AEs in this patient population

Risk-Benefit Analysis

Conversion studies in three different indications, kidney, liver and heart transplantation, have shown that conversion from Prograf to MR4 at the same daily dose resulted in equivalent systemic exposure to tacrolimus. The efficacy profile was maintained and no new safety concerns were identified. However, across all conversion studies, systemic exposure to tacrolimus following MR4 was 5 to 11% lower than that following administration of Prograf and this was more evident (up to 30% lower) in the initial few days. Monitoring of tacrolimus whole blood concentrations is essential.

Comparative *de novo* studies performed in kidney and liver transplant recipients have demonstrated low incidences of acute rejection episodes for MR4 and Prograf, and have shown a comparable safety profile. Systemic exposure to tacrolimus following MR4 was again lower than following administration of Prograf in the initial few days (on Day 1 30% lower in kidney transplantation and 50% lower in liver transplantation). In the pivotal study (02-0-158) in *de novo* kidney transplantation there was a higher rate of BCAR for MR4 (22 cases) compared to Prograf (16 cases). In the supportive study (FG-506E-12-03) in *de novo* kidney transplantation the non-inferiority criterion was not met for BCAR at week 24 and at 1 year, although HLA DR mismatch potentially contributed to these results. Although the efficacy endpoint of efficacy failure at 12 months is preferred to BCAR, there is some evidence of lower acute rejection rates with Prograf than MR4 in de novo kidney transplantation.

The Delegate agreed with the evaluator's conclusion on safety that across all studies, the safety profile of MR4 was comparable to that of Prograf.

The evaluator concluded that the overall benefit risk assessment for MR4 appears to be positive, and Prograf can be substituted with MR4 in each of the claimed indications: (1) Prophylaxis of transplant rejection (primary immunosuppression and maintenance therapy) in adult kidney or liver allograft recipients, (2) Conversion from Prograf capsules taken twice daily to Prograf MR prolonged-release capsules taken once daily in adult allograft recipients and (3) Treatment of allograft rejection resistant to treatment with other immunosuppressive drugs in adult patients.

The Delegate concurred with this conclusion.

The Delegate proposed to register modified release tacrolimus capsules, Prograf-XL, in 0.5 mg, 1 mg, and 5 mg strengths. PROGRAF and Prograf-XL are indicated for use as an adjunct to liver, kidney, heart and lung allograft transplantation in adults and children. Allograft transplant patients converted from Prograf (twice daily) to Prograf-XL (once daily) should be converted on a 1:1 (mg:mg) total daily dose basis. When initiated de novo after organ transplantation Prograf-XL is administered once daily with a starting dose varying for the particular allograft between 0.075 to 0.3 mg/kg/day in adults and 0.15 to 0.3 mg/kg/day in children.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal. ACPM recommended approval for the indication:

Adjunct to liver, kidney, heart or lung allograft transplantation in adults and children

In making this recommendation, the ACPM was satisfied on clinical grounds regarding the new dose form of tacrolimus. The Committee agreed with the Delegate and clinical evaluator that efficacy profile was maintained and no new safety concerns were identified. The Committee noted that a recent application in the USA had been withdrawn after the sponsoring company considered the clinical challenges in performing additional studies necessary to meet FDA expectations to support approval. The Committee considered the data package submitted in Australia to be acceptable.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Prograf-XL capsules containing tacrolimus 0.5 mg, 1 mg and 5 mg for the indication:

as an adjunct to liver, kidney, lung or heart allograft transplantation in adults and children.

Attachment 1. Product Information

PROGRAF®

0.5 mg, 1 mg, 5 mg Capsules &
5 mg/mL Concentrated Injection

*PROGRAF® XL

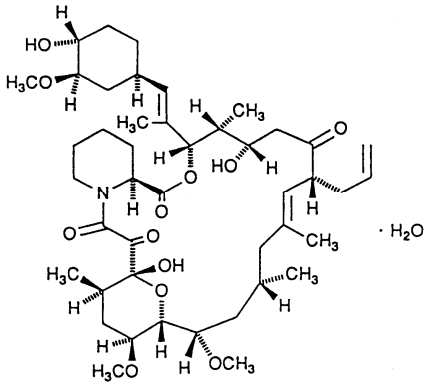
0.5 mg, 1 mg, 5 mg Prolonged-Release Capsules

PRODUCT INFORMATION

NAME OF THE DRUG

Tacrolimus

[3S-[3R[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a*-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy- 3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido [2,1-c] [1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.



Molecular Formula: $C_{44}H_{69}NO_{12}.H_20$
Molecular Weight: 822.03. CAS 104987-11-3

DESCRIPTION

Tacrolimus appears as white crystals or a crystalline powder, very soluble in methanol, and chloroform, freely soluble in acetone and ethanol and practically insoluble in hexane and water. Tacrolimus is obtained by fermentation as a single enantiomer but exists in tautomeric equilibration in aqueous solution.

PHARMACOLOGY

Tacrolimus is a macrolide lactone with potent *in vitro* and *in vivo* immunosuppressive activity. Studies suggest that tacrolimus inhibits the formation of cytotoxic lymphocytes which are

regarded as being primarily responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell-dependent B-cell proliferation, as well as the formation of lymphokines such as interleukins-2 and -3 and gamma-interferon and the expression of the interleukin-2 receptor. At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP), which is responsible for the intracellular accumulation of the compound. A complex of tacrolimus-FKBP-12, calcium, calmodulin and calcineurin is formed and the phosphatase activity of calcineurin inhibited.

Studies in animals and man have shown that PROGRAF is able to prevent and treat graft rejection following transplantation of the liver, kidney, and other solid organs.

PHARMACOKINETICS

Absorption

In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Available tacrolimus is generally rapidly absorbed.
Following oral administration of PROGRAF capsules peak concentrations (C_{max}) of tacrolimus in blood are achieved in approximately 1 - 3 hours. **PROGRAF-XL is a prolonged-release formulation of tacrolimus resulting in an extended oral absorption profile with an average time to C_{max} of approximately 2 hours.* In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile. The mean oral bioavailability of PROGRAF is in the range of 20% - 25%.
After oral administration (0.30 mg/kg/day) to liver transplant patients, steady-state concentrations of PROGRAF were achieved within 3 days in the majority of patients.
In healthy subjects, PROGRAF 0.5 mg, PROGRAF 1 mg and PROGRAF 5 mg capsules have been shown to be bioequivalent, when administered as equivalent dose.
The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases both the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.
In stable liver transplant patients, the oral bioavailability of PROGRAF was reduced when it was administered after a meal of moderate fat (34% of calories) content. Decreases in AUC (27%) and C_{max} (50%), and an increase in t_{max} (173%) in whole blood were evident.
In a study of stable renal transplant patients who were administered PROGRAF immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12%) and C_{max} (15 to 38%), and an increase in t_{max} (38 to 80%) in whole blood were evident.
Bile flow does not influence the absorption of PROGRAF.
A strong correlation exists between AUC and whole blood trough levels at steady-state for PROGRAF and PROGRAF-XL. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

Distribution and elimination

In man, the disposition of tacrolimus after intravenous infusion may be described as biphasic.
In the systemic circulation, tacrolimus binds strongly to erythrocytes resulting in an approximate 20:1 distribution ratio of whole blood/plasma concentrations. In plasma, tacrolimus is highly bound (> 98.8%) to plasma proteins, mainly to serum albumin and α-1-acid glycoprotein.
Tacrolimus is extensively distributed in the body. The steady-state volume of distribution based on plasma concentrations is approximately 1300 l (healthy subjects). Corresponding data based on whole blood averaged 47.6 l.
Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. Paediatric liver transplant recipients have a TBC approximately twice that of

adult liver transplant patients. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of tacrolimus, or corticosteroid-induced increased metabolism are considered to be responsible for the higher clearance rates observed following transplantation.
The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood is approximately 43 hours. In adult and paediatric liver transplant patients, it averaged 11.7 hours and 12.4 hours, respectively, compared with 15.6 hours in adult kidney transplant recipients. Increased clearance rates contribute to the shorter half-life observed in transplant recipients.

Metabolism and biotransformation

Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4. Tacrolimus is also considerably metabolised in the intestinal wall. There are several metabolites identified. Only one of these has been shown *in vitro* to have immunosuppressive activity similar to that of tacrolimus. The other metabolites have only weak or no immunosuppressive activity. In systemic circulation only one of the inactive metabolites is present at low concentrations. Therefore, metabolites do not contribute to pharmacological activity of tacrolimus.

Excretion

Following intravenous and oral administration of ^{14}C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2% of the radioactivity was eliminated in the urine. Less than 1% of unchanged tacrolimus was detected in the urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

Pharmacokinetics in special populations

The pharmacokinetics of tacrolimus in special populations have not been studied in detail. See DOSAGE AND ADMINISTRATION for dose adjustments in special populations.

**CLINICAL TRIALS*

PROGRAF

Liver

The efficacy and safety of a PROGRAF based immunosuppressive regimen following orthotopic liver transplantation was assessed in two prospective, randomised, non-blinded multicentre trials. The active control groups were treated with a cyclosporin based regimen. In a European trial, patients received a tacrolimus-steroid based regimen (n=264) or a cyclosporin-azathioprine-steroid (with or without anti-lymphocyte globulin) based regimen (n=265).

Equivalent graft survival (77.5 vs 72.69%) and patient survival (82.9 vs 77.5%) was seen. Significant reductions were seen in the tacrolimus treated patients for incidence of acute rejection (40.5 vs 49.8%), refractory acute rejection (0.8 vs 5.3%) and chronic rejection (1.5 vs 5.3%). In American trial patients received a tacrolimus-steroid regimen (n=263) or a cyclosporin (mainly triple therapy) based regimen (n=266). Equivalent graft survival (82 vs 79%) and patient survival (88 vs 88%) rates were observed. Tacrolimus was associated with significant reductions in the incidence of acute rejection (68 vs 76%), steroid resistant rejection (19 vs 36%) and refractory rejection (3 vs 15%).

Kidney

Two randomised, multicentre non-blinded comparative trials were performed in cadaveric kidney transplantation. In an American trial patients received a tacrolimus based (n=205) or cyclosporin based (n=207) regimen. All patients also received maintenance azathioprine and corticosteroids and an induction course of an antilymphocyte antibody preparation. Equivalent graft survival (91.2 vs 87.9%) and patient survival (95.6 vs 96.6%) was seen for the tacrolimus and cyclosporin treated patients respectively. A significantly reduced one year incidence rate of biopsy confirmed acute rejection (30.7 vs 46.4%), moderate to severe acute rejection (10.7 vs 26.6%) and use of antilymphocyte antibody preparation for treatment of rejection (10.7 vs 25.1%) was seen in the tacrolimus treated patients.

A European trial compared triple drug based immunosuppression with tacrolimus or cyclosporin centred regimens, with 303 and 145 patients randomised to the tacrolimus and cyclosporin arms respectively. Equivalent one year graft survival (82.5 vs 86.2%) and one year patient survival (93.0 vs 96.5%) rates were observed, but with significantly reduced one year acute rejection rate (32.3 vs 54.5%), rate of corticosteroid sensitive rejections (24.4 vs 42.1%) and rate of corticosteroid resistant rejections (10.2 vs 20.7%).

Heart

Two open-label, randomized, comparative studies evaluated the safety and efficacy of tacrolimus-based and cyclosporin-based immunosuppression in primary orthotopic heart transplantation. In a Phase 3 study conducted in Europe, 314 patients received a regimen of antibody induction, corticosteroids and azathioprine in combination with tacrolimus or cyclosporin modified for 18 months. In a 3-arm study conducted in the US, 331 patients received corticosteroids and tacrolimus plus sirolimus, tacrolimus plus mycophenolate mofetil (MMF) or cyclosporin modified plus MMF for 1 year.

In the European Phase 3 study, patient / graft survival at 18 months post-transplant was similar between treatment arms, 91.7% in the tacrolimus group and 89.2% in the cyclosporin group. In the US study, patient and graft survival at 12 months was similar with 93.5% survival in the tacrolimus plus MMF group and 86.1% survival in the cyclosporin modified plus MMF group. In the European study, the cyclosporin trough concentrations were above the pre-defined target range (ie 100-200 ng/mL) at Day 122 and beyond in 32-68% of the patients in the cyclosporin treatment arm, whereas the tacrolimus tough concentrations were within the pre-defined target range (ie. 5-15 ng/mL) in 74-86% of the patients in the tacrolimus treatment arm.

The US study contained a third arm of a combination regimen of sirolimus, 2mg per day, and full-dose tacrolimus; however, this regimen was associated with increased risk of wound healing complications, renal function impairment, and insulin dependent post transplant diabetes mellitus, and is not recommended in *de novo* heart transplant patients (see PRECAUTIONS).

Lung

In a prospective, 2-centre, open-label randomized trial, 74 lung transplant patients (aged 20-66 years old) were randomised to tacrolimus-based (n=37) and cyclosporin-based (n=37) immunosuppression. The drugs were given in combination with mycophenolate mofetil and corticosteroids. Tacrolimus was started immediately after transplantation as continuous intravenous infusion at a dose of 0.015mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/mL in the first month and 9 to 12 ng/mL thereafter. The 6-months and 1-year patient survival data was similar in both groups (89% vs 84% and 82% vs 71%, cyclosporin vs tacrolimus respectively). Freedom from acute rejection was comparable at 1 year, 35% in the cyclosporin group and 46% in the tacrolimus group.

Another prospective, randomised, open-label study included 66 patients on tacrolimus versus 67 patients on cyclosporin, aged 20 to 66 years old. The drugs were given in combination with azathioprine and corticosteroids. Tacrolimus was started 6 to 8 hours after transplantation as continuous intravenous infusion at a dose of 0.025 mg/kg/day and oral tacrolimus was administered at a dose of 0.15 mg/kg/day with subsequent dose adjustments to target trough levels of 10 to 20 ng/mL. The 1-year patient survival was 83% in the tacrolimus group and 71% in the cyclosporin group, the 2-year survival rates were 76% and 66%, respectively. The differences between groups were not statistically significant. Freedom from acute rejection after at least 37 weeks follow-up was also comparable (14% in the tacrolimus group and 11.5% in the cyclosporin group).

A number of published, open, uncontrolled studies have examined the use of tacrolimus in lung transplant patients who have developed refractory acute rejection or bronchiolitis obliterans syndrome while receiving cyclosporin-based immunosuppressive regimens. In these studies, conversion from cyclosporin to tacrolimus has been associated with improved clinical outcomes such as reduced frequency of further acute rejection episodes and stabilisation or improvement in declining FEV_1 values.

PROGRAF XL

Three Phase III non-inferiority studies have been conducted, confirming the safety and efficacy of PROGRAF XL is comparable to PROGRAF in de novo kidney transplant patients aged 12 years and older (n=638 and 667) and de novo liver transplant patients aged 18 years and older (n=471). Patient survival and graft survival at 1 year post transplant ranged from 91% to 99%. In these studies tacrolimus was used in combination with corticosteroids (liver transplant), with corticosteroids and mycophenolate mofetil (kidney), or with corticosteroids, mycophenolate mofetil and basiliximab (kidney).

The results of all conversion studies demonstrate that conversion from PROGRAF-based immunosuppression regimens to PROGRAF XL-based immunosuppression regimens on 1:1 (mg:mg) basis has been performed in adult kidney, liver and heart transplant recipients without any increase in incidences of acute rejection, graft loss or effects on patient survival rates. Long-term following up of patients in the conversion studies (up to 2 years) confirm patient survival and graft survival with PROGRAF XL were consistent across all conversion studies, ranging from 97% to 100%.

INDICATIONS

Indicated for use as an adjunct to liver, kidney, lung or heart allograft transplantation in adults and children.

CONTRAINDICATIONS

Tacrolimus is contra-indicated in patients hypersensitive to tacrolimus or other macrolides, or to other ingredients of the capsules.

PROGRAF Concentrated Injection should not be used in patients known to be hypersensitive to polyoxyethylene hydrogenated castor oils.

*PRECAUTIONS

Tacrolimus therapy requires careful monitoring in hospital units equipped and staffed with adequate laboratory and supportive medical resources. The drug should only be prescribed, and changes in immunosuppressive therapy should be initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients. The physician

responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Post Transplant Diabetes Mellitus (PTDM)
Post transplant insulin dependent diabetes mellitus (PTDM - use of insulin for 30 or more consecutive days, with < 5 day gap, by patients without a prior history of insulin or non insulin-dependent diabetes mellitus) was reported in 20% (30/151) and 6% (17/281) of PROGRAF treated kidney transplant patients in the U.S. and European randomised trials respectively. The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these patients at one year and in 50% at two years post transplant. Black and Hispanic patients were found to be at increased risk of development of PTDM in the U.S. trial. The risk benefit ratio should be carefully considered before using tacrolimus in kidney transplant patients with a pre-transplant diabetic condition.

In liver transplantation PTDM was reported in 18% (42/239) and 11% (26/239) of PROGRAF treated patients and was reversible in 45% and 31% of these patients at one year post transplant in the U.S. and European randomised trials respectively**.**

Insulin-dependent post-transplant diabetes mellitus was reported in 13% (10/75) and 22% (29/132) of PROGRAF-treated heart transplant patients receiving mycophenolate mofetil or azathioprine and was reversible in 30% and 17% of these patients at one year post transplant, in the US and European randomised studies, respectively.

Neurotoxicity
Neurological and CNS disorders have been reported with PROGRAF therapy. Symptoms include tremor, headache, changes in motor function, sensory function or mental status, insomnia, seizures, coma and delirium. Patients experiencing such events should be carefully monitored. In cases of severe or worsening neurological disorder, adjustment of the immunosuppressive regimen should be considered.

****Posterior reversible encephalopathy syndrome (PRES)***
Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

****Nephrotoxicity***
Tacrolimus can cause renal impairment charactered by increases in serum creatinine as a result of a reduced glomerular filtration rate, particularly when used in high doses. These changes have been observed to be dose dependent and improvement have been associated with reduced dosing. The mechanism leading to these changes is not fully understood. Use of PROGRAF with sirolimus in heart transplantation patients in a US study was associated with increased risk of renal function impairment, and is not recommended. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced.
Care should be taken in using tacrolimus with other nephrotoxic drugs. In particular, tacrolimus should not be used simultaneously with cyclosporin. Tacrolimus or cyclosporin should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated tacrolimus or cyclosporin concentrations, dosing with the other drug usually should be further delayed.

Hyperkalaemia
Mild to severe hyperkalaemia was reported in patients treated with PROGRAF, especially in patients with renal impairment. Patients may require treatment, and should avoid high dietary potassium intake. Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during tacrolimus therapy.

Anaphylaxis with IV Administration
PROGRAF Concentrated Injection contains PEG-60 Hydrogenated Castor oil, which has been reported to cause anaphylactoid reactions. These reactions consist of flushing of the face and upper thorax, acute respiratory distress with dyspnoea and wheezing, blood pressure changes and tachycardia. Caution is therefore necessary in patients who have previously received, by intravenous injection or infusion, preparations containing PEG-60 Hydrogenated Castor Oil and in patients with an allergenic predisposition. Studies in the dog have show that the risk of anaphylaxis may be reduced by slow infusion of PROGRAF or by prior administration of an H_1 antihistamine. PROGRAF or PROGRAF-XL capsules 1mg and 5mg do not contain PEG-60 Hydrogenated Castor Oil.

Malignancies
As with other potent immunosuppressive compounds, patients treated with tacrolimus are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.
Lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. In patients switched to PROGRAF, this may be attributable to over-immunosuppression before commencing therapy with this agent. Very young (<2 years), EBV-sero-negative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV serology should be ascertained before starting treatment with tacrolimus. During treatment, careful monitoring is recommended.

****Infections***
Like other immunosuppressants, tacrolimus predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections. Oversuppression of the immune system can also increase susceptibility to opportunistic infections, sepsis and fatal infections. Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

Hypertension
Hypertension is a common adverse effect of tacrolimus therapy. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating Prograf-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction.

Myocardial Hypertrophy
Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies have been observed in a few cases in association with administration of PROGRAF. Most of these have been reversible, occurring primarily in patients having tacrolimus blood trough levels higher than the recommended level. Mean tacrolimus whole blood trough concentrations during the period prior to diagnosis of myocardial hypertrophy in 20 patients with pre and post treatment echo cardiograms ranged from 10.6 to 53.3 ng/mL in infants (N= 10, age 0.4 to 2 years), 4.0 to 45.7 ng/mL in children (N= 7, age 2 to 15 years) and 10.9 to 24.3 ng/mL in adults (N= 3, age 37 to 45 years). Other factors observed to increase the risk of these clinical conditions are, for example, previously existing heart diseases, corticosteroid usage, hypertension, renal or hepatic dysfunction, and fluid overload. Accordingly, high-risk patients should be monitored, e.g., with echocardiography or ECG. If abnormalities develop, dose

reduction of tacrolimus therapy, or change of treatment to other immunosuppressive agent should be considered.

Conversion between agents

Conversion between tacrolimus formulations

Various formulations of tacrolimus are available. Medication errors have resulted in incorrect dosing or unsupervised switching between tacrolimus formulations. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under exposure or over exposure to tacrolimus. Therefore it is appropriate to prescribe and dispense tacrolimus by tradename, taking care to specify appropriate daily dosing (e.g. PROGRAF - twice daily, PROGRAF-XL – once daily). It should be emphasised that patients, once titrated to an effective dose of a particular formulation of tacrolimus, should not be changed to another formulation of tacrolimus without blood trough level monitoring, clinical assessment and re-titration (see ***DOSAGE AND ADMINISTRATION****).*

Conversion with cyclosporin

Tacrolimus should not be administered concurrently with cyclosporin as the half-life of the latter may be increased. Synergistic/additive nephrotoxic effects can also occur. Care should be taken when administering tacrolimus to patients who have previously received cyclosporin and when converting patients from cyclosporin- to tacrolimus -based therapy. It is recommended that cyclosporin blood levels are monitored prior to the administration of PROGRAF or PROGRAF-XL. The most appropriate time to initiate PROGRAF or PROGRAF-XL therapy should be based upon information on cyclosporin blood levels and the clinical condition of the patient. Dosing may be delayed in the presence of elevated cyclosporin levels. Monitoring of cyclosporin blood levels should be continued following conversion as the clearance of cyclosporin may be affected. A 24 hour interval between stopping cyclosporin and starting PROGRAF or PROGRAF-XL has been commonly used.

Patients switched to PROGRAF or PROGRAF-XL rescue therapy should not be given anti-lymphocyte treatment concomitantly.

Driving / Operation of Machinery

Tacrolimus may cause visual and neurological disturbances. Patients treated with tacrolimus who are affected by such disorders should not drive a car or operate dangerous machinery.

Effects on fertility

Oral treatment of rats with tacrolimus had no effect on male or female fertility at oral doses up to 3.2 mg/kg (blood exposure was less than the exposure achieved after the maximum recommended clinical dose, 0.3 mg/kg, based on AUC).

Use in Pregnancy

Category C

In reproduction studies in rats and rabbits, adverse effects on the fetus were observed mainly at dose levels that were toxic to the dams. Tacrolimus at oral doses of 0.32 mg/kg during organogenesis in rabbits was associated with maternal toxicity as well as an increase in the incidence of abortions. At 1.0 mg/kg increased incidences of malformations and developmental variations were also seen (a dose of 1.0 mg/kg resulted in a blood exposure approximately equivalent to the exposure achieved after the maximum recommended clinical dose, 0.3mg/kg, based on AUC). Tacrolimus, at oral doses of 3.2mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births and decreased pup weight and viability (a dose of 3.2 mg/kg resulted in a blood exposure less than the exposure achieved after the maximum recommended clinical dose, 0.3 mg/kg, based on AUC). Tacrolimus given orally at 1.0 and 3.2 mg/kg to pregnant rats after organogenesis and during lactation was associated with reduced pup weights. No reduction in male or female fertility was evident.

There are no adequate and well-controlled studies in pregnant women. The use of tacrolimus during pregnancy has been associated with neonatal hyperkalaemia and renal dysfunction. Tacrolimus should be used during pregnancy only if the potential benefit to the mother justifies potential risk to the fetus.

Use in Lactation
Tacrolimus is excreted into breast milk. It is therefore recommended that mothers should not breast-feed while receiving tacrolimus.

Carcinogenicity
Tacrolimus did not show any tumourigenic effects in long term carcinogenicity studies using the mouse and rat. The maximum dose tested in the rat resulted in a blood exposure less than, and a plasma exposure 1.4 times the exposure achieved after the maximum recommended clinical dose, 0.3 mg/kg, based on AUC. In mice the maximum dose was 0.8 times the recommended clinical dose based on body surface area.
Patients receiving long-term immunosuppressive therapy are at an increased risk of developing lymphomas and other malignancies (see PRECAUTIONS, Malignancies).

Genotoxicity
No evidence of genotoxicity was seen in a series of assays for gene mutations and clastogenicity. Tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes but high concentrations of tacrolimus have been reported to increase the frequency of sister chromatid exchanges in human lymphocytes *in vitro.*

Interactions With Other Medicines

Metabolic Interactions
Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of drugs or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is therefore recommended to monitor tacrolimus blood levels whenever drugs which have the potential to alter CYP3A metabolism are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure.

Inhibitors of Metabolism
Clinically the following substances have been shown to increase tacrolimus blood levels:
Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin or HIV protease inhibitors (e.g. ritonavir). Concomitant use of these drugs may require decreased tacrolimus doses in nearly all patients.
Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, danazol, ethinylestradiol, omeprazole and nefazodone.
In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethindrone, quinidine, tamoxifen, (triacetyl)oleandomycin.
Grapefruit juice has been reported to increase the blood level of tarcrolimus and should therefore be avoided.
Lansoprazol and cyclosporin may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

Inducers of Metabolism
Clinically the following substances have been shown to decrease tacrolimus blood levels:
Strong interactions have been observed with rifampicin, phenytoin or St John's Wort (Hypericum perforatum) which may require increased tacrolimus doses in almost all patients.

Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.
High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels.
Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

Effect of Tacrolimus on the Metabolism of Other Drugs
Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with drugs known to be metabolised by CYP3A4 may affect the metabolism of such drugs.
The half-life of cyclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of cyclosporin and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received cyclosporin.
Tacrolimus have been shown to increase the blood level of phenytoin.
As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures.
Limited knowledge of interactions between tacrolimus and statins is available. Available data suggests that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus.
Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine.

Other potential interactions that may increase systemic exposure of tacrolimus:
- *Prokinetic agents such as metoclopramide and cisapride.*
- *Cimetidine.*
- *Magnesium-aluminum-hydroxide.*

Other Interactions which have led to Clinically Detrimental Effects
Concurrent use of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase these effects (e.g. aminoglycosides, gyrase inhibitors, vancomycin, cotrimoxazole, NSAIDs, ganciclovir or aciclovir).
Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.
As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g. amiloride, triamterene or spironolactone) should be avoided.
Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

Protein Binding Considerations
Tacrolimus is extensively bound to plasma proteins. Possible interactions with other drugs known to have high affinity for plasma proteins should be considered (e.g. NSAIDs, oral anticoagulants or oral antidiabetics).

**ADVERSE EFFECTS*

The adverse drug reaction profile associated with immunosuppressive agents is often difficult to establish owing to the underlying disease and the concurrent use of multiple medications.

**The most commonly reported adverse drug reactions (occurring in > 10% of patients) are tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension and insomnia.*

Many of the adverse drug reactions stated below are reversible and/or respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse drug reactions compared with intravenous use. Adverse drug reactions are listed below in descending order by frequency of occurrence: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000, including isolated reports).

Infections and infestations

As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.
**Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including tacrolimus.*

Neoplasms benign, malignant and unspecified

Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Blood and lymphatic system disorders

common: anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal
uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia
rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia

Immune system disorders

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see PRECAUTIONS).

Endocrine disorders

rare: hirsutism

Metabolism and nutrition disorders

very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia,

metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities
uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Psychiatric disorders

very common: insomnia
common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders
uncommon: psychotic disorder

Nervous system disorders

very common: tremor, headache
common: seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders
uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia
rare: hypertonia
very rare: myasthenia

Eye disorders

common: vision blurred, photophobia, eye disorders
uncommon: cataract
rare: blindness

Ear and labyrinth disorders

common: tinnitus
uncommon: hypoacusis
rare: deafness neurosensory
very rare: hearing impaired

Cardiac disorders

common: ischaemic coronary artery disorders, tachycardia
uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal, QT prolongation, Torsades de pointes.
rare: pericardial effusion
very rare: echocardiogram abnormal

Vascular disorders

very common: hypertension
common: haemorrhage, thrombembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
uncommon: infarction, venous thrombosis deep limb, shock

Respiratory, thoracic and mediastinal disorders

common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations
uncommon: respiratory failures, respiratory tract disorders, asthma
rare: acute respiratory distress syndrome

Gastrointestinal disorders

very common: diarrhoea, nausea
common: gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms
uncommon: ileus paralytic, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastrooesophageal reflux disease, impaired gastric emptying
rare: subileus, pancreatic pseudocyst

Hepatobiliary disorders

very common: liver function test abnormal
common: bile duct disorders, cholestasis and jaundice, hepatocellular damage and hepatitis
rare: hepatitic artery thrombosis, venoocclusive liver disease
very rare: hepatic failure

Skin and subcutaneous disorders

common: pruritus, rash, alopecias, acne, sweating increased
uncommon: dermatitis, photosensitivity
rare: toxic epidermal necrolysis (Lyell's syndrome)
very rare: Stevens Johnson syndrome

Musculoskeletal and connective tissue disorders

common: arthralgia, muscle cramps, pain in limb, back pain
uncommon: joint disorders

Renal and urinary disorders

very common: renal impairment
common: renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms
uncommon: anuria, haemolytic uraemic syndrome
very rare: nephropathy, cystitis haemorrhagic

Reproductive system and breast disorders

uncommon: dysmenorrhoea and uterine bleeding

General disorders and administration site conditions

common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed

uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased
rare: thirst, fall, chest tightness, mobility decreased, ulcer
very rare: fat tissue increased

Injury, poisoning and procedural complications

common: primary graft dysfunction
**Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. A number of associated cases of transplant rejection have been reported (frequency cannot be estimated from available data).*

**DOSAGE AND ADMINISTRATION*

The dosage recommendations given below for oral and intravenous administration should act as a guideline. PROGRAF and PROGRAF-XL doses should be adjusted according to individual patient requirements.
If allograft rejection or adverse events occur, alteration in the immunosuppressive regimen should be considered.

Method of Administration

It is recommended that the oral daily dose of PROGRAF be administered as two divided doses, in the morning and in the evening.

It is recommended that the oral daily dose of PROGRAF-XL be administered once daily in the morning.

PROGRAF and PROGRAF-XL capsules should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximum absorption (see under Pharmacokinetics).

PROGRAF and PROGRAF-XL capsules should be taken immediately following removal from the blister. The capsules should be swallowed with fluid (preferably water).

Oral administration of PROGRAF or PROGRAF-XL should commence as soon as practicable. In some transplantation patients, therapy has commenced orally by administering the PROGRAF capsule contents suspended in water via an intranasal gastric tube.

PROGRAF Concentrated Injection should be diluted in 5% glucose solution in polyethylene or glass bottles or in 0.9% Sodium Chloride Injection solution in polyethylene bottles. The concentration of a solution for final infusion produced in this way should be in the range 0.004 - 0.1 mg/ml. The solution should not be given as a bolus.

Liver Transplantation:

Oral tacrolimus therapy should commence at 0.10-0.20 mg/kg/day administered as two divided doses for PROGRAF or as a total daily dose for PROGRAF-XL. Administration should start approximately 6 hours after the completion of liver transplant surgery. If the clinical condition of the patient does not allow for oral dosing then intravenous tacrolimus therapy should be initiated as a continuous 24 hour infusion, at 0.01 to 0.05 mg/kg/day.

Kidney Transplantation:

Oral tacrolimus therapy should commence at 0.15-0.30 mg/kg/day administered as two divided doses for PROGRAF or as a total daily dose for PROGRAF-XL. Administration should start within 24 hours of kidney transplant surgery. If the clinical condition of the

patient does not allow for oral dosing then intravenous tacrolimus therapy should be initiated as a continuous 24 hour infusion, at 0.04 to 0.06 mg/kg/day.

Lung Transplantation:

Oral tacrolimus therapy should commence at 0.10-0.30 mg/kg/day administered as two divided doses for PROGRAF or as a total daily dose for PROGRAF-XL. Administration should start within 24 hours of lung transplant surgery. If the clinical condition of the patient does not allow for oral dosing then intravenous tacrolimus therapy should be initiated as a continuous 24 hour infusion, at 0.01-0.05 mg/kg/day.

Heart Transplantation:

Oral tacrolimus therapy should commence at 0.075 mg/kg/day administered as two divided doses for PROGRAF or as a total daily dose for PROGRAF-XL. Administration should start within 24 hours of heart transplant surgery. If the clinical condition of the patient does not allow for oral dosing then intravenous tacrolimus therapy should be initiated as a continuous 24 hour infusion, at 0.01-0.02 mg/kg/day.

Further information for all indications follows:

Children

Higher mg/kg doses may be required in children compared with adults to achieve the same tacrolimus blood concentration. It is recommended that the initial intravenous dose if needed should be 0.05-0.06mg/kg/day: initial oral doses should be 0.15-0.30mg/kg/day as two divided doses.

Therapy Dose Levels for Kidney, Liver, Lung or Heart Allograft Rejection Resistant to Existing Immunosuppressive Regimens

In patients experiencing rejection episodes, which are unresponsive to conventional immunosuppressive therapy, PROGRAF and PROGRAF-XL treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.

****Conversion***

Conversion of PROGRAF-Treated Patients to PROGRAF-XL

Allograft transplant patients maintained on twice daily PROGRAF capsules dosing requiring conversion to once daily PROGRAF-XL should be converted on a 1:1 (mg:mg) total daily dose basis. PROGRAF-XL should be administered in the morning. Following conversion, tacrolimus trough levels should be monitored and if necessary dose adjustments made to maintain similar systemic exposure.

In stable patients converted from PROGRAF (twice daily) to PROGRAF-XL (once daily) on a 1:1 (mg:mg) total daily dose basis, the systemic exposure to tacrolimus (AUC_{0-24}) for PROGRAF-XL was approximately 10% lower than that for PROGRAF. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC_{0-24}) for PROGRAF-XL is similar to that of PROGRAF. When converting from PROGRAF capsules to PROGRAF-XL tacrolimus trough levels should be measured prior to conversion and within two weeks after conversion. Dose adjustments should be made to ensure that similar systemic exposure is maintained.

In de novo kidney and liver transplant patients AUC_{0-24} of tacrolimus for PROGRAF-XL on Day 1 was 30% and 50% lower respectively, when compared with that for Prograf at equivalent doses. By Day 4, systemic exposure as measured by trough levels is similar for both kidney and liver transplant patients with both formulations. Careful and frequent monitoring of tacrolimus trough levels is recommended in the first two weeks post-transplant with PROGRAF-XL to ensure adequate drug exposure in the immediate post-transplant period. As tacrolimus is a substance with low clearance, adjustments to the PROGRAF-XL dose regimen may take several days before steady state is achieved.

Conversion from cyclosporin to PROGRAF or PROGRAF-XL

*Care should be taken when converting patients from cyclosporin-based to tacrolimus-based therapy (see **PRECAUTIONS** and **Interactions with Other Drugs**). Tacrolimus-based therapy should be initiated after considering cyclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated cyclosporin blood levels. In practice, tacrolimus-based therapy has been initiated 12-24 hours after discontinuation of cyclosporin. Monitoring of cyclosporin blood levels should be continued following conversion as the clearance of cyclosporin might be affected.*

Conversion between tacrolimus formulations
Differences between oral formulations of tacrolimus can lead to important differences in systemic exposure to tacrolimus. Inadvertent or unsupervised switching between formulations is unsafe and could lead to graft rejection or increased incidence of side effects. Therefore it is appropriate to prescribe and dispense tacrolimus by tradename, taking care to specify appropriate daily dosing (e.g. PROGRAF - twice daily, PROGRAF-XL – once daily). Patients must only be switched from one tacrolimus formulation to another under the close supervision of a transplant specialist.

Dose adjustments in special populations

Elderly
Experience in the elderly is limited. There is no evidence presently available to suggest that doses should be altered in elderly patients.

Patients with Renal Impairment
No dose adjustment is required. However, careful monitoring of renal function is recommended.

Patients with Liver Impairment
Tacrolimus is extensively metabolised by the liver. In patients with liver impairment dose reduction is recommended.

Tacrolimus is normally administered together with other immunosuppressive drugs. In isolated cases, successful maintenance therapy with tacrolimus alone has been described. Tacrolimus should not be given concurrently with cyclosporin.

**Race*
In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

**Gender*
There is no evidence that male and female patients require different doses to achieve similar trough levels.

Monitoring Advice

Monitoring of tacrolimus WHOLE BLOOD trough concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting drugs and the post-transplant time. Blood trough concentration monitoring is not a replacement for renal or liver function monitoring and tissue biopsies.

Various assays have been used to measure blood or plasma concentrations of tacrolimus. Comparison of the concentrations in published literature to patient concentrations should be made with care and knowledge of the assay methods employed.

Trough blood concentrations should be measured at 12 hours after a PROGRAF dose or 24 hours after a PROGRAF-XL dose. The majority of patients (adults and children) can be successfully managed if the trough blood concentrations are maintained within the following range:

- Liver transplant: 5-20 ng/mL for the first 3 month, 5-15 ng/mL thereafter.
- Kidney transplant: 10-20 ng/mL for the first 3 months, 5-15 ng/mL thereafter
- Heart transplant: 10-20 ng/mL for the first 3 months , 5-15 ng/mL thereafter
- Lung transplant: 10-20 ng/mL for the first month, then 5-15 ng/mL thereafter

During the first months post-transplant, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, visual status, blood glucose levels, electrolytes (particularly potassium), creatinine, BUN, urinary output, haematology parameters, coagulation values, and liver and renal function tests. If clinically relevant changes are seen, adjustment of the immunosuppressive regimen should be considered.

Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of PROGRAF and PROGRAF-XL. This should be considered when deciding upon a maintenance regimen.

Compatibility

Tacrolimus is incompatible with PVC plastics. Tubing, syringes, and other equipment used to administer tacrolimus should not contain PVC.

OVERDOSAGE

Experience of overdosage is limited.

Early clinical experience (when initial induction doses were 2 -3 times greater than those currently recommended) suggested that symptoms of overdosage may include glucose intolerance, renal, neurological and cardiac disorders, hyperkalaemia and hypertension. Over immunosuppression may increase risk of severe infections.

Liver function clearly influences all pre- and post-operative pharmacokinetic variables. Patients with failing liver grafts or those switched from other immunosuppressive therapy to PROGRAF should be monitored carefully to avoid overdosage.

No specific antidote to tacrolimus therapy is available. If overdosage occurs, general supportive measures and symptomatic treatment should be conducted.

Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that PROGRAF will not be dialysable. Data on haemoperfusion are not available. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

PRESENTATION

PROGRAF Capsules

PROGRAF capsules 0.5 mg: light yellow hard gelatine capsules with ‘0.5 mg’ and ‘[f]607’ printed in red. Each capsule contains 0.5 mg tacrolimus.

PROGRAF capsules 1 mg: white, hard gelatine capsules with '1 mg' and '[f]617' printed in red. Each capsule contains 1 mg tacrolimus.

PROGRAF capsules 5 mg: greyish-red, hard gelatine capsules with '5 mg' and '[f]657' printed in white. Each capsule contains 5 mg tacrolimus.

PROGRAF capsules also contain hypromellose 2910, cellulose, croscarmellose sodium, lactose and magnesium stearate. The capsule shell contains gelatin, purified water and titanium oxide and a dye (ferric oxide yellow E172 for 0.5 and 1 mg capsules, and ferric oxide red E172 for 5 mg capsules). The capsules have a trace of printing ink (that used in the 0.5 and 1 mg capsules contains shellac, soya lecithin, dimethylpolysiloxane and ferric oxide red E172; that used in the 5 mg capsules has ferric oxide red E172 replaced by titanium dioxide).

PROGRAF capsules are supplied as blister strips each containing 10 capsules packed within a protective aluminium wrapper. The 1 and 5 mg capsules should be stored below 30°C, and the 0.5 mg capsules below 25°C. After opening the aluminium wrapper, PROGRAF capsules are stable for 12 months when stored at room temperature. The blister strips should be kept in a dry place and the capsules should be left in the blister until required for use.

PROGRAF-XL Prolonged-Release Capsules

PROGRAF-XL 0.5 mg prolonged-release capsules: oblong capsules with a light yellow cap imprinted with "0.5 mg" and an orange body imprinted with "647".

PROGRAF-XL 1 mg prolonged-release capsules: oblong capsules with a white cap imprinted with "1 mg" and an orange body imprinted with "677".

PROGRAF-XL 5 mg prolonged-release capsules: oblong capsules with a greyish red cap imprinted with "5 mg" and an orange body imprinted with "687".

PROGRAF-XL prolonged-release capsules contain hypromellose, ethylcellulose, lactose and magnesium stearate. The capsule shells contain gelatin, titanium dioxide, iron oxide yellow CI77492, iron oxide red CI77491 and sodium lauryl sulfate. The capsules also have a trace of printing ink, Opacode S-1-15083 red, which contains shellac, soya lecithin, simethicone and iron oxide red CI77491.

PROGRAF-XL prolonged-release capsules are supplied as blister strips each containing 10 capsules packed within a protective aluminium wrapper. PROGRAF-XL prolonged-release capsules should be stored below 25°C. After opening the aluminium wrapper, PROGRAF-XL prolonged-release capsules are stable for 12 months when stored at room temperature. The blister strips should be kept in a dry place and the capsules should be left in the blister until required for use.

PROGRAF Concentrated Injection

PROGRAF Concentrated Injection 5 mg/mL: colourless, clear, sterile liquid in transparent glass ampoules. Each mL of Concentrated Injection contains 5 mg tacrolimus together with PEG-60 Hydrogenated Castor Oil and Ethanol.

PROGRAF Concentrated Injection should be protected from light and stored below 25°C. Once an ampoule is opened, the contents should be used immediately. Following reconstitution in either 5% w/v glucose solution in polyethylene or glass containers or in 0.9% Sodium Chloride Injection in polyethylene containers, the resulting infusion mixture should be used immediately.

Package Quantities

PROGRAF Capsules 0.5 mg	Cartons of 100 capsules
PROGRAF Capsules 1 mg	Cartons of 100 capsules

PROGRAF Capsules 5 mg	Cartons of 50 capsules
PROGRAF XL Prolonged-Release Capsules 0.5 mg	*Cartons of 30 capsules*
PROGRAF XL Prolonged-Release Capsules 1 mg	*Cartons of 60 capsules*
PROGRAF XL Prolonged-Release Capsules 5 mg	*Cartons of 30 capsules*
PROGRAF Concentrated Injection 5 mg/mL	Cartons of 10 ampoules

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Road, North Ryde, NSW 2113, Australia

Date of TGA Approval: 19 March 2010

*Please note change(s) presented as **italicised text* in Product Information