# SCIENTIFIC DISCUSSION

## 1 Introduction

Transplantation is the most appropriate therapy for several conditions of end-stage organ failure, such as renal, hepatic or cardiac failure. Hepatic and cardiac transplantation are life-saving measures and are undertaken when conservative therapies have failed. The number of liver transplants performed in Europe has increased, reaching plateau of close to 4000 liver transplants performed annually. Renal transplantation rescues patients from the fate of chronic dialysis and improves patient quality of life to near normality. Transplantation has become a very successful procedure with success rates greater than 90% at 1-year post-transplant, regardless of the kind of transplanted organ.
In current clinical practice the oral formulations of available calcineurin inhibitors, cyclosporine and tacrolimus, are generally administered on a twice daily basis. Poor compliance has been shown to be one of the factors associated with late graft loss demonstrated a statistically significant association for adherence to medication regimen with once daily dosing versus twice daily dosing in adult kidney transplant recipients.
Advagraf is a new oral formulation of tacrolimus with prolonged-release characteristics compared to the currently authorised product Prograf(t). Because the later product is nationally authorised, the invented name may vary depending on the country of authorisation. Advagraf is the first calcineurin inhibitor formulated to enable once daily dosing and it is expected that it may help to improve compliance with dosing and cause less interference with the daily life activities of the patient.
The active substance, tacrolimus, belongs to the pharmacological class of calcineurin inhibitors and originally derives from the fungus streptomyces tsukubaensis: it has a macrolide structure.
Tacrolimus has been in use as an immunosuppressant in a variety of organ transplantation settings since 1989; there is extensive existing therapeutic experience with the substance.
The proposed indication for Advagraf is in the (1) prophylaxis of transplant rejection (primary immunosuppression and maintenance therapy) in adult kidney or liver allograft recipients; (2) conversion from Prograf(t) capsules taken twice daily to Advagraf prolonged-release capsules taken once daily in adult allograft recipients; (3) treatment of allograft rejection resistant to treatment with other immunosuppressive drugs in adult patients. The proposed dosage is based on starting dose that depends on type of indication and transplanted organ and followed by therapeutic drug monitoring including measurement of through whole blood concentrations.

## 2 Quality aspects

**Introduction**
Advagraf is presented as prolonged-release hard capsules containing 0.5, 1 or 5 mg tacrolimus as active substance. Tacrolimus has been formulated to achieve once daily dosing with identical capsule strengths to the immediate release Prograf(t) formulation, which requires twice daily dosage.
The 0.5 mg strength is encapsulated in size 5 capsules with orange body and light yellow cap, the 1 mg in size 4 capsules with orange body and white cap and the 5 mg in 0 size capsules with orange body and greyish red cap.

Advagraf prolonged-release capsules are packaged a transparent polyvinyl chloride (PVC)-polyvinylidene chloride (PVDC) /aluminium blister wrapped in an aluminium pouch with a desiccant.
0.5 mg capsules are provided in pack sizes of 30 and 50 capsules, 1 mg capsules are provided in pack sizes of 30, 50, 60 and 100 capsules and 5 mg in pack sizes of 30 and 50 capsules.

**Active Substance**

Tacrolimus is a product of fermentation of Streptomyces tsukubaensis, which is not yet subject of a pharmacopoeial monograph, Ph.Eur. or other national pharmacopoeia. The molecular formula is $C_{44}H_{69}NO_{12} \cdot H_2O$ and the Relative Molecular Mass is 822.
Tacrolimus appears as white crystals or crystalline powder. Tacrolimus contains one water molecule as a water of crystallization, and does not intake or release any water under atmospheric conditions.
Tacrolimus drug substance is practically insoluble in water and in hexane, freely soluble in ethanol and very soluble in methanol. The partition coefficient in *n*-octanol/water system is greater than 1000.

It does not display polymorphism and neither any solvates have been observed. In the solid state tacrolimus exists as one conformer, cis-form.

- Manufacture

Tacrolimus is obtained by fermentation in line with Ph.Eur.'s General Monograph on "Products of Fermentation". Since 1988, three methods have been developed and used, i.e. Process I and Methods I and II, in order to improve productivity. The clinical and stability batches were manufactured by the original manufacturing method, Process I, as well as by the current manufacturing method, method I. Commercial batches have been manufactured by the current method, method I. While Method I was used originally, Method II was introduced in response to the need for larger batch sizes (approx. 15 kg versus 58 kg).
Batch analyses confirmed that and the impurity profiles and physical properties of tacrolimus drug substance produced by Method II are equivalent to those of tacrolimus drug substance manufactured by Method I.
The manufacturing route is divided into two parts: a) Fermentation process and b) Extraction and purification process. There is no intermediate compound involved in the manufacturing process of tacrolimus drug substance.
a) Fermentation process: Apart from the original strain Streptomyces tsukubaensis No. 9993, variant or mutant strains have been also introduced to increase tacrolimus yield in fermentation broth. A spore suspension of the microorganism is prepared and stored in liquid nitrogen. The tacrolimus fermentation broth is produced by a 4-stage scale-up fermentation process. The fermentation process was optimized by modification of medium composition and, modified cultivating conditions and a larger fermentor (Method 2).
b) Extraction and purification: The fermentation broth is extracted and filtered. Tacrolimus is purified by chromatography and crystallized. In method II, the introduction of new adsorbents for chromatography and new devices resulted in higher efficiency of purification and reduced environmental impact. In addition, the polar crystallisation solvent system of Method I is replaced with non-polar solvent system in Method II to increase the efficiency of crystallisation process. However, the final crystallisation solvent system at the final step remains unchanged to obtain drug substance of the same physicochemical properties as that manufactured by Method I. After final crystallisation, tacrolimus is dried and packaged.
The process validation results of both fermentation and purification process for both methods show that each production step is reproducible and well controlled within the pre-determined manufacturing acceptance criteria. The impurity profile of tacrolimus obtained at each purification process was evaluated. The results of analysis demonstrate that the purification can produce highly purified tacrolimus drug substance that meets all the specifications.

- Specification

The specifications for tacrolimus manufactured by Method I and II are identical except for residual solvents. The specification for the control of the drug substance includes tests for appearance, identification (IR, HPLC, colour reaction, optical rotation (USP)), heavy metals (USP), residue on ignition (USP), water (USP), assay (HPLC), related substances (HPLC), bacterial endotoxins (USP), microbial limit test (USP), and residual solvents (GC). The two sets of solvents from the different methods of synthesis (I and II) are assayed under slightly different GC conditions.
Batch results from 14 commercial batches manufactured by Method I (1996-2000) and from three batches manufactured by Method II have been reported. All results for all parameters are well within the set specification. Medicinal products with tacrolimus as drug substance have been on the market worldwide for more than 10 years and more than 230 batches have been produced so far.

- Stability

Stability data on four production and three pilot scale batches manufactured by Method I have been submitted. The production batches were packaged into triple PE bags within an iron drum and were stored at 30°C for 36 months and 40°C/75% RH for 6 months. All results at both storage conditions met the specification during the testing period. No significant change of any test parameter compared with initial value was detected. In addition, the samples of pilot batches (Method I) were stored in an open petri dish at 30°C/75% RH for 3 months and exposed to light (1000 lux) for 50 days, without detecting any significant change of any test parameter.

Stability data for three production batches and three pilot scale batches manufactured by Method II have been submitted. The production batches were packaged into triple PE bags within an iron drum and were stored at 25°C/60% RH (normal conditions) for 36 months and at 40°C/75% RH (accelerated) for 6 months. The pilot batches were stored at normal conditions for 36 months and at accelerated for 6 months. All results at normal conditions over the whole period of 36 months met the specification. Neither new impurities nor new degradation products were observed. After 6 months storage at accelerated conditions no significant change of any test parameter compared with initial values was detected either.
Comparison of the stability data, obtained from tacrolimus manufactured by either Method showed no difference. These results indicate that the stability of the drug substance manufactured by both methods is equivalent and not dependent on the method of manufacture.
Therefore, the proposed re-test period is justified when the bulk drug substance is stored in the proposed packaging material and conditions.

**Medicinal Product**

- Pharmaceutical Development

Advagraf capsules have been developed to provide once a day dosing with similar safety and efficacy profiles to the current twice a day formulation of Prograf(t) capsules. Based on the composition of Prograf(t) capsules, a granule formulation has been developed to prolong the drug release profile of tacrolimus.
Initial investigations led to two possibilities, i.e. the hypromellose system, which modifies the drug release profile by forming a polymer gel layer, and the ethylcellulose diffusion matrix system, which modifies the release profile by controlling water penetration and thus drug release. The objective was to achieve 90% drug release at 6 to 12 hours.
Two formulations that showed the best dissolution characteristics (Prototype 3 and 4) were promoted for further development.
Hypromellose is known to increase oral absorption in the GIT of poorly soluble drugs so it was decided a small amount to be added and investigate its effect on the drug release (Prototype 5). Formulations with hypromellose displayed better overall dissolution characteristics, and therefore, hypromellose became part of the granule formulation.
Five further prototype formulations were investigated with varying ethylscellulose, hypromellose and lactose monohydrate concentrations. Formulations designated MR4 and MR3 respectively were selected for a single-dose biopharmaceutics study (99-0-060), while it had been demonstrated that the release profiles of these two formulations were not affected by the dissolution conditions.
The biopharmaceutics study showed that MR4 exhibits similar AUC and equal or reduced Cmax compared to immediate release Prograf(t) capsules, thus it was selected for further development. Subsequently, the amount of lactose monohydrate and magnesium stearate of the final blend for MR4 prototype capsules was optimized for the three strengths 0.5 mg, 1 mg and 5 mg. The excipient drug substance ratio is identical for all three capsule strengths, and the only differences being the filling amount into the capsule and the capsule size. One batch of each strength was prepared and used in single dose bioequivalence study and dissolution comparisons. The dissolution curves of the three capsule strengths have been shown to be very similar. The same quantitative composition has been used for all clinical batches, stability batches and proposed commercial production batches.
With regard to the drug substance, there were no particle size considerations as it is dissolved in ethanol during the manufacturing process. However, the influence of kneading time and particle size distribution of intermediate granules on the dissolution profile was investigated, and a particle size specification has been established for the intermediate granules. In addition, the influence of drying temperature, thickness of the paste on the drying tray on dissolution characteristics, residual solvent and related substances levels was investigated. Finally, the influence of the rotating speed of the blender and the blending time on content uniformity and dissolution profile was investigated but neither of them was found to affect these parameters.
All excipients are well established and commonly used excipients in the manufacture of solid oral dose forms and are described in pharmacopoeia. The compatibility of the tacrolimus with the excipients has been studied and deemed established.
The final dosage form is an oral capsule, which is formulated to achieve prolonged release in order to allow a once daily dosage.

- Adventitious Agents

Magnesium stearate is of plant origin. Lactose monohydrate and gelatin meet current TSE requirements.

- Manufacture of the Product

The manufacturing process consists of two distinct processes: i) granule manufacture by wet granulation and ii) capsule filling. Tacrolimus is granulated with dehydrated ethanol, ethylcellulose, hypromellose and lactose monohydrate. The resulting paste undergoes drying and sizing to produce intermediate granules. The granules are then mixed with lactose monohydrate and magnesium stearate and that mixture is filled into capsules. Different capsule strengths are achieved by varying fill weight. Capsules are packed into the proposed commercial packs. Reprocessing operations are not employed.

- Product Specification

The specification for Advagraf prolonged release capsules includes tests for appearance of capsules and content (visual), identification of tacrolimus (TLC, HPLC), assay (HPLC), content uniformity (Ph.Eur.), dissolution (Ph.Eur., USP), related substances (HPLC), residual solvents (GC), and microbial limits (USP). Since dissolution is an important control test for a prolonged release product, two separate methods are used and release is measured at two time points in each method.
Data are presented for six commercial batches of all three strengths manufactured at the proposed manufacturing site in 2004 and 2005. The batches utilised different batches of drug substance. All 18 batches comply with set release specifications.
The tests and limits of the specifications Advagraf capsules are appropriate to control the quality of the finished product for the intended purpose.

- Stability of the Product

Stability data are reported for three production scale batches of each capsule strength for 24 months at 25°C/60% RH (normal conditions) and 30°C/60% RH. These are supplemented by data at 40°C/75% RH over 6 months. Further data have been generated at 50°C/3 months, 25°C/80% RH/3 months and exposure to light (D65)/50 days.
The following parameters were tested: appearance, identification, related substances, content uniformity, dissolution, assay, microbial limits, and water and all the results after storage under normal conditions were well within the specifications limits.
Data at 40°C/75% RH showed increased by-product levels after 6 months' exposure. The dissolution pattern followed that exhibited at the normal conditions.
Storage over 3 months at 50°C did increase by-product levels quite considerably, with some variable effects on dissolution. Exposure to light (D65) during 50 days showed no effect.
Matrixing design has been applied as the same powder mix is used for filling all three capsule strengths, The design is in accordance with ICH Guideline "Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products" has been applied for long term, intermediate and accelerated conditions.
Additional results from primary stability studies for one full scale batch of all strengths has been stored at 25°C/60% RH and 30°C/60% RH for up to 3 years and 40°C/75% RH for up to 6 months have been provided. These batches were used in Phase 3 clinical studies.
No significant changes in all test items have been observed up to available storage periods.
Furthermore, stability data after first opening of the aluminium pouch (In-use Stability) have been provided establishing an acceptable in-use stability period as stated in the SPC.
Finally, the stability of intermediate granules has been studied at 25°C/60 % RH, 30°C/60 % RH, 40°C/75 %RH and in addition at 50°C, 25°C/75 % RH (open to the atmosphere) and under light (D65). Data up to 27 months are available. The granules show adequate stability is maintained and the proposed granule stability period is considered established when granules are stored in the proposed packaging material.

In conclusion, based upon the overall stability data presented, the proposed shelf life and storage conditions for the intermediate granules and the finished product as stated in the SPC are acceptable.

**Discussion on chemical, pharmaceutical and biological aspects**

The quality of Advagraf prolonged-release hard capsules is adequately established. In general, sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug substance and drug product has been presented. There are no major deviations from EU and ICH requirements. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

## 3 Non-clinical aspects

### Introduction

No new non-clinical studies were presented in support of this application. The submitted pharmacology, pharmacokinetics and toxicology studies of tacrolimus have been fully established during the development of Prograf/Prograft together with a non-clinical overview based on the expert report that had been submitted during nation registration procedures for Prograf/Prograft in Austria, Belgium, Denmark, France, Ireland, Italy, Netherlands, Norway, Spain, Sweden, Switzerland and the United Kingdom [Expert Report on the Pharmaco-Toxicological Documentation, 1993]. The document has been updated by mainly published information becoming available during the time after submission of national dossiers. Most of studies were conducted according to the GLP standards.

### Pharmacology

- Primary pharmacodynamics

Tacrolimus has been demonstrated to act via several mechanisms of actions with the central mechanism for its immunosuppressive action being the inhibition of the activated serine threonine phosphatase, calcineurin, in T-lymphocytes. In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection. The drug suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines (such as interleukins-2, -3, and γ-interferon) and the expression of the interleukin-2 receptor.
The pharmacodynamics of tacrolimus have been extensively characterised within the literature and various models of organ transplantation as well as being clinically well established and used world wide for the 10 years as an immunosuppressive agent. The new formulation is not expected to alter the pharamacodynamics of tacrolimus.

- Secondary pharmacodynamics and safety pharmacology

Following a request from the Swedish Health Authority a review of the data regarding the effect of tacrolimus on QTc interval was performed. At doses (i.v.) above 0.1 mg/kg, QTc prolongation was consistently observed and based on the results of these studies it appears that tacrolimus does have the ability to affect ventricular repolarisation. The proposed wording of the Summary of product Characteristics (SPC) for section 4.8 (Undesirable effects) is considered to address this point. In addition, the special precautions for use in the SPC advocate ECG monitoring on a routine basis during the initial post-transplant period.

- Pharmacodynamic drug interactions

No new pharmacodynamic drug interaction studies have been submitted. Pharmacodynamic drug interactions with tacrolimus are known and have been documented in the literature. Tacrolimus is extensively metabolised by hepatic and intestinal wall cytochrome P450 (CYP) 3A isoenzymes. Therefore, concomitant use of tacrolimus with drugs metabolized by this enzyme should be taken with caution.

### Pharmacokinetics

No new pharmacokinetic or drug interaction studies have been submitted in relation to the new prolonged release formulation. The applicant submitted existing pharmacokinetic data as well as published literature with respect to Prograf/Prograft in support of the pharmacokinetics of the new Prograft MR4.

- Absorption and Distribution

Based on existing data presented, tacrolimus has been studied using various routes of administration (oral, i.v. and i.m.) in a number of species. Absorption is found to occur throughout the gastro-intestinal tract, in particular in the jejunum and duodenum and is rapid but bioavailability was low and variable. A number of factors are considered to contribute to the low and variable bioavailability including extensive first pass metabolism, p-glycoprotein mediated efflux and the presence of food. Fasting is found to improve absorption and the development of a once daily dosing may improve the absorption profile, reduce the variability and be more convenient for patients.

Distribution studies revealed that tacrolimus is highly protein bound (> 98%) and is strongly partitioned into red blood cells and is extensively distributed throughout the body. The major organs of distribution in the rat were found to be the adrenal gland, lung and heart which showed up to 29 times the plasma concentration. Other organs of distribution included the liver and the kidney as well as the gastro-intestinal tract. These were also observed to be the major organs of distribution in the monkey. Tacrolimus was found to accumulate quickly over the first week with the increase becoming gradual by week three and with steady state being reached by week 4-5.

- Metabolism and Excretion

Elimination was found to be slow from various well perfused tissues such as the kidney, liver, spleen, lung and gastro-intestinal tract. Toxicities have been associated with some of these tissues (kidney, nervous system, heart and lymphoid organs). These tissues have been associated with higher tacrolimus concentrations and/or long elimination times.

When tacrolimus is administered intravenously or orally it is extensively metabolised by hydroxylation and demethylation to at least nine metabolites, with eight metabolites identified and characterised. Despite differences with respect to the rate of formation of the metabolites the metabolite profile of various species (including humans) appears qualitatively similar, with M-I (13-O-demethylated tacrolimus) being identified as the major metabolites with negligible immunosuppressive activity in vitro. Cytochrome P450 3A enzymes in the liver and small intestine are major enzymes responsible for tacrolimus phase I metabolism, with 3A2 being principally responsible in the rat, DPB-1 in the dog and 3A4 in humans and there was found to be no involvement of phase two enzymes.

The amount of unchanged tacrolimus excreted was found to be <2%, with biliary secretion and subsequent faecal excretion (80-95%) comprising the major route of elimination. No changes were observed with respect to excretion following repeated administration. Following oral dosing tacrolimus was found in milk, at similar levels to those observed in the plasma at eight hours post-administration. Prograft has been extensively used for a number of years and subsequently the potential pharmacokinetic drug interactions have been extensively reviewed and documented in the literature (Venkataramanan et al., 1995; Matsuda et al., 1996; Mignat, 1997; Christians et al., 2002; van Gelder, 2002, Scott et al., 2003).

**Toxicology**

- Repeat dose toxicity

No new repeat dose toxicity studies have been submitted in relation to the prolonged release form of Prograf. The toxicity of tacrolimus has been previously well established in relation to signs of general toxicity as well as the identification of the target organs of toxicity including the kidney, pancreas, eyes, nervous system and the heart as well as lymphoid organs. Over the past decade of clinical use

with tacrolimus, clinically toxicity has been associated with the kidney, pancreas/glycaemic control, eye and heart in treated patients and appears consistent with the findings of the repeat-dose studies.

- Genotoxicity

The genotoxicity of tacrolimus has been studied *in vitro* with respect to gene mutation in bacteria (Ames test), *in vitro* Chromosomal aberration in Chinese hamster lung V79 cells, *in vitro* HGPRT gene mutation test in Chinese hamster ovary cells, *in vitro* Unscheduled DNA synthesis test (UDS test) in rat hepatocyte cells, *in vivo* Micronucleus test in mice.

The studies *in vitro* of reverse mutation with bacteria showed that tacrolimus even at the highest concentration (2000-5000 µg/plate) did not inhibit the growth of any bacterial strains (*Salmonella typhimurium* TA 98, 100, 1535, 1537 cell lines and *Escherichia coli* WP2 cell line). Under the conditions of the test, tacrolimus did not induce gene mutation in any bacterial strains tested with or without metabolic activation by a rat liver microsomal fraction (S9 mix). Tacrolimus also did not induce a concentration dependent increase in the frequency of 6-thioguanine resistant colonies, with or without metabolic activation by S9, and was, therefore, evaluated as negative in the *in vitro* HGPRT gene mutation test in Chinese hamster ovary cells.
On the other hand, tacrolimus inhibited growth of the V79 Chinese hamster lung cells at concentrations of 50 µg/ml or higher in the test without metabolic activation by S9, and the $IC_{50}$ was about 70 µg/ml. In these cells tacrolimus decreased the mitotic index dose-dependently in the tests with and without metabolic activation by S9. In cultured V79 Chinese hamster lung cells tacrolimus did not induce chromosomal aberrations. Moreover, it was negative in the *in vitro* rat hepatocyte DNA repair assay.

The *in vivo* effects of tacrolimus on the chromosomes and the mitotic apparatus were investigated in the bone marrow cells of mice (Micronucleus test). This test was negative up to oral doses of 500 mg/kg tacrolimus, the maximum feasible dose for gavage in mice. This dose is more than 1,000 times higher than the expected doses for clinical use. The number of polychromatic erythrocytes decreased in mice dosed with 125 and 500 mg/kg, pointing to tacrolimus induced inhibition of erythropoiesis. Under these test conditions, tacrolimus did not induce chromosomal damage and/or damage to the mitotic apparatus.

In conclusion, the results of these experiments indicate that tacrolimus is devoid of any mutagenic property under the conditions of the test systems up to the limits of cytotoxicity.

- Carcinogenicity

Despite reaching the maximum tolerated dose, oral carcinogenicity studies were not associated with any carcinogenicity findings. However the performance of topical application studies resulted in the formation of lymphomas. These findings in the topical application studies were associated with high systemic exposure levels of tacrolimus. The development of lymphomas was considered to be treatment related and associated with the immunosuppressive action of tacrolimus. Immuno-suppression with various agents and the development of malignancies is a well-documented phenomenon and appears to be virus related.

- Reproduction Toxicity

Exposure to high doses of tacrolimus resulted in poor weight gain, reduced mating behaviour, prolonged dietrus, delayed parturition, increased pre- and post-implantation losses, reduced pup viability, increased F1 variations and malformations (with relatively high ventricular septal defect) There was no effect on the developmental or mating parameters of those pups that survived to weaning. The maximum non-toxic dose levels were considered to be 0.32 mg/kg/day and 0.1 mg/kg/day tacrolimus in rats and rabbits respectively.

A negative effect of tacrolimus on male fertility in the form of reversible reduction of sperm counts and motility was observed in a rat study using subcutaneous administration of tacrolimus at doses of 1 and 3 mg/kg/day. This was further supported by histopathological changes of male reproductive

organs, which were noted following repeated administration of tacrolimus to rats (Hisatomi et al, 1996).

Despite the lack of experience with the administration of MR4 during pregnancy, the new prolonged release formulation would be considered to represent an equal risk. According to the adverse animal experience and as the safety of tacrolimus in human pregnancy has not been adequately established, it is recommended that MR4 should not be administered to pregnant women unless the perceived benefit justifies the potential risk to mother and foetus (see SPC, Section 4.6 Pregnancy and lactation). Furthermore, after systemic administration to lactating women or animals, tacrolimus is excreted into breast milk (Jain et al., 1997). Therefore, women should not breast-feed during treatment with tacrolimus.

- Local tolerance

The local tolerance of tacrolimus was investigated in rabbits using peri-venous, intra-arterial and intramuscular administration. As MR4 is an oral formulation of tacrolimus, these studies are not relevant for the prolonged-release formulation.

**Ecotoxicity/environmental risk assessment**

The environmental risk assessment of MR4 oral formulation of tacrolimus followed primarily the draft of guidelines related to this issue. From the results obtained, it is concluded that MR4 is of no immediate risk to the environment and no proposals for labelling provisions are necessary to reduce any potential environmental risks.

**Discussion on the non-clinical aspects**

The pharmacology of an oral prolonged-release formulation of tacrolimus (Advagraf) is based on the pharmacological data which were obtained during development of its hard capsules and solution for infusion which as Prograf/Prograft has been approved for clinical use in many countries, including most EEA states.

The toxicity of tacrolimus both pre-clinical and clinical has previously been well established with the organs of toxicity identified. The proposed new formulation would not be considered to result in any new toxicity concerns. The alteration in the release profile would be expected to improve the variability in the exposure to tacrolimus. It would therefore not be considered to alter the toxicity profile and may potentially improve the safety of tacrolimus and subsequently the lack of further studies with the new prolonged-release formula is considered acceptable.

Animal data clearly indicate that systemic treatment with tacrolimus adversely affects male and female reproduction. With respect to reproductive toxicity and carcinogenicity findings for Prograf, the new prolonged release formulation (MR4) would be considered to represent an equal safety concern and the proposed wordings in the SPC are considered to adequately address these concerns.

The use of Advagraf is not considered to pose a risk to the environment.

# 4 Clinical aspects

## Introduction

## GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

## Pharmacokinetics

## Analytical Methods

A high performance liquid chromatography/mass spectrometry (HPLC/MS) assay was used for the characterisation of tacrolimus and its metabolites. The lower limit of quantification in whole blood is 0.1 ng/mL, with linearity demonstrable to 30 ng/mL. The inter-assay accuracy ranges from 90.2% to 106.3% over the concentration range 0.1 ng/mL to 100 ng/mL. .

For therapeutic drug monitoring, an enzyme multiplied immunoassay is used on whole blood with spectrophotometric detection. The assay has a limit of detection of 1.2 ng/mL.

## General Methodology

Conventional pharmacokinetic methods have been used and data analysis has been carried out using wel validated computer software. Clinical trial methodology for both healthy volunteer and transplant patients has been conventional and apparently carried out to high standards.

It is noted that the clinical study programme was over reliant on white (Caucasian) male volunteers. A warning on the limited experience in non-Caucasian patients has been added to section 4.4 of the SPC.

- Pharmacokinetics in healthy volunteers

***Single dose healthy volunteer studies***
**Study 99-0-060** was a three-way crossover comparison of Prograf and two modified release formulations of tacrolimus - MR3 and MR4. It was conducted at a single US centre in August and September 1999. Twelve healthy male volunteers took single 5 mg doses (one capsule) of each formulation after a ten hour fast. There was a ten day washout period between treatments. Blood levels of tacrolimus were measured over the subsequent 72 hours. All subjects completed the study.

The derived pharmacokinetic indices for the immediate release and delayed release formulations are shown in Table 1.

**Table 1 Derived pharmacokinetic indices of immediate and delayed formulations of tacrolimus figures are group mean (SD).**

| | $T_{max}$ (h) | $C_{max}$ (ng.mL) | $AUC_{0\rightarrow\infty}$ (ng.h/mL) | t½ (h) | Kel (1/h) |
|---|---|---|---|---|---|
| Prograf | 1.37 (0.57) | 22.19 (8.36) | 196.6 (115.0) | 31.4 (2.6) | 0.022 (0.002) |
| MR4 | 2.83 (1.40) | 7.37 (2.62) | 172.6 (47.89) | 28.4 (6.3) | 0.026 (0.007) |
| MR3 | 2.25 (1.49) | 11.0 (3.91) | 222.3 (73.03) | 31.4 (3.5) | 0.022 (0.002) |

The study in healthy volunteers indicates that of the two candidate delayed release formulations the exposure (AUC) following MR4 was slightly closer to Prograf than that of MR3. Consequently MR4 went forward for development as the proposed market modified release formulation.

**Study 00-0-076** was a two-way crossover comparison of Prograf and modified release MR4 formulations of tacrolimus. It was conducted at a single US centre in November and December 2000. Sixteen healthy male volunteers took a single dose of 1.5 mg (3 x 0.5 mg) of each formulation after a ten hour fast. There was a fourteen day washout period between treatments. Blood levels of tacrolimus were measured over the subsequent 72 hours. All subjects completed the study. The derived pharmacokinetic indices are in Table 2.

**Table 2 Derived pharmacokinetic indices of immediate and delayed formulations of tacrolimus**

| | $T_{max}$ (h) | $C_{max}$ (ng.mL) | $AUC_{0\rightarrow\infty}$ (ng.h/mL) | t½ (h) | Kel (1/h) |
|---|---|---|---|---|---|
| Prograf | 1.44 (0.5) | 7.4 (1.8) | 74.3 (24.7) | 37.2 (6.4) | 0.02 (0.003) |
| MR4 | 3.0 (2.0) | 2.29 (0.58) | 65.6 (17.6) | 36.1 (6.7) | 0.02 (0.003) |

**Study 00-0-078** was a two-way crossover comparison of Prograf and MR4 formulations of tacrolimus. It was conducted at a single US centre in November and December 2000. Sixteen healthy male volunteers took single 5 mg doses (one capsule) of each formulation after a ten hour fast. There was a fourteen day washout period between treatments. Blood levels of tacrolimus were measured over the subsequent 72 hours. All subjects completed the study. The derived pharmacokinetic indices are in Table 3.

**Table 3 Derived pharmacokinetic indices of immediate and delayed formulations of tacrolimus**

| | $T_{max}$ (h) | $C_{max}$ (ng.mL) | $AUC_{0\rightarrow\infty}$ (ng.h/mL) | t½ (h) |
|---|---|---|---|---|
| Prograf | 2.00 | 26.7 | 297 | 37.5 |
| MR4 | 2.00 | 9.15 | 198 | 35.9 |

***Effects of food on drug levels***

Two single dose crossover studies in healthy male volunteers investigated the effects on food on the pharmacokinetics, principally absorption, of Prograf and MR4.

**Study 02-0-153** examined the relationship between the timing of a meal and subsequent blood levels of tacrolimus. Twenty three subjects completed the study which showed that in the presence of food there was an increase of approximately 80% in time to maximum plasma concentration and a reduction of approximately 20% in maximum plasma concentration and a reduction of 26% in AUC in the presence of food. The length of fast before food, and the timing of the dose, whether immediately or one and a half hours after food did not appear to make an important difference.

**Study 01-0-123** was a prospective, randomized, open-label, single dose, three-period, six sequence crossover study in 21 healthy volunteers to determine whether a high fat meal affects the rate and extent of tacrolimus absorption from the MR4 (modified release) formulation relative to that in the

fasted state. Derived pharmacokinetic data from 'fed and fasting' Study 01-1-123 are tabulated below.

**Table 4 Derived pharmacokinetic indices from 'fed and fasting'**

| Study 01-1-123 – one 5 mg capsule – n = 18 | | | | |
|---|---|---|---|---|
| | $T_{max}$ (h) | $C_{max}$ (ng.mL) | $AUC_{0\rightarrow t}$ (ng.h/mL) | t½ (h) |
| MR4 fasted | 2 | 9.04 | 182.3 | 35.5 |
| MR4 fed | 3.5 | 6.8 | 136.3 | 35.2 |
| Fed/fasted ratio (90% CI ) | NA | 75.0 (61.2, 88.9) | 75.0 (66.0, 84.0) | NA |

Dosing MR4 immediately following a high fat meal significantly reduced the rate and extent of tacrolimus absorption relative to that in the fasted state. The mean $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ were reduced by approximately 25% in the presence of food. The mean $C_{max}$ was also reduced by approximately 25% relative to that in the fasted state

***Multiple dose healthy volunteer studies***

The summary pharmacokinetic data from two healthy male volunteer studies are shown in tabular form below. All doses were administered following a two hour fast. The studies were conducted as single dose (Day 1) and multiple dose (Day 10) for ease of comparison only the multiple dose data are shown.

**Study FG-506-04-21** was conducted at a single UK centre between September and December 2000. All doses were administered following a 2 hour fast. Prograf (1 mg capsule) was administered twice daily for 10 days. MR4 (2 x 1 mg capsules) was administered once daily for 10 days. A washout interval of at least 14 days separated the two treatment periods. Fourteen out of sixteen subjects completed both phases of the study.

The elimination kinetics was similar for the two formulations, with a mean terminal elimination half-life of approximately 41 h for both MR-4 and Prograf. Based upon AUC(0-24 h), there was approximately a 2 and 2.5-fold accumulation of tacrolimus in the blood following 10 days multiple dosing with Prograf and MR-4, respectively. On Day 1, systemic exposure to tacrolimus, as assessed by AUC(0-24 h), was similar for the two formulations. Upon attainment of steady state, once daily dosing with 2 mg MR-4 resulted in an 18% increase in 24 h systemic exposure of tacrolimus when compared to twice daily dosing with 1 mg Prograf

**Table 5 Derived pharmacokinetic indices at steady-state**

| Study FG-506-04-21 – 2 mg daily – n = 16 | | | | |
|---|---|---|---|---|
| | $T_{max}$ (h) | $C_{max0\rightarrow 24}$ (ng.mL) | $AUC_{0\rightarrow 24}$ (ng.h/mL) | t½ (h) |
| Prograf Day 10 | 1.0 (1 – 3) | 6.1 (39.4) | 70.7 (46.3) | 40.8 (13.4) |
| MR4 Day 10 | 2.0 (1 – 5) | 5.8 (37.6) | 83.7 (35.2) | 40.9 (12.6) |

* Tmax is median and range

**Study FG-506-04-25** was conducted at a single UK centre between April and August 2001. All doses were administered following a 2 hour fast. Prograf (2 x 2 mg capsules) was administered twelve hourly for 10 days. MR4 (4 x 1 mg capsules) was administered once daily for 10 days (a dose similar to the average dose used in long term maintenance immunosuppression). A washout interval of at least 14 days separated the two treatments. Twenty-four out of twenty-five subjects completed both phases of the study.

Based upon both $AUC_{0\text{-}24}$ and Cmax, there was an approximate 2-fold accumulation of tacrolimus in the blood following 10 days multiple dosing with MR-4 and Prograf. Following morning administration, the rate of absorption of tacrolimus was rapid for both formulations, with a median tmax of approximately 1 and 2 h being obtained for the Prograf and MR-4 formulations, respectively. Following the evening dose of Prograf, the rate and extent of absorption of tacrolimus was reduced,

with total systemic exposure as assessed from AUC(0-∞) and Cmax being 17 and 50% lower, respectively, following the evening dose compared to the morning dose when at steady-state.
For both MR-4 and Prograf, Cmin(24 h) and AUC(0- 24 h) were highly correlated. This correlation was numerically slightly higher for the MR-4 formulation, but was statistically not different for both formulations. The elimination kinetics were similar for the two formulations, with a mean terminal elimination half-life of approximately 38 h for both MR-4 and Prograf.

Table 6 **Derived pharmacokinetic indices at steady-state**

| Study FG-506-04-25 – 4 mg daily – n = 25 | | | | |
|---|---|---|---|---|
| | $T_{max}$ (h) | $C_{max0\rightarrow24}$ (ng.mL) | $AUC_{0\rightarrow24}$ (ng.h/mL) | t½ (h) |
| Prograf Day 10 | 1.0 (1 – 2) | 14.9 (32.7) | 160 (34.6) | 37.6 (9.53) |
| MR4 Day 10 | 2.0 (1 – 3) | 11.1 (31.6) | 148 (32.9) | 37.8 (8.78) |

* Tmax is median and range

- Distribution

Tacrolimus binds strongly to erythrocytes with a distribution ratio of whole blood:plasma of approximately 20:1. In plasma the drug is highly protein bound (>98.8%). Tacrolimus is extensively distributed in the body with a steady state volume of distribution ($V_{ss}$), estimated from plasma at 1300 L.

- Elimination

Tacrolimus is cleared by hepatic metabolism, principally via cytochrome P450 3A4 isoenzyme (CYP3A4). Orally administered tacrolimus is also metabolised by the gut wall, most likely by gastro-intestinal CYP3A4. Possible metabolic phase I reactions of tacrolimus appear to include mono-demethylation, di-demethylation, hydroxylation, and a combination of mono-demethylation and hydroxylation. The only pharmacologically active metabolite is the 31-O-demethylated metabolite which has immunosuppressive potency approximately equal to that of the parent compound.

The average total body clearance of tacrolimus in adults is approximately 2.25 L/h in healthy subjects, 6.7 L/h in kidney transplant patients, 4.05 L/h in liver transplant patients and 3.9 L/h in heart transplant patients. The elimination half-life ($t_{½}$) of tacrolimus in healthy subjects was approximately 43 hours.

Following i.v. and oral administration of $^{14}C$-labelled tacrolimus, most of the radioactivity was eliminated in the faeces, while less than 2% was eliminated in the urine.

- Pharmacokinetics in target populations

***Pharmacokinetic Studies with MR4 in de novo Kidney and Liver Transplant Recipients***

Two Phase II studies were performed to compare the pharmacokinetics of tacrolimus following once daily administration of MR4 (in the morning) and twice daily administration of Prograf in *de novo* kidney (study FG-506E-12-01) and liver (study FG-506-11-01) transplant recipients.

Comparisons of systemic exposure ($AUC_{0-24}$), $C_{max}$ and trough levels ($C_{24}$) were performed following the first dose and under steady state conditions (Day 14 and Week 6 post-transplantation). Both studies were of 6-week duration, at the end of which patients randomised to MR4 treatment arm had the option to continue into Phase III follow up study. Brief details of these studies are provided in Table 7 and 8.

**Table7. Pharmacokinetic Studies with MR4 in De Novo Kidney and Liver Transplant Recipients**

| Study No. /Design | Lot No./Expiration | Dose/ Subjects | Study objectives | Results |
|---|---|---|---|---|
| FG-506E-12-01<br>***De Novo*** Kidney Transplant Recipients<br><br>Phase II, multi-centre, open, prospective, 1:1 randomised, comparative PK study 6-week PK evaluation period | **MR4**<br>0.5 mg capsules M0Y 300 2B<br>1 mg capsules M1Y 300 1A<br>5 mg capsules M5Y 900 7A<br><br>**Prograf**<br>0.5 mg capsules 0Y4 057 B, 0Y4 108 A, 0Y4 128 A<br>1 mg capsules 1Y4 497 A, 1Y4 514 E, 1Y4 602 D<br>5 mg capsules 5Y5 093 C, 5Y5 097 D | Prograf (0.10 mg/kg twice daily)<br>MR4- 0,20 mg/kg /122 | To compare the pharmacokinetics of tacrolimus when administered as MR4 or Prograf in primary kidney transplant recipients. | Following kidney transplantation patients received tacrolimus as either MR4 or Prograf for a period of 6 weeks.<br>The first total daily dose for MR4 and Prograf was comparable; however, the systemic exposure to tacrolimus on Day 1 was approximately 32% lower for MR4 than for Prograf. By Day 14 and Week 6, the systemic exposure to tacrolimus for MR4 was within 10% of that for Prograf. When normalised to an equivalent dose for both formulations (0.1 mg/kg/day), the geometric mean AUC0-24 ratio of MR4:Prograf was 98% and 82% on Day 14 and at Week 6, respectively. |
| FG-506-11-01:<br>***De Novo*** Liver Transplant Recipients<br><br>Phase II, multi-centre, open, prospective, 1:1 randomised, comparative PK study 6-week PK evaluation period | **MR4**<br>0.5 mg capsules M0Y 300 2B<br>1 mg capsules M1Y 300 1A<br>5 mg capsules M5Y 900 5A, M5Y 900 7A<br><br>0.5 mg capsules 0Y4 057 B, 0Y4 108 A<br>1 mg capsules 1Y4 497 A, 1Y4 514 E, 1Y4 602 D<br>5 mg capsules 5Y5 093 C, 5Y5 097 D | 0.10 to 0.15 mg/kg for both MR4 and Prograf /133 | To compare the pharmacokinetics of tacrolimus when administered as MR4 or Prograf in primary liver transplant recipients. | Following liver transplantation patients received tacrolimus as either MR4 or Prograf for a period of 6 weeks.<br>The first total daily dose for MR4 and Prograf was comparable; however, the systemic exposure to tacrolimus on Day 1 was approximately 50% lower for MR4 than for Prograf. By Day 14 and Week 6, the systemic exposure to tacrolimus for MR4 was approximately 10% to 20% higher than for Prograf; however, the corresponding total daily doses of MR4 were approximately 25% higher than Prograf. When normalized to an equivalent dose for both formulations (0.1 mg/kg/day) the geometric mean AUC0-24 ratio of MR4: Prograf was approximately 88% and 91% on Day 14 and at Week 6, respectively. |

**Table 8: Comparison of Systemic Exposure to Tacrolimus Administered as MR4 and Prograf in *De Novo* Kidney and Liver Transplant Recipients**

| | **Geometric mean ratio MR4:Prograf [90%CI]** | | |
|---|---|---|---|
| | **Day 1** | **Day 14** | **Day 42** |
| **Study FG-506E-12-01 kidney transplant recipients** | | | |
| **ln(AUC0-24)** | 67.6% (54.9 to 83.3) | 107.0% (94.3 to 121.4) | 89.1% (78.7 to 100.9) |
| **ln(AUC0-24).** | 65.6% (53.6 to 80.4) | 98.0% (83.1 to 115.4) | 82.4% (68.8 to 98.7) |
| **Study FG-506-11-01 liver transplant recipients** | | | |
| **ln(AUC0-24)** | 50.3% (39.0 to 65.0) | 111.4% (97.6 to 127.3) | 117.9% (106.1 to 131.0) |
| **ln(AUC0-24).** | 47.7% (37.0 to 61.6) | 88.3% (74.4 to 104.7) | 91.4% (76.1 to 109.6) |

There was good correlation of AUC0-24 and trough levels in both studies. In Study FG-506E-12-01 correlation coefficients were 0.83 and 0.94 for MR4 and Prograf, respectively; in Study FG-506-11-01, correlation coefficients were 0.92 and 0.83 for MR4 and Prograf, respectively. Moreover, the slope of the line of best fit was similar for both formulations in both studies, indicating that for therapeutic drug monitoring, the same target trough level range can be targeted for both formulations.
In both studies, the lower systemic exposure to tacrolimus observed for MR4 on Day 1 can be attributed to an absence of diurnal effect on the absorption of tacrolimus for Prograf formulation administered in the evening relative to the morning on the first day post-transplant.

However, despite the 32% lower (kidney) and 50% lower (liver) exposure to tacrolimus on Day 1 observed for MR4 compared to Prograf, the efficacy and safety of MR4 did not appear to be different to that of Prograf. The finding of lower blood drug levels is clearly indicated in the SPC (section 4.2 Posology and method of administration). Careful and frequent monitoring of tacrolimus trough levels is recommended in the first two weeks post-transplant with Advagraf to ensure adequate drug exposure in the immediate post-transplant period.

***Pharmacokinetic Studies in Stable Kidney, Liver and Heart Transplant Recipients Converted from Twice Daily Prograf to Once Daily MR4***

The applicant has carried out a series of studies in which adult patients with stable organ transplantation of at least six months were switched on an equal dose basis from Prograf to MR4. One study was conducted in children. Prograf and MR4 pharmacokinetics were evaluated at steady state, generally Prograf on study days 1 to 7 and MR4 from day 14 onwards. Prograf was given twice daily and MR4 once daily. Dosages were to be kept constant other than in a situation where there were clinical signs of toxicity or graft rejection.

**Study 02-0-131** is a Phase II one-way conversion from Prograf to MR4 in stable kidney transplant recipients. The patient population for this study was fairly representative of the overall adult kidney transplant population, including 24/66 (36.4%) female patients, 12/66 (18.2%) black patients and 13/66 (19.7%) diabetics. This population profile allowed for adequate analysis for equivalence of exposure for both males and females, among patients with diabetes, and within black and white populations. Patients were followed within the pharmacokinetic treatment period for at least 28 days post conversion to MR4 and provided data for two steady state pharmacokinetic profiles while patients were taking Prograf, and two steady state pharmacokinetic profiles while patients were taking MR4.

The derived pharmacokinetic indices are shown in tabular form below.

**Table 9. Derived pharmacokinetic indices at steady-state (study 02-0-131)**

| Study 02-0-131 **Renal** transplantation | | (data are mean and s.d.) |
|---|---|---|
| | $C_{max}$ (ng.mL) | $AUC_{0\rightarrow24}$ (ng.h/mL) |
| MR4 | 14.3 (4.7) | 200.7 (57.5) |
| Prograf | 16.0 (6.5) | 206.6 (58.4) |
| Ratio and 90% CI | 86 (80, 92) | 94 (90, 99) |

The findings indicate that conversion to MR4 may offer benefits, including: equivalence of exposure with Prograf on a mg: mg basis that was consistent regardless of gender, race or diabetic status; less inter- and intra-subject variability in exposure when compared to Prograf; exposure highly correlated with Cmin, indicating no need to change the current therapeutic monitoring system; a safety profile equivalent to Prograf, with no indication of over- or under-immunosuppression, as indicated by laboratory results and clinical signs and symptoms, through 4 weeks after converting to MR4; and, lower Cmax with less variability in concentrations over time, which may prove beneficial in the long-term. Kidney transplant recipients can be easily converted from a Prograf-based immunosuppression regimen to a MR4-based immunosuppression regimen on a 1:1 (mg: mg) total daily dose basis with minimal dose adjustments required after conversion.

**Study 02-0-152** is a Phase II four-period replicate design, conversion from Prograf to MR4 in stable liver transplant patients. The trial had an 8-week PK evaluation period, with a planned 2 to 3 year long-term extension period. The patient population (pharmacokinetic evaluable set) for this study was fairly diversified in respect to gender (26/62, 41.9% female) and diabetics (11/62, 17.7% with PTDM at baseline; 12/62, 19.4% with diabetes mellitus type I or II prior to transplant). The population was predominantly white (57/62, 91.9%). The study provided data for two steady state pharmacokinetic profiles while patients were taking Prograf, and two steady state pharmacokinetic profiles while patients were taking MR4. Equivalence of exposure between Prograf and MR4 at steady state was demonstrated. The 90% CI for ln(AUC0-24) was (85.42, 92.29), and was completely contained within the 80% to 125% limits. An analysis using dose-adjusted data confirmed the results.

Liver transplant recipients can be easily converted from a Prograf-based immunosuppression regimen to an MR4-based immunosuppression regimen on a 1:1 (mg: mg) total daily dose basis with minimal dose adjustments required after conversion.

The derived pharmacokinetic indices are shown in tabular form below.

**Table 10. Derived pharmacokinetic indices at steady-state (study 02-0-152)**

| Study 02-0-152 **Liver** transplantation | | (data are mean and s.d.) |
|---|---|---|
| | $C_{max}$ (ng.mL) | $AUC_{0\rightarrow24}$ (ng.h/mL) |
| MR4 (D28) | 13.3 (5.6) | 184.0 (62.7) |
| Prograf (D14) | 17.9 (9.9) | 215.6 (77.8) |
| Ratio and 90% CI | 81 (74, 87) | 89 (85, 93) |

**Study FG506-15-02** is a Phase II one-way conversion from Prograf to MR4 5-week PK evaluation period (long-term follow-up for MR4 patients performed in Study FG-506-14-02). All patients in the PK Evaluable Set remained on the same dose of tacrolimus throughout the study. The mean systemic exposure to tacrolimus (AUC0-24) following the administration of MR4 was within 10% of unity when compared with Prograf in stable heart transplant patients. The AUC was within the bioequivalence criteria based on the 90% confidence intervals for the ratio of treatment means and an acceptance interval of 80% to 125%. The trough levels of tacrolimus following MR4 administration were similar to those following Prograf administration, suggesting the same trough target therapeutic range for MR4 and Prograf. There was good correlation of trough to AUC for both formulations.
This study has shown that stable heart transplant patients can be safely converted from Prograf to MR4 on a 1:1 (mg:mg) basis. It should be noted that as the mean AUC ratio MR4: Prograf is 0.91, following conversion patients may need to be monitored to ensure maintenance of similar systemic exposure.

The derived pharmacokinetic indices are shown in tabular form below.

**Table 11. Derived pharmacokinetic indices at steady-state (study FG506-15-02)**

| Study FG506-15-02 **Heart** transplantation n = 85 | | |
|---|---|---|
| | $C_{max}$ (ng.mL) | $AUC_{0\rightarrow24}$ (ng.h/mL) |
| MR4 | 14.8 | 220 |
| Prograf | 18.6 | 243 |
| Ratio and 90% CI | 79 (73, 86) | 91 (86, 95) |

**Study 03-0-160** is a Phase II one-way conversion, 2 week PK evaluation study in stable paediatric liver transplant recipients converted from a Prograf-based immunosuppressive regimen to an MR4-based immunosuppressive regimen. The sample size was relatively small (pharmacokinetic evaluable set n = 18) but was fairly diversified in terms of race (61.1% Caucasian; 38.9% Black) and gender (72.2% female; 27.8% male).

Equivalence of exposure between Prograf and MR4 at steady state was demonstrated.
The 90% CI for ln(AUC0-24) was (90.8, 112.1) and entirely contained within the 80% to 125% limits. An analysis using dose-adjusted parameters provided similar results. There was a strong correlation between AUC0-24 and Cmin (trough) for MR4 and Prograf at steady state, with the correlation coefficient for MR4 on day 14 (0.90) being similar to that of Prograf on day 7 (0.94). Additionally, the CIs for ln(Cmin), using both non-dose adjusted values and dose-adjusted values, were entirely contained within the 80% to 125% limits when trough concentrations at steady state were considered. This indicates that trough values for MR4 and Prograf were equivalent at steady state.

The derived pharmacokinetic indices are shown in tabular form below.

**Table 12. Derived pharmacokinetic indices at steady-state (study 03-0-160)**

| Study 03-0-160 Liver transplantation in children n = 18 (mean and s.d.) | | |
|---|---|---|
| | $C_{max}$ (ng.mL) | $AUC_{0\rightarrow24}$ (ng.h/mL) |
| Prograf (n=18) | 20.7 (13.3) | 198.2 (99.2) |
| MR4 (n=18) | 15.2 (5.7) | 193.0 (78.0) |
| Lognormal ratio and 90% C.I. | 82 (70, 96) | 101 (91, 112) |

There was good correlation of AUC0-24 and trough levels in the conversion studies, with results indicating that the AUC 0-24 and C24 of tacrolimus for the MR4 formulation was equivalent to that for the standard formulation, Prograf, i.e the 90% CI lies within the acceptance interval of 0.8 – 1.25, with the exception of the CI for $C_{24}$ which was marginally outside the acceptance interval in Study 02-0-152. [Data from the paediatric study are not shown as only indications for adults are applied for].

**Table 13: Comparison of Systemic Exposure to Tacrolimus and $C_{24}$ for Tacrolimus in Patients Converted from Twice Daily Prograf to Once Daily MR4**

| Transplant Population | Study (N)† | Parameter (ng.h/mL) | Geometric mean ratio MR4:Prograf [90% CI] |
|---|---|---|---|
| **Adult kidney** | 02-0-131 (N=67) | ln($AUC_{0-24}$) | 95.0% [90.7 to 99.4] |
| | | ln($C_{24}$) | 87.2% [82.7 to 91.9] |
| | FG-506E-12-02 (N=60) | ln($AUC_{0-24}$) | 92.6% [89.7 to 95.7] |
| | | ln($C_{24}$) | 90.5% [87.1 to 94.0] |
| | FJ-506E-KT01 (N=35) | ln($AUC_{0-24}$) | 95% [88 to 103] |
| | | ln($C_{24}$) | 101% [94 to 109] |
| **Adult liver** | 02-0-152 (N=62) | ln($AUC_{0-24}$) | 88.8% [85.4 to 92.3] |
| | | ln($C_{24}$) | 81.4% [77.9 to 85.1] |
| **Adult heart** | FG-506-15-02 (N=45) | ln($AUC_{0-24}$) | 90.5% [86.8 to 94.3] |
| | | ln($C_{24}$) | 86.9% [82.6 to 91.4] |

† PK Evaluable Set

- Dose proportionality and time dependencies

**Study FJ-506e-0002** was a three way crossover study designed to examine the dose proportionality of tacrolimus following single doses of the modified release formulation in healthy male Japanese subjects. Subjects received single 1.5 mg, 4 mg, 10 mg doses; whole blood tacrolimus levels were measured for 120 hours following each dose and at least fourteen days were allowed for treatment washout. The study was conducted at a single Japanese centre between July and October 2004. Seventeen subjects completed the study. The derived pharmacokinetic indices for the modified release formulation are shown in Table 14.

**Table 14. Pharmacokinetic indices according to dose figures are mean (sd)**

| Dose | Tmax (h) | Cmax (ng/mL) | $AUC_{0\rightarrow120}$ (ng.hr/mL) |
|---|---|---|---|
| 1.5 mg | 2.44 (1.59) | 3.41 (1.51.) | 67.42 (30.23) |
| 4 mg | 2.44 (1.26) | 9.02 (3.09) | 187.7 (74.92) |
| 10 mg | 2.65 (0.86) | 26.53 (7.99) | 475.24 (179.41) |

The pharmacokinetics of tacrolimus after single oral administration of MR4 at 3 different dose levels by a crossover method demonstrated dose-linearity in the dose range of 1.5 mg to 10 mg.

**Study 02-0-148** examined the pharmacokinetics of tacrolimus following morning and evening 5 mg doses (single capsule) of Prograf and MR4 in healthy male subjects. Whole blood tacrolimus levels were measured for 120 hours following each dose and ten to twenty days were allowed for treatment washout. In order to avoid the known food interaction with tacrolimus morning and evening doses were given at the mid-point of an eight hour fast. The study was conducted at a single, US, centre between February and April 2003. Twenty-two subjects completed the study. The derived pharmacokinetic indices for the modified release formulation are shown in Table 15.

**Table 15. Derived pharmacokinetic indices of MR4 and Prograf formulations of tacrolimus administered as evening or morning 5mg doses**

| | $C_{max}$ (ng.mL) | $AUC_{0\rightarrow\infty}$ (ng.h/mL) |
|---|---|---|
| MR4 Evening | 6.41 | 116 |
| MR4 Morning | 7.29 | 178 |
| MR4 pm/am ratio (90% CI) | 78.9 (60.0, 116) | 65.2 (48.8, 81.6) |
| Prograf Evening | 9.22 | 168 |
| Prograf Morning | 23.0 | 254 |
| Prgraf pm/am ratio (90% CI) | 40.1 (31.3, 48.9) | 66.0 (54.5, 77.5) |

Although the diurnal reduction of approximately one-third following a single evening dose is likely to be less marked following multiple dosing, it is still an effect comparable in magnitude to the food interaction. Hence, SPC and PL provide reference to the time of dosing during the day.

- Special populations

*Impaired renal function*

No new data have been generated. The SPC indicates that the pharmacokinetics of tacrolimus are unaffected by renal function and no dose adjustment should be required. It also warns about the nephrotoxic potential of tacrolimus and advises monitoring of renal function.

*Impaired hepatic function*

No new data have been presented. Study 90-0-0020 (consisting of two reports dated 1996 and 1998) evaluated the pharmacokinetics of tacrolimus in patients with mild and severe hepatic dysfunction. The reports indicate that the elimination of tacrolimus is prolonged in mild hepatic dysfunction and markedly prolonged in severe hepatic dysfunction. It is concluded that in the case of severe hepatic dysfunction whole blood, as distinct from plasma, monitoring is still valid. The SPC warns that a dose adjustment may be necessary in severe hepatic dysfunction.

*Race*

**Study FJ-506e-0001** was conducted in February and March 2003 at a single Japanese site. Eligible subjects were healthy adult Japanese males. Subjects received a single 3 mg dose of tacrolimus MR4 in the fasting state, whole blood drug concentrations were measured over the following 120 hours. Twenty subjects completed the study. Historical data from US single centre Study 00-0-077 were used to compare the pharmacokinetics of tacrolimus in Japanese and US Caucasian subjects.
The ratios of Japanese to Caucasians for the geometric means of Cmax, and AUC were 1.406 and 1.353, respectively, with 90% confidence intervals of 1.183 to 1.672 and 1.101 to 1.662. On average the Japanese subjects were 14 kg lighter than the American subjects and when adjusted for body weight the ratios of Japanese to Caucasians for Cmax and AUC were 1.147 and 1.103, respectively with 90% confidence intervals of 0.975 to 1.349 and from 0.907 to 1.341, respectively.

*Elderly*

No new data have been provided. The proposed SPC indicates that a dosage adjustment is not necessary in the elderly.

*Children*

**Study 03-0-160** was conducted from January to June 2004 at five sites in the US. Eligible patients were to be no more than twelve years old, to have received a liver transplant at least six months previously, and to be on a Prograf based immunosuppressive regimen with a stable total daily dose of no more than 20 mg. Patients with a rejection episode in the pervious 90 days were excluded. Enrolled patients continued to receive Prograf until the evening of day 7. On the morning of day 8 they were converted to MR4 on an equivalent daily dose until Day 14. Twenty-four hour pharmacokinetic profiling was done on Day 7 and Day 14.

Eighteen patients provided evaluable pharmacokinetic data; their median age was 9 years with an age range of 5 - 13; thirteen were female. The pharmacokinetic results are presented in table 12 (see above).

- Pharmacokinetic interaction studies

No new interaction studies have been performed with the new formulation (MR4). However, interactions between tacrolimus and other medicinal products have been thoroughly investigated recently and the most relevant information has been added to the SPC, section 4.5.

The following drugs strongly inhibit CYP3A4 and have been shown to increase the blood levels of tacrolimus: ketoconazole; fluconazole; itraconazole; voriconazole; erythromycin; and HIV protease inhibitors (e.g. ritonavir).

The following drugs inhibit CYP3A4 and have been shown to increase the blood levels of tacrolimus requiring dose adjustment in some patients: clotrimazole; calcium channel blockers such as nifedipine, nicardipine, diltiazem, verapamil; clarithromycin; josamycin; danazol; ethinylestradiol; omeprazole; nefazodone.

Grapefruit juice has also been reported to increase the blood level of tacrolimus by inhibiting the activity of CYP3A4.

The following drugs strongly induce CYP3A4 and have been shown to decrease the blood levels of tacrolimus requiring an increased dose in almost all patients: rifampicin; rifampin; phenytoin; St. Johns Wort (*Hypericum perforatum*). Phenobarbitone is also an inducer of CYP3A4 but to a lesser extent.

Corticosteroids are inducers of CYP3A4 and withdrawal of steroids has been shown to increase tacrolimus blood levels. Maintenance doses of corticosteroids may reduce tacrolimus blood levels by enzyme inhibition, thus increases or decreases in the dose of corticosteroids may decrease or increase tacrolimus levels. High dose prednisolone or methylprednisolone, as given for acute rejection, have the potential to increase or decrease tacrolimus blood levels.

As tacrolimus may reduce the clearance of steroid-based contraceptive agents leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures.

Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus. The half-life of ciclosporin is prolonged when tacrolimus is administered concomitantly, in addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporin and tacrolimus is not recommended.

There is also potential for synergistic impairment of renal function or neurotoxicity when tacrolimus is co-administered with compounds such as aminoglycosides, gyrase inhibitors, vancomycin, cotrimoxazole, non-steroidal anti-inflammatory drugs, ganciclovir or aciclovir. A high potassium

intake, or potassium-sparing diuretics, should be avoided due to the potential for inducing hyperkalaemia as tacrolimus can adversely influence potassium levels.

Tacrolimus is extensively bound to plasma proteins (> 98.8%). Concomitant administration of drugs which are also highly protein-bound may displace tacrolimus from its binding proteins. Thus, co-administration of drugs such as oral anticoagulants, oral anti-diabetics and non-steroidal anti-inflammatory drugs should be undertaken with caution.

**Pharmacodynamics**

The key pharmacodynamic action of tacrolimus is inhibition of cytokine gene transcription. It enters T-lymphocytes by nonspecific mechanisms, and binds to a 12 kDa cis-trans rotamase, termed FK506 binding protein (FKBP12), in the cytoplasm. The tacrolimus-FKBP12 complex binds to the phosphatase calcineurin, and thereby inhibits the dephosphorylation of the nuclear factor of activated T-cells (N-FAT) preventing translocation of N-FAT into the nucleus of the T-lymphocyte. The inhibition of signal transduction pathways prevents transcription of a set of lymphokine genes, in particular those encoding interleukin (IL)-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, granulocyte macrophage colony stimulating factor, tumour necrosis factor-α, interferon-γ and the gene encoding the IL-2 receptor. Tacrolimus suppresses T-cell activation, and the subsequent generation of cytotoxic lymphocytes, thereby down-regulating processes leading to acute graft rejection. T-helper cell dependent B-cell proliferation is also affected.

**Clinical efficacy**

- Dose response studies

The applicant has not conducted any dose response studies. Dose requirements for tacrolimus are well understood from existing clinical experience with Prograf and apart from the immediate peri-operative period are determined on the basis of therapeutic drug monitoring.

- Main studies

The development programme for MR4 encompassed one pivotal and two supportive studies. Primary evidence of the efficacy of MR4 for the prophylaxis of organ rejection is provided by the large, comparative Phase III study of MR4, Prograf and ciclosporin in *de novo* kidney transplant recipients (02-0-158). Supportive efficacy data for MR4 are provided by Phase II pharmacokinetic studies in *de novo* kidney transplant recipients (FG-506E-12-01) and in *de novo* liver transplant recipients (FG-506-11-01).

***Prophylaxis in liver transplantation***

**Study FG506-11-01** was an open multicentre comparison of the pharmacokinetics of tacrolimus in adult (18 – 65 yrs) patients undergoing primary liver transplantation. The study was conducted at 21 centres in Europe, Canada and Australia. Eligible patients were randomised 1:1 to a Prograf or an MR4 based immunosuppressive regimen (129 liver transplant recipients with 62 patients randomised to Prograf and 67 patients randomised to MR4). 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 at Day 14 and Week 6. The primary endpoint was the systemic exposure $AUC_{0-24}$ of tacrolimus on Day 1, Day 14 and Week 6.

The mean daily dose of MR4 increased from 0.118 mg/kg on Day 1 to 0.221 mg/kg on Day 14 and mean total daily doses of Prograf increased from 0.112 mg/kg on Day 1 to 0.176 mg/kg on Day 14. Trough blood levels in the early transplant period were higher for Prograf-treated patients than MR4-treated patients; however, by Day 4 they were comparable.

**Table 16. Derived pharmacokinetic indices of MR4 and Prograf formulations of tacrolimus (study FG506-11-01)**

| | MR4 n = 45 | Prograf n=32 | Ratio (90% CI) |
|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| D1 | *$AUC_{0\rightarrow24}$ | 145.97 | 463.82 | 55.3% (36.9,73.8) |
| D1 | **$C_{max}$ | 10.59 | 19.75 | 53.6% (39.4, 67.8) |
| D14 | $AUC_{0\rightarrow24}$ | 324.19 | 286.99 | 113.05 (98.6, 127.4) |
| D14 | $C_{max}$ | 25.65 | 25.07 | 102.8% (84.2, 120.5) |
| D42 | $AUC_{0\rightarrow24}$ | 364.28 | 301.1 | 121.0% (89.0, 113.7) |
| D42 | $C_{max}$ | 29.2 | 28.25 | 102.4% (87.8, 117.0) |

* AUC = ng.h/mL **Cmax = ng/nL

As a secondary endpoint, biopsy-confirmed acute rejection (BCAR) was evaluated. During the first 2 weeks of the study, there were 11 cases of first biopsy-confirmed acute rejection in the Prograf group and there were 11 cases of first biopsy-confirmed acute rejection in the MR4 group. Based on the Full Analysis Set, N=62 in the Prograf group and N=67 in the MR4 group, incidences of biopsy-confirmed acute rejection were 17.7% for the Prograf group and 16.4% for the MR4 group. There were 13 cases of first biopsy-confirmed acute rejection beyond Week 2 of the study, 6 patients in the Prograf group and 7 patients in the MR4 group.

During the first 2 weeks of the study, there were three graft losses in the Prograf group and there were two graft losses in the MR4 group. There was one case of graft loss beyond Week 2 of the study in the Prograf group.

The main efficacy outcomes from Study FG-506-11-01 for MR4 and Prograf are presented below.

**Table 17 Main Efficacy Results – Study FG-506-11-01**

| | **MR4 (N=67)** | **Prograf (N=62)** |
|---|---|---|
| **Incidence** | **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 |

***Prophylaxis in Renal Transplantation***

Phase II study **FG-506E-12-01,** is an open multicentre comparison of the pharmacokinetics of tacrolimus in adult patients undergoing kidney transplantation. The study was conducted at 23 centres in Europe and Australia. Eligible patients were randomised 1:1 to a Prograf or an MR4 based immunosuppressive regimen. Kaplan-Meier estimate of freedom from biopsy-confirmed acute rejection was 86.2% and 83.1% at 6 weeks post-transplantation in the MR4 and Prograf groups, respectively. Kaplan-Meier estimated graft survival rates at Week 6 were 98.3% and 93.1% for MR4 and Prograf, respectively. There was no graft loss beyond Week 2 for the MR4-treated patients and no graft loss beyond Week 1 for the Prograf-treated patients.

In this study, patients who were being re-transplanted were eligible for inclusion; however, patients with panel reactive antibody (PRA) grade > 50% or with a history of a former graft loss due to rejection within 1 year of transplantation were excluded. Out of 129 patients in the Full Analysis Set, 6 patients were undergoing re-transplantation and 15 patients had a PRA grade > 0%. Details of acute rejection episodes and graft losses in patients undergoing re-transplantation or who had a PRA grade > 0% are presented in Table 18.

**Table 18 Study FG-506E-12-01 - Acute Rejection Episodes and Graft Losses in 'High Risk' *De Novo* Kidney Transplant Recipients**

| | Number of patients | | | | | |
|---|---|---|---|---|---|---|
| | MR4 | | | Prograf | | |
| | N | BCAR | Graft loss | N | BCAR | Graft loss |
| **Total** | 60 | 8 (13.3) | 1 (1.7) | 59 | 9 (15.3) | 2 (3.4) |
| **Re-transplant** | 4 | 0 | 0 | 2 | 0 | 0 |
| **PRA > 0%** | 10 | 0 | 0 | 5 | 2 (40.0) | 0 |
| **Re-transplant or PRA > 0%** | 11 | 0 | 0 | 7 | 2 (28.6) | 0 |

The subgroup of patients who were re-transplanted or who had positive PRA grades and who received MR4 (N=11) had 100% patient, graft and freedom from biopsy-confirmed acute rejection at 6 weeks post-transplant. The subgroup of patients who were re-transplanted or had positive PRA grades and who received Prograf (N=7) had 100% patient and graft survival at 6 weeks post-transplant; freedom from biopsy-confirmed acute rejection was 71.4%.

**Study 02-0-158** was a one-year, multi-centre, Phase III, randomised (1:1:1), open-label, comparative (Prograf/ mycophenolate mofetil [MMF], MR4/MMF or Neoral/MMF), non-inferiority trial conducted in the USA, Canada and Brazil.

METHODS

*Study Participants*

Adult and adolescent patients (at least 12 years old) undergoing first or repeat renal transplantation were eligible.

The initial dose of randomized study drug (Prograf, MR4, or Neoral) was to be administered prior to or within 48 hours of the completion of the transplant procedure. Patients unable to take the first dose of study drug orally or via a nasogastric tube within 48 hours following completion of the transplant procedure were discontinued from the study.

*Treatments*

All patients were to receive MMF and corticosteroids concomitantly with the randomized study drug. Additionally, all patients were to receive induction therapy (basiliximab). All patients received two 20 mg i.v. doses of basiliximab induction therapy and concomitant MMF and corticosteroids. Dosing of MMF was conducted according to the package insert [2003]. 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. 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. Target whole blood ciclosporin 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 an alternative primary calcineurin inhibitor regimen (either the Prograf/MMF or Neoral/MMF treatment arms) to address an adverse event which led to randomized study drug discontinuation or in the case of severe or refractory rejection. Crossover to the MR4/MMF treatment arm was not permitted.

All episodes of kidney dysfunction were to be evaluated for possible rejection after exclusion of other causes. All patients were to have biopsy confirmation of rejection episodes before treatment for rejection was begun, or within 48 hours of initiation of treatment for acute rejection. The pathologist at the clinical site was responsible for grading all biopsies using the 1997 Banff criteria. Initial rejection episodes were to be treated with oral or intravenous corticosteroids with the dose not to exceed 1 g/day

for a maximum of 3 to 5 days. Subsequently, corticosteroids were to be tapered according to institutional practice. If a patient had histologically-proven Banff Grade II or III rejection, the patient could be initiated on anti-lymphocyte antibodies (OKT3, Thymoglobulin, ATGAM) as per institutional protocol.

*Outcomes/endpoints*

- Primary endpoint was the 1-year graft failure rate as judged by the composite of death, graft failure (permanent return to dialysis or re-transplant), biopsy-confirmed acute rejection or loss to follow-up.

- Secondary endpoints:
  - 1-year patient and graft survival rates;
  - 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;
  - Number of clinically treated acute rejection episodes;
  - Incidence of treatment failure (up to 12 months);
  - Incidence of crossover for treatment failure; and,
  - Evaluation of renal function.

- SAFETY concerns of special interests: bacterial, viral, and fungal infections and gastrointestinal disturbances were summarized. Glucose intolerance was summarized for the at-risk population (patients who did not present with diabetes mellitus at baseline).

*Sample size and statistical methods*

There were two data sets for analysis:

• The full analysis set was defined as all randomized patients who received at least one dose of study drug. All safety and primary efficacy analyses were performed using this data set.

• The per protocol set was defined as all randomized patients who had no major protocol violations or other events during the study that would make the patient inevaluable.

The planned total number of patients was 660 in a 1:1:1 ratio. Estimates of the 1-year efficacy failure rate for Neoral / MMF (30%) and Prograf / MMF (25%) were used as the basis for the sample size. All assessments of non-inferiority were made using a margin of 10%.

RESULTS

*Participant flow*

Recruitment of patients and their disposition is depicted in Table 19.

**Table 19. Patient Population and Disposition.**

| Data Set | Prograf/MMF (n = 219) | MR4/MMF (n = 226) | Neoral/MMF (n = 223) | Total (n = 668) |
|---|---|---|---|---|
| All Randomized Patients | 219 (100.0%) | 226 (100.0%) | 223 (100.0%) | 668 (100.0%) |
| Full Analysis Set | 212 (96.8%) | 214 (94.7%) | 212 (95.1%) | 638 (95.5%) |
| Per Protocol Set | 209 (95.4%) | 211 (93.4%) | 209 (93.7%) | 629 (94.2%) |
| Crossover † | 6 (2.7%) | 10 (4.4%) | 39 (17.5%) | 55 (8.2%) |
| | | | | |
| **Final Disposition (Full Analysis Set)** | | | | |
| **Disposition** | **(n = 212)** | **(n = 214)** | **(n = 212)** | **(n = 638)** |
| Completed 1-year of Randomized Therapy | 179 (84.4%) | 183 (85.5%) | 151 (71.2%) | 513 (80.4%) |
| Discontinued Randomized Therapy | 33 (15.6%) | 31 (14.5%) | 61 (28.8%) | 125 (19.6%) |
| Adverse Event | 23 (10.8%) | 19 (8.9%) | 37 (17.5%) | 79 (12.4%) |
| Rejection | 0 | 1 (0.5%) | 16 (7.5%) | 17 (2.7%) |
| Non-compliance | 4 (1.9%) | 2 (0.9%) | 5 (2.4%) | 11 (1.7%) |
| Graft Failure | 3 (1.4%) | 2 (0.9%) | 1 (0.5%) | 6 (0.9%) |
| Withdrawal of Consent | 0 | 4 (1.9%) | 1 (0.5%) | 5 (0.8%) |
| Lost to Follow-up | 1 (0.5%) | 0 | 0 | 1 (0.2%) |
| Other § | 2 (0.9%) | 3 (1.4%) | 1 (0.5%) | 6 (0.9%) |

*Conduct of the study*

There were a total of 260 patients who were screened for participation in the study but were not randomised to treatment. For 76 patients, the reason for non-randomisation was 'Selection criteria not met', for 159 patients the reason for non-randomisation was 'Other', and for 25 patients the reason for non-randomisation was 'Missing'.

Altogether 668 randomised and 638 received at least one dose of study medication. Protocol deviations were observed in 9 subjects randomised to treatment: three patients from each treatment group. Overall there were no major imbalances as regards reported deviations comparing treatment groups

*Outcomes and estimation*

The principal efficacy outcome is shown in Table 20.

**Table 20 Study 02-0-158 Main outcomes.**

| | Prograf | MR4 | Neoral |
|---|---|---|---|
| ITT population | 212 | 214 | 212 |
| Male gender (%) | 64.2 | 64.5 | 61.3 |
| Mean age (sd) years | 48.6 (12.9) | 47.8 (13.0) | 47.6 (13.0) |
| Completed 1 year's treatment | 179 | 183 | 151 |
| Met primary endpoint (treatment failure) | 32 (15.1) | 30 (14.0) | 36 (17.0) |
| - death | 9 | 3 | 5 |
| - graft failure | 9 | 5 | 4 |
| - biopsy confirmed acute rejection | 16 | 22 | 29 |
| - lost to follow up | 4 | 3 | 1 |
| p value Chi-square test reference Neoral | 0.597 | 0.398 | |
| p value Chi-square test Prograf vs. MR4 | 0.753 | | |

MR4/MMF was statistically non-inferior to Neoral/MMF with regard to 1-year patient survival, graft survival and incidence of biopsy-confirmed acute rejection. Prograf/MMF was statistically non-inferior to Neoral/MMF with regard to 1-year patient survival and graft survival, and statistically superior to Neoral/MMF with regard to the 1-year incidence of biopsy-confirmed acute rejection. MR4/MMF was statistically non-inferior to Prograf/MMF with regard to 1-year incidence of biopsy-confirmed acute rejection, with a treatment difference of 2.7% (95.2% CI: -2.7% to 8.2%)

Kaplan-Meier estimates with data censored at the time of the last follow-up for patient survival, graft survival, and incidence of biopsy-confirmed acute rejection provided comparative results consistent with those obtained considering lost to follow-up as a failure.

Patients in the MR4/MMF group had significantly ($p<0.05$; two-way ANOVA) lower mean serum creatinine values at Month 12 and higher mean calculated creatinine clearance values at multiple time points compared with those in Neoral/MMF group.

Significantly fewer patients in the Prograf/MMF group ($p=0.012$, chi-square test) or the MR4/MMF group ($p=0.040$, chi-square test) received anti-lymphocyte antibody therapy for treatment of rejection compared with those in the Neoral/MMF treatment group.

Fewer patients in either the Prograf/MMF treatment group or the MR4/MMF group discontinued the study due to rejection compared with those in the Neoral/MMF treatment group (none and 0.5% versus 7.5%, $p<0.001$, chi-square test).

Significantly fewer ($p \leq 0.001$; chi-square test) patients in the MR4/MMF treatment group, or Prograf/MMF treatment group, experienced treatment failure or crossover due to treatment failure compared with patients in the Neoral/MMF treatment group.

*Ancillary analyses*

Subgroups: age (too small >65 years population), sex, sex-mismatched graft (too small population), race (too small black population); ethnicity; diabetes at baseline, donor type, and geographic region.

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 sample size of the elderly population was small, as were event rates for death and graft failure; therefore, comparisons should be made with caution.

*Sex.* A numerically higher incidence of BCAR (10.5% vs. 5.9%) was observed in females compared to males for both Prograf/MMF and MR4/MMF: the opposite was true for the Neoral/MMF treatment group. The incidence of BCAR was significantly lower for male patients in the Prograf/MMF (p-value = 0.012; chi-square test) and MR4/MMF (p-value =0.010; chi-square test) treatment groups compared to the Neoral/MMF treatment group.

*Race.*
Non-Caucasian patients were under-represented. Comparisons of the composite endpoint and the individual components of this composite endpoint in white and black transplant recipients are presented in Table 21

**Table 21: Study 02-0-158: Comparison of Efficacy Failure and Components Between White and Black Patients**

| Parameters | MR4/MMF | | Prograf/MMF | |
|---|---|---|---|---|
| | White Patients (N=160) | Black Patients (N=41) | White Patients (N=152) | Black Patients (N=51) |
| **Efficacy Failure†** | 20 (12.5%) | 8 (19.5%) | 21 (13.8%) | 11 (21.6%) |
| **Death** | 2 ( 1.3%) | 0 ( 0.0%) | 8 ( 5.3%) | 1 ( 2.0%) |
| **Graft Failure** | 4 ( 2.5%) | 1 ( 2.4%) | 4 ( 2.6%) | 5 ( 9.8%) |
| **Biopsy-confirmed Acute Rejection** | 15 ( 9.4%) | 6 (14.6%) | 11 ( 7.2%) | 5 ( 9.8%) |

† Composite endpoint of biopsy-confirmed acute rejection, graft failure and death.

*Diabetes.* 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. The incidence of death for patients who did not have diabetes at baseline was significantly higher (9/152, 5.9% vs 2/154, 1.3%; p-value = 0.030; chi-square test) in the Prograf/MMF treatment group compared to the Neoral/MMF treatment group.

*Donor type.* 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. In patients who received grafts from a deceased donor, the efficacy failure rate was numerically lower in the Prograf/MMF and MR4/MMF treatment groups and the incidence of BCAR was significantly lower in the Prograf/MMF (p-value = 0.006; chi-square test) and MR4/MMF (p-value = 0.015; chi-square test) treatment groups compared with the Neoral/MMF treatment group. It should be noted that event rates for death and graft failure were low; therefore, comparisons should be made with caution.

*Geography.* Efficacy failure rates were numerically higher in Brazilian patients who received Prograf/MMF (6/30, 20% vs 26/182, 14%) or MR4/MMF (5/31, 16.1% vs. 25/183, 13.7%) compared to patients in the US and Canada. The efficacy failure rate was similar for both cohorts in the Neoral/MMF treatment group. There was a significantly (4/30, 13.3% vs 5/182, 2.7%; p-value = 0.038; chi-square test) higher incidence of graft failure for Brazilian patients who received Prograf/MMF compared with those who received Neoral/MMF.

*High-risk population.*
Out of 426 patients who received MR4 or Prograf, 15 patients were undergoing re-transplantation and 53 patients had a panel reactive antibody (PRA) grade > 0%. The subgroup of patients who were re-transplanted and who received MR4 (N=8) had 100% patient and graft survival at 1 year post-transplant; freedom from biopsy-confirmed acute rejection was 75.0%. The subgroup of patients with PRA grade > 0% and who received MR4 (N=27) included 1 patient with graft failure at 1 year post-transplant; freedom from biopsy-confirmed acute rejection was 77.8%. The subgroup of patients who were re-transplanted and who received Prograf (N=7) had 100% patient and graft survival and freedom from biopsy-confirmed acute rejection at 1 year post-transplant. The subgroup of patients with PRA grade > 0% and who received Prograf (N=26) included 2 patients with graft failure at 1 year post-transplant; freedom from biopsy-confirmed acute rejection was 92.3%.

Although the number of 'high risk' patients included in the clinical studies performed with MR4 to-date was relatively low, there was no indication of reduced efficacy for MR4 in these patients. A warning has been added to SPC section 4.4, stating the limited experience in patients at elevated immunological risk.

***Conversion from twice daily Prograf to once daily MR4 in transplant recipients***

Clinical development programme of conversion from twice daily Prograf to once daily MR4 in transplant patient included five adult Phase II studies (N=339) performed in ***stable*** (at least 6 months post transplant): adult kidney (three studies: 02-0-131, FG-506E-12-02, and FJ-506E-KT01, Japan study), liver (study 02-0-152) and heart (study FG-506-15-02) transplant recipients. These studies

were 2 to 12 weeks PK evaluation studies, without primary efficacy endpoint (but one, Japan study). Incidences of acute rejection, and patient and graft survival were captured as safety parameters. Three studies relevant for claimed indication have planned 1 to 3 year long-term extension periods: two kidney studies (02-0-131 and FG-506E-12-02, as a FG-506E-14-02) and liver study (02-0-152).

**Study FG-506E-12-02.** This was a 4-period crossover replicate design, comparative study performed in stable, adult Kidney transplant recipients (at least 6 months post-transplant) evaluated the equivalence of tacrolimus exposure (AUC0-24) for MR4 versus Prograf under steady state conditions. Mean oral daily doses were comparable among groups. The mean whole blood trough concentrations were lower in the MR4 treatment periods than in the Prograf treatment periods (6.4 ng/mL vs 7.7 ng/mL at Day 7).

**Study FG-506E-14-02:** This was a multi-centre, open-label, prospective, single-arm study to assess the safety and efficacy of MR4 as long term treatment in converted kidney transplant patients. Patient survival and graft survival ($\geq$ 1 year) with MR4 were consistent across all conversion studies, ranging from 97% to 100%. There were no biopsy-confirmed acute rejections in Study FG506E-12-02; in Study 02-0-131, also performed in stable kidney transplant recipients converted from Prograf to MR4, the incidence of biopsy-confirmed acute rejection at 2 years post-conversion was 6.0% (4/67 patients).

In **Study 02-0-152**, performed in stable liver transplant recipients, the incidence of biopsy-confirmed acute rejection at 2 years post-conversion was 5.8% (4/69 patients). The incidence of biopsy-confirmed acute rejection in stable heart transplant recipients (Study FG-506-15-02) was 3.8% (3/79 patients). Efficacy was 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.

In summary, across the conversion studies, tacrolimus trough levels remained stable in studied population after conversion to MR4 and the majority of patients remained at their original 'conversion' dose level long-term. Where dose changes were performed these were usually small dose corrections of approximately 1 mg/day.

***Rescue therapy***

There have been *no studies* performed with MR4 to investigate the treatment of rejection in transplant recipients; however, since tacrolimus is the active substance in MR4 and Prograf, mechanism of action is the same and since the therapeutic equivalence of Prograf and MR4 has been demonstrated in kidney, liver and heart transplantation, it is proposed to expect that MR4 is safe and effective in the treatment of rejection in these indications at similar doses and MR4 is expected to be therapeutically equivalent in these indications at similar doses.

- Discussion on clinical efficacy

The applicant has demonstrated in a Phase III trial in renal transplantation that tacrolimus in its Prograf and MR4 formulations are therapeutically equivalent as prophylaxis in *de novo* renal transplantation. Ideally, it might have been desirable to demonstrate such equivalence in Phase III trials in all organ transplant situations in which a therapeutic indication is sought. However, sound evidence was provided that the exposure (AUC) generated by the two formulations is almost equivalent on a milligram for milligram basis in adult cardiac and liver transplantation and renal transplantation. It is therefore highly unlikely that there would be differences in clinical safety or efficacy in such settings and the PK data are accepted as a valid surrogate.

**Clinical safety**

The active substance in MR4, tacrolimus, is identical to that in the established formulation, Prograf. Consequently, the approach to assess the safety profile of MR4 administered to transplant recipients was to compare against the established safety profile for Prograf.

- Patient exposure

Three hundred and forty-one patients received MR4-based immunosuppression in *de novo* kidney and liver transplantation studies. A further 348 patients (including 19 paediatric patients) were converted from Prograf-based immunosuppression to MR4-based immunosuppression (kidney, liver and heart transplantation). Two hundred and forty-two healthy volunteers received MR4 during Phase I studies. The number of patients and details of the principal MR4 studies contributing safety data are tabulated below.

**Table 21: Patient exposure (principal studies)**

| 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;

The principal source of safety data under "therapeutic use" conditions is study 02-0-158. An overview of the safety profile of that study is presented below.

**Table 22: Overview of Safety Events in MR4 Studies**
Overview of Safety Events in MR4 Studies (158)

| Event | MR4 + MMF n = 214 | | Prograf + MMF n = 212 | | Neoral +MMF n = 212 | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Any treatment-emergent adverse event | 214 | (100) | 212 | (100) | 210 | (99.1) |
| Drug-related treatment emergent adverse events (>5% incidence) | 129 | (60.3) | 135 | (63.5) | 132 | (62.3) |
| Severe of life threatening treatment emergent adverse events (>1% incidence) | 71 | (33.2) | 67 | (31.6) | 68 | (32.1) |
| **Adverse event leading to discontinuation** | 19 | (8.9) | 23 | (10.8) | 37 | (**17.5**) |
| Serious adverse events | 97 | (45.3) | 110 | (51.9) | 111 | (52.4) |
| Treatment emergent serious AE not resulting in death (>1% incidence) | 97 | (45.3) | 109 | (51.4) | 110 | (51.9) |
| Deaths during randomized therapy | 0 | (0) | 0 | (0) | 2 | (0.9) |
| Deaths (including after discontinuing therapy) | 3 | (1.4) | 10 | (**4.7**) | 6 | (2.8) |
| Deaths (>10 days after discontinuing therapy) | 2 | (0.9) | 4 | (1.9) | 2 | (0.9) |

Overall, the incidence of treatment-emergent adverse events considered by the investigator to be related (possible, probable, definite) to both primary study drug and MMF and to primary study drug only was similar among the three treatment groups. Any notable differences in the incidence of adverse events considered by the investigator to be related to both primary study drug and MMF (e.g., diarrhea, tremor) and primary study drug only (tremor, diabetes mellitus, hyperlipidaemia) were not unexpected and consistent with the safety profiles for Prograf and Neoral.

- Adverse events

Summary of treatment-emergent adverse events with an incidence difference ≥ 5% or statistically significant difference between Prograf/MMF and MR4/MMF treatment groups (Study 02-0-158) is presented below.

**Table 23: Study 02-0-158: Adverse events with an incidence difference ≥ 5% or statistically significant difference between Prograf/MMF and MR4/MMF treatment groups**

| MedDRA (v. 6.1) | Treatment Group | | |
|---|---|---|---|
| System Organ Class | Prograf/MMF | MR4/MMF | p-value† |
| Preferred Term | (n = 212) | (n = 214) | |
| **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 |

ITT population †Fisher's exact test ; *significance at 0.05; *** significance at 0.001.

- Serious adverse event/deaths/other significant events

A summary of the incidence of mortality in Study 02-0-158 is presented in Table 24 and treatment emergent serious adverse events in Table 25. Approximately 21% to 23% of the patients in each treatment group experienced a treatment-emergent serious adverse event considered by the investigator to be related to primary study drug. The overall incidence of serious adverse events was similar among the three treatment groups, and was consistent with the established safety profile of tacrolimus and ciclosporin.

**Table 24 Study 02-0-158: Summary of incidence of mortality**

| Patient Status | Treatment Group | | | |
|---|---|---|---|---|
| | Prograf/MMF (n = 212) | MR4/MMF (n = 214) | Neoral/MMF (n = 212) | Total (n = 638) |
| Total | 10 (4.7%) | 3 (1.4%) | 6 (2.8%) | 19 (3.0%) |
| Died during randomised therapy | 0 | 0 | 2 (0.9%) | 2 (0.3%) |
| Died after discontinuing randomised therapy† | 10 (4.7%) | 3 (1.4%) | 4 (1.9%) | 17 (2.7%) |

Patient base: Full analysis set; all randomised patients who received at least one dose of study drug.

**Table 25 Study 02-0-158: Summary of most frequently reported treatment-emergent serious adverse events considered to be related to primary 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 | 49 (23.1%) | 45 (21.0%) | 45 (21.2%) |
| **Infections and Infestations** | | | |
| Cytomegalovirus Infection | 9 (4.2%) | 5 (2.3%) | 5 (2.4%) |
| Human Polyomavirus Infection | 4 (1.9%) | 1 (0.5%) | 0 (0.0%) |
| Sepsis | 3 (1.4%) | 2 (0.9%) | 1 (0.5%) |
| Urosepsis | 3 (1.4%) | 1 (0.5%) | 0 (0.0%) |
| Gastroenteritis | 0 (0.0%) | 4 (1.9%) | 0 (0.0%) |
| Urinary Tract Infection | 0 (0.0%) | 3 (1.4%) | 3 (1.4%) |
| **Metabolism and Nutrition Disorders** | | | |
| Diabetes Mellitus | 2 (0.9%) | 5 (2.3%) | 2 (0.9%) |
| Hyperglycaemia | 2 (0.9%) | 3 (1.4%) | 0 (0.0%) |
| **Injury, Poisoning, and Procedural Complications** | | | |
| Therapeutic Agent Toxicity | 4 (1.9%) | 2 (0.9%) | 1 (0.5%) |
| Graft Dysfunction | 3 (1.4%) | 1 (0.5%) | 1 (0.5%) |
| **Investigations** | | | |
| Blood Creatinine Increased | 7 (3.3%) | 4 (1.9%) | 6 (2.8%) |
| **Renal and Urinary Disorders** | | | |
| Renal Failure Acute | 1 (0.5%) | 3 (1.4%) | 1 (0.5%) |
| **Blood and Lymphatic System Disorders** | | | |
| Anaemia | 3 (1.4%) | 0 (0.0%) | 1 (0.5%) |

Patient base: Full Analysis Set; all randomised patients who received at least one dose of study drug

- Laboratory findings

Generally, the clinical laboratory findings were consistent with the clinical laboratory findings observed in transplant recipients administered Prograf.

- Discontinuation due to adverse events

A summary of treatment-emergent adverse events leading to discontinuation of primary randomised treatment in Study 02-0-158 is provided in Table 26.

**Table 26 Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Primary Randomised Treatment**

| | Treatment Group | | |
|---|---|---|---|
| | **Prograf/MMF (n = 212)** | **MR4/MMF (n = 214)** | **Neoral/MMF (n = 212)** |
| Any Adverse Event that Led to Discontinuation | 23 (10.8%) | 19 (8.9%) | 37 (17.5%) |
| Related to Study Drug – Overall | 15 (7.1%) | 14 (6.5%) | 25 (11.8%) |
| Related to Primary Study Drug Only | 9 (4.2%) | 9 (4.2%) | 22 (10.4%) |
| Related to Primary Study Drug and MMF | 6 (2.8%) | 6 (2.8%) | 4 (1.9%) |

The incidence of adverse events leading to discontinuation of treatment was significantly greater in the Neoral group than the MR4 group (p = 0.010; Fisher's exact test) and numerically greater than the Prograf group. The most common treatment-emergent adverse events leading to discontinuation were nephropathy toxic (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 (3/212; 1.4% Neoral and 2/214, 0.9% MR4 groups)

- Post marketing experience

To date MR4 has not been approved or marketed anywhere worldwide; however, tacrolimus is approved in more than 70 countries for use in organ transplantation and has been on the market for more than 10 years. Since the first marketing authorisation, experience with the intravenous and Prograf capsule formulations of tacrolimus has been extensive, both through exposure to the marketed product and through clinical studies; e.g. in the period April 2004 to March 2005 the exposure to tacrolimus was estimated as 210,000 patient years worldwide.

All safety information is presented using the MedDRA terminology, and Prograf G-CCSI 4.0 as a basis. Section 4.8 (Undesirable Effects) of the proposed Summary of Product Characteristics (SPC) for MR4 in Europe are listed in MedDRA and summarises the data on safety.

- Discussion on clinical safety

MR4 is a reasonably well tolerated with two main types of ADRs: (1) those caused by (over)-immunosuppression and (2) those caused by drug toxicity that are mainly dose dependent. Safety database for tacrolimus is quite comprehensive. Maintenance of whole blood concentrations within therapeutic range improves clinical safety of tacrolimus. MR4 clinical development encompasses an additional safety experience of dual therapy using MMF as concomitant drug.

## Pharmacovigilance

### Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

### Risk Management Plan

The MAA submitted a risk management plan.

**Summary of the risk management plan for Advagraf 0.5 mg / 1 mg / 5 mg prolonged-release hard capsules**

| Safety concern | Proposed pharmacovigilance activities | Proposed risk minimisation activities |
|---|---|---|
| Potential medication errors due ro confusion between this once daily formulation of tacrolimus with the twice daily formulation, Prograf(t) | • Routine pharmacovigilance | • Different capsule appearance (colour and imprint)<br>• Indication of correct use "once daily" in product information (SPC, package leaflet, box, blister and aluminium wrapping) |
| Off-label use | | The proposed MR4 SPC indicates in Section 4.4 "Special warnings and precautions for use" that due to the lack of data, MR4 should not be used for the treatment of children and as primary therapy in heart transplant recipients |
| Interactions with other medications and herbal preparations | | Warnings in Section 4.4 and 4.5 of the SPC. |
| Hypertension, cardiac arrhythmias, neurological and visual disorders, diabetogenicity, electrolyte changes, hepatic and renal dysfunction, blood cell changes, coagulopathies | • Routine pharmacovigilance | Warnings and Section 4.4 of the proposed MR4 SPC as follows:<br>During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.<br><br>Mentioned in section 4.8 of the SPC |
| Ventricular hypertrophy, cardiomyopathies | • Routine pharmacovigilance | Warnings in Section 4.4 of the proposed MR4 SPC as follows:<br>Ventricular hypertrophy or hypertrophy of the septum reported as cardiomyopathies, have been observed in Prograf treated patients on rare occasions and may therefore also occur with Advagraf. Most cases have been reversible, occurring with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at 3 months and then at 9 to 12 months). If |

| | | |
|---|---|---|
| | | abnormalities develop, dose reduction of MR4 therapy, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for causing Torsades de Pointes. Caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome.<br><br>Mentioned in section 4.8 of the SPC |
| Diarrhoea | • Routine pharmacovigilance | Warnings in Section 4.4 of the proposed MR4 SPC as follows:<br>Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea.<br>Mentioned in section 4.8 of the SPC |
| Neoplasms | • Routine pharmacovigilance | Warnings in Section 4.4 of the proposed MR4 SPC as follows:<br>As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see Section 4.8).<br>As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.<br>Mention in section 4.8 of the SPC |
| EBV-associated lymphoproliferative disorders | • Routine pharmacovigilance | Statement in Section 4.4 of the proposed MR4 SPC as follows:<br>Patients treated with tacrolimus have been reported to develop EBV-associated lymphoproliferative disorders. A combination of immunosuppressives such as antilymphocytic antibodies given concomitantly increases the risk of EBV-associated lymphoproliferative disorders. EBV-viral capsid antigen (VCA)-negative patients have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with Advagraf. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma.<br>Mention in section 4.8 of the SPC. |
| Pregnancy | • Routine pharmacovigilance | Statement in Section 4.6 of the proposed MR4 SPC as follows:<br>Human data show that tacrolimus crosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse events on the course and |

| | | |
|---|---|---|
| | | outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. To date, no other relevant epidemiological data are available. Tacrolimus treatment can be considered in pregnant women, when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus. In case of *in utero* exposure, monitoring of the newborn for the potential adverse events of tacrolimus is recommended (in particular the effects on the kidneys). There is a risk for premature delivery (<37 week) as well as for hyperkalaemia in the newborn. |
| Lactation | • Routine pharmacovigilance | Statement in Section 4.6 of the proposed MR4 SPC as follows:<br>Human data demonstrate that tacrolimus is excreted in breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving Advagraf. |

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

## 5 Overall conclusions, risk/benefit assessment and recommendation

**Quality**
The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

**Non-clinical pharmacology and toxicology**
The active substance, tacrolimus, belongs to the pharmacological class of calcineurin inhibitors and originally derives from the fungus streptomyces tsukubaensis: it has a macrolide structure. Advagraf is a new oral formulation of tacrolimus with prolonged-release characteristics compared to the currently authorised product Prograf(t). No new preclinical studies were undertaken with the new formulation. The toxicity of tacrolimus has previously been well established with the organs of toxicity identified. As regards reproductive potential adverse effects, pre-clinical reproductive studies of tacrolimus suggest the possibility of a detrimental effect on male and female reproduction. An appropriate warning has been added to the SPC.

**Efficacy**
The applicant has demonstrated that the prolonged release MR4 formulation is exchangeable for the Prograf formulation on a weight for weight basis. In a repeat dose situation it gives a slightly lower Cmax and AUC than Prograf dosed twice daily but there is less diurnal variation in drug level. One Phase III study in renal transplantation shows therapeutic equivalence between the two formulations, and pharmacokinetic data in other organ transplantations are used to extrapolate to similar efficacy.

**Safety**
The safety of the prolonged released formulation of tacrolimus is consistent with that known for the Prograf formulation.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

- Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

User testing has been performed on the Patient Information Leaflet and from the results it can be concluded that the relevant information is accessible and understandable for the patients.

**Risk-benefit assessment**
The benefit risk of Prograf prolonged released hard capsules is considered as positive. It has an efficacy and safety profile comparable to the widely used immediate release formulation and offers an advantage in the convenience of once daily rather than twice daily dosing.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

**Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Advagraf in: "Prophylaxis of transplant rejection in adult kidney or liver allograft recipients. Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients", was favourable and therefore recommended the granting of the marketing authorisation.