European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/306253/2009

ASSESSMENT REPORT
FOR

Modigraf

International Nonproprietary Name: **tacrolimus**

Procedure No. EMEA/H/C/000954

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Astellas Pharma Europe B.V. submitted on 27 November 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Modigraf, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 19 July 2007. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application, for a known active substance.

The applicant applied for the following indication prophylaxis of transplant rejection (liver, kidney and heart) and treatment of allograft rejection.

Licensing status:
The product was not licensed in any EEA country at the time of submission of the application.
Modigraf has been given a Marketing Authorisation in Japan on 12 January 2001 under the name Prograf granules.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Tomas P Salmonson	Co-Rapporteur :	Romaldas Maciulaitis

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 27 November 2007.
- The procedure started on 26 December 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 March 2008.
- During the meeting on 21-24 April 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 April 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 October 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 28 November 2008.
- During the CHMP meeting 15-18 December 2008 the CHMP agreed on a List of Outstanding Issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the written responses to the CHMP List of Outstanding Issues on 16 February 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 2 March 2009.
- During the CHMP meeting 16-19 March 2009, the CHMP based the applicant’s written responses to the List of Outstanding Issues considered that an oral explanation was no longer necessary.
- During the meeting on 16-19 March 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Modigraf on 19 March 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 March 2009.

- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 15 May 2009.

2 SCIENTIFIC DISCUSSION

2.1 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.
Modigraf contains the active substance tacrolimus, which is a macrolide lactone with a potent immunosuppressive activity. 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.
Modigraf is a granule formulation of tacrolimus, as 0.2 mg and 1 mg sachets. The composition of the granule formulation is based on the composition of the intermediate granule formulation which is used in the manufacture of the established immediate release capsule formulation of Prograf capsules 0.5, 1 and 5 mg. A granule formulation was launched in Japan 2001 for use in paediatric and adult solid organ transplantations. These granules are identical to those in the present application.

In lack of an approved oral formulation suitable for children and for seriously ill adults with difficulties to swallow capsules, there has been a widespread off-label clinical practice to break the Prograf capsules and use the granules. The granules have been used for preparation of a water dispersion, for swallowing or for administration via a (non-polyethylene) nasogastric tube.
In current clinical practice the oral formulations of available calcineurin inhibitors, cyclosporine and tacrolimus are generally administered on a twice daily basis. After having obtained marketing authorization for tacrolimus (capsules and solution for i.v. infusion), the company engaged in therapy optimisation for paediatric patients, investigating combination therapies, aiming for steroid-avoidance and side-effect minimization strategies, as well as in development in a dosage formulation suitable for small children unable to swallow intact capsules. To this end an oral granule formulation of tacrolimus for suspension was developed by the Applicant to provide a dosing formulation suitable for paediatric transplant recipients, and to provide a formulation that allows fine dose adjustments. This granule formulation was approved and launched in Japan in 2001.

2.2 Quality aspects

Introduction

Tacrolimus is a product of fermentation of Streptomyces tsukubaensis, which is not yet subject of a pharmacopoeial monograph, Ph.Eur. or other national pharmacopoeia. Its chemical name is (-)-(1*R*, 9*S*, 12*S*, 13*R*, 14*S*, 17*R*, 18*E*, 21*S*, 23*S*, 24*R*, 25*S*, 27*R*)-17-Allyl-1, 14-dihydroxy-12-[(*E*)-2[(1*R*, 3*R*, 4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylvinyl]-23, 25-dimethoxy-13, 19, 21, 27-tetramethyl-11, 28-dioxa-4-azatricyclo-[22.3.1.$0^{4.9}$] octacos-18-ene-2,3,10,16-tetrone hydrate corresponding to the molecular formula of $C_{44}H_{69}NO_{12} \cdot H_2O$ and having a Relative Molecular Mass of 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.

Active Substance

- 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 manufacturing method, Method I. Commercial batches have been manufactured by 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 II).
b) Extraction and purification: The fermentation broth is extracted and filtered. Tacrolimus is purified by chromatography and crystallized. In the current manufacturing method, the introduction of new adsorbents for chromatography and new devices resulted in higher efficiency of purification and reduced environmental impact compared to previous methods employed. In addition, a non-polar crystallisation solvent system increased the efficiency of crystallisation process. However, the final crystallisation solvent system at the final step remained unchanged to obtain drug substance of the same physicochemical properties as that manufactured by other methods utilized in the past. 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 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 manufacturing (I and II) are assayed under slightly different GC conditions.
Batch results from 3 batches manufactured by the current method (Method II) and from a number of batches manufactured by the previous method 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.

- Stability

Stability tests for Tacrolimus drug substance were performed on three pilot scale batches and three process validation production scale batches manufactured by the current manufacturing method. Long-term and accelerated stability data the six above batches are available up to 36 months and 6 months, respectively. Additionally, long-term and accelerated stability data for up to 36 months and up to 6 months respectively for three production scale batches manufactured with the previous method were presented as supportive data All results at storage conditions of 25°C/60% RH over a period of up to 36 months met the specification. No significant change of any test parameter compared with initial

values was detected. No new impurities or new degradation products were observed. After 6 months storage at 40°C/75% RH also no significant change of any test parameter compared with initial values was detected.
Light stability studies were performed on the tacrolimus drug substance as per ICH guidelines. Tacrolimus stored on a Petri dish under luminous light of 1000 lux over a period of 50 days meet the requirements of the specification, without detecting any significant change of any test parameter.
In acidic and alkaline suspension conditions, the same major decomposition product was observed in both conditions.
Stressed studies
The degradation pathway of tacrolimus and its related substances was investigated under stress testing conditions (high temperature, light exposure, oxidation, acid and alkaline treatment).
Degradation products of tacrolimus at high temperature (90ºC for 10 days) could not be found by HPLC, even if the decomposition percentage of tacrolimus proceeded to around 10%. However, numerous breakdown products were observed as a broad band on TLC chromatogram. As a result, tacrolimus were assumed to produce numerous breakdown products, less than 1% each, under extremely high temperature.
Tacrolimus drug substance is very stable in solid state at accelerated stability testing (40°C/75% RH, 6 months) as well as long-term stability (30°C / 36 months). None of degradation products was detected on HPLC chromatograms as well as on TLC chromatograms. It can be considered that the degradation products formed at high temperatures would not be generated during usual conditions for transportation and storage.

Considering all the data presented, the proposed re-test period is deemed justified when the bulk drug substance is stored in the proposed packaging material and conditions.

Medicinal Product

- Pharmaceutical Development

The aim of the development program was to develop an oral dosage form, which guarantees a fast and complete release of the practically water insoluble tacrolimus drug substance.
During the development of the oral solid dosage form of tacrolimus nine formulations of three types of dosage forms were studied (aqueous solutions, non-aqueous solutions and solid forms). The solid dispersion formulation (SDF) based formulation was determined to be the optimal formulation of tacrolimus for oral administration. Since this SDF was already used in the manufacture of the established Prograf capsules, a complete pharmaceutical development program was considered as not necessary, because all relevant investigations on the SDF were already performed and completed in relation to the development of the established Prograf capsules which are already commercially available for years.
Modigraf tacrolimus granule formulation is based on the composition of the intermediate granules (*Solid Dispersion Formulation or SDF*) used in the manufacture of the marketed immediate release capsule formulation of Prograf 0.5 mg, 1 mg and 5 mg capsules
The development of the appropriate oral dosage form was concentrated on increasing bioavailability of active ingredient through improvement of the solubility as well as the dissolution rate of tacrolimus from the formulation. This was achieved by dissolving the crystalline tacrolimus and then applying it in amorphous form onto a carrier mixture. By doing so, the apparent solubility was improved by a factor of 20 resulting from a dramatic surface enlargement. Since the drug substance is dissolved, the particle size of the tacrolimus drug substance needs not to be considered.
A solid dispersion formulation was selected as an oral dosage form and the following excipients were used: hydroxypropyl methylcellulose, lactose monohydrate, croscarmellose sodium and ethanol dehydrated.
It was further demonstrated that tacrolimus existed as the amorphous form in SDF.
The composition of clinical batches of tacrolimus granules which were used in clinical trials complies with the composition of finished product in pharmaceutical development.
There is no overage of the active drug substance or any other ingredient to compensate for losses during the production processes for SDF or tacrolimus granules. However, in the filling process of the 0.2 mg sachets there is an overfill of 1.4 % added to ensure the withdrawal of the labelled content of

0.2 mg tacrolimus from the sachet. The remaining amounts of tacrolimus granules in the sachets have been calculated and results justify the overfill.

- Adventitious Agents

Lactose monohydrate manufacturer has presented a TSE statement confirming the compliance with the relevant guidelines.
Tacrolimus drug substance manufacturer Astellas Pharma Inc. has presented a TSE statement confirming the compliance with the relevant guidelines.

- Manufacture of the Product

The manufacturing process comprises kneading, drying and sizing to form intermediate granules which are then filled into the sachets.

- Product Specification

The specifications of the drug product at release and shelf-life include tests for appearance (visual), identity (TLC, HPLC), assay (HPLC), content uniformity (Ph.Eur.), related substances (HPLC), dissolution (Ph.Eur.), microbial limit tests (USP).
Batch results are given for four production scale batches of each strength tested according to the specification. All results comply with the specifications, confirm consistency of the product and support the specification acceptance criteria.

- Stability of the Product

The major stability data consists of 18 months data at long term conditions for one batch of each strengths of granulae with the current intermediate SDF. No data at accelerated conditions are available. All results comply with the specifications after 6 months at long term conditions 25 °C / 60% RH.
Supportive stability studies have been submitted for granulae including the former intermediate with a different particle size. Long term stability data (25 °C/ 60 % RH) up to 39 months is available for 3 production scale batches of each strength. 6 months stability data at accelerated conditions (40°C / 75 % RH) is also available.
Generally, accelerated studies on the current granules should have been provided. However, the shelf life of the current granule is considered sufficiently supported by the presented data and the overall experience acquired on tacrolimus.
<u>In use stability</u>
The in use stability of Modigraf in mineral water and tap water and in the beverages orange juice, apple juice, milk and apple sauce has been examined. Suspensions were stored at room temperature (23°C to 28°C) under fluorescent light (about 500 lux) for 6 hours. All results for the parameters tested complied with the specifications after 6 hours.

In conclusion the proposed shelf life and storage conditions are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Modigraf granules for oral suspension is adequately established. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented. 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.

2.3 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 national 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

Immunosuppressive drugs such as ciclosporin and tacrolimus act by inhibiting calcineurin activity. The mechanism of action seems to involve binding to a specific protein (immunophilin) that subsequently blocks calcineurin leading to inhibition of translocation of the cytosolic activation factor (NF-ATc) to the nucleus. Calcineurin is a phosphatase that activates many transcription factors involved in cytokine transcription, including the upregulation of the mRNA for IL-2 in T lymphocytes. Tacrolimus has shown activity in various animal models of organ transplantation including heart, liver, kidney, lung and small bowel. The ubiquitous tissue distribution of calcineurin indicates that inhibitors may alter a variety of biochemical processes apart form immunosuppression. This property may also account for adverse effects coupled to therapy with this type of immunosuppressants.

Pharmacokinetics

No new pharmacokinetic data have been submitted. Available data are sufficient to adequately characterise the pharmacokinetics of tacrolimus. These include low, variable oral absorption, the low bioavailability being attributed to extensive metabolism by liver and gut, P-glycoprotein mediated drug efflux, and influence of intake of food. Tacrolimus is highly bound to proteins, shows rapid and extensive distribution with high amounts detected in the spleen, mesenteric node, thymus, small intestine, skin and brown fat. Metabolism is extensive and proceeds mainly via hydroxylation and demethylation. Tacrolimus is excreted via faeces and unchanged drug accounted for less than 2 % of excreta. The compound has the potential to interact with other drugs and this issue is dealt with in the clinical section.

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

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 granule formulation (Modigraf) would be considered to represent an equal safety concern and the proposed wordings in the SPC are considered to adequately address these concerns.

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).

Ecotoxicity/environmental risk assessment

The use of tacrolimus granules is not expected to lead to any significant increase in environmental exposure. However, considering the currently applicable guideline, the potential environmental risk should be further addressed. This can be done as a follow up measure.

Discussion on the non-clinical aspects

The pharmacology of the granule formulation of tacrolimus (Modigraf) 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.

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 granule formulation (Modigraf) would be considered to represent an equal safety concern and the proposed wordings in the SPC are considered to adequately address these concerns.

The potential environmental risk should be further addressed (FUM).

2.4 Clinical aspects

Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. Studies conducted before 1996 were performed according to regional clinical practice requirements at that time.

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

- Absorption

In man, tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Following oral administration of capsules C_{max} of tacrolimus in blood are achieved in approximately 1 - 3 hours. In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile. The mean oral bioavailability of tacrolimus is in the range of 20% - 25%. After oral administration (0.30 mg/kg/day) to liver transplant patients, steady-state concentrations were achieved within 3 days in the majority of patients. In healthy subjects, 0.5 mg,

1 mg and 5 mg hard capsules have been shown to be bioequivalent, when administered as equivalent dose. The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases both rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced. In stable liver transplant patients, the oral bioavailability was reduced when it was administered after a meal of moderate fat (34% of calories) content. Decreases in AUC (27%) and C_{max} (50%), and an increase in T_{max} (173%) in whole blood were evident. In a study of stable renal transplant patients who were administered tacrolimus immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12%) and C_{max} (15 to 38%), and an increase in T_{max} (38 to 80%) in whole blood were evident.

Bile flow does not influence the absorption. A strong correlation exists between AUC and whole blood trough levels at steady-state. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

- Distribution

The disposition of tacrolimus after intravenous infusion may be described as biphasic. In the systemic circulation, tacrolimus binds strongly to erythrocytes resulting in an approximate 20:1 distribution ratio of whole blood/plasma concentrations. In plasma, tacrolimus is highly bound (> 98.8%) to plasma proteins, mainly to serum albumin and α-1-acid glycoprotein. Tacrolimus is extensively distributed in the body. The steady-state volume of distribution based on plasma concentrations is approximately 1300 l (healthy subjects). Corresponding data based on whole blood averaged 47.6 l.

- Elimination

Tacrolimus is a low-clearance substance. In healthy subjects, the average total clearance estimated from whole blood concentrations was 2.25 l/h. In adult liver, kidney and heart transplant patients, values of 4.1 l/h, 6.7 l/h and 3.9 l/h, respectively, have been observed. Paediatric liver transplant recipients have a total clearance approximately twice that of adult liver transplant patients. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of tacrolimus, or corticosteroid-induced increased metabolism, are considered to be responsible for the higher clearance rates observed following transplantation. The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood is approximately 43 hours. In adult and paediatric liver transplant patients, it averaged 11.7 hours and 12.4 hours, respectively, compared with 15.6 hours in adult kidney transplant recipients. Increased clearance rates contribute to the shorter half-life observed in transplant recipients.

- Excretion

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

- Metabolism

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

- Interactions

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

- Effect of tacrolimus on the metabolism of other medicinal products

Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolised by CYP3A4 may affect the metabolism of such medicinal products. The half-life of ciclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporin and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin. Tacrolimus has been shown to increase the blood level of phenytoin.

As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures. Limited knowledge of interactions between tacrolimus and statins is available. Clinical data suggest that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus. Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine.

New pharmacokinetic data in support of the present application

Two relevant new PK studies have been presented in support of the application:

- a single Phase I study (Study 95-0-001) to compare the bioequivalence of tacrolimus immediate-release capsules (Prograf) and tacrolimus granules in healthy subjects
- a Phase II study (FG-506-01-08) was conducted to assess the safety, efficacy and pharmacokinetics of tacrolimus granules in children undergoing liver allograft transplantation

Study **95-0-001** was a single dose, four-period, four-sequence, randomised crossover, replicate design study. It was performed to determine the bioequivalence of tacrolimus granular and capsule formulations (1 mg) when administered as single, oral 5 mg doses. The pivotal bioequivalence study was performed already 1995, however, the applicant has reassured that the results are representative for the present formulations.

Thirty-two healthy subjects were enrolled with 30 subjects completing all four periods. Tacrolimus was administered following an overnight fast, and tacrolimus whole blood concentrations were determined up to 72 hours post-dose. Eight subjects returned to receive an intravenous infusion of tacrolimus to enable estimation of oral bioavailability.

Following single dose administration, the capsule and granular formulation were not bioequivalent as the confidence intervals for the mean ratios of C_{max} and AUC did not fall within the bioequivalence limits. The data was consistent throughout the study and the granular formulation resulted in 23 % and 18 % greater means for C_{max} and AUC, respectively. The corresponding 90 % confidence intervals were 15-31 and 8-28, respectively. Intraindividual variability was approximately 15 % and 20 % for Cmax and AUC, respectively, for both formulations. The corresponding figures on interindidual variability were 30-50 %.

The observed difference in AUC between the two formulations in study 95-0-001 is unexpected and was to be explained at day 120. One possible explanation given by the applicant is that when Modigraf

granules are suspended in water, a small amount of tacrolimus is solubilised in vitro prior to intake. Thus, when administered orally, the solubilised tacrolimus is immediately absorbed, resulting in a more rapid rate of absorption with a higher C_{max} and shorter T_{max} compared to the Prograf formulation. This may also explain the higher extent of absorption of tacrolimus from the granule formulation as this scenario could also lead to a larger saturation of the first pass effect compared to what is observed following administration of Prograf.

During the assessment rounds, the clinical relevance of the 18 % difference in AUC between Prograf and Modigraf, in the context of the proposed 1:1 mg switch, was thoroughly discussed. It is deemed that difference in exposure is acceptable given the rather strict and informative SPC text on conversion. Subjects will be under close supervision and monitoring of whole blood tacrolimus levels within a week will ensure a transient state, if any, on an incorrect dose. A phase IV study to monitor safety and efficacy in stable paediatric allograft recipients is suggested by the applicant as FUM.

Study **FG-01-08** was an open label, pilot, non-comparative study of tacrolimus granules in paediatric patients who were undergoing primary liver transplantation. Whole blood concentrations of tacrolimus were determined following the initial i.v. infusion of tacrolimus, following the first oral dose of tacrolimus granules and on the last day of hospitalization during steady state tacrolimus granules dosing. Following the first oral dose, C_{max} was 38.3 ± 40.9 ng/mL and T_{max} was 1.1 hours. At steady-state the corresponding values were 19.6 ± 11.1 ng/mL (C_{max}) and 2.1 hours (T_{max}). The mean bioavailability of 22.8% observed in this study is similar to what has been observed in other studies in paediatric liver transplant patients.

General PK considerations

As this is a stand alone application, the PK data on tacrolimus from the paediatric population is considered limited and the Applicant was requested to provide more PK data from the paediatric population. Studies are now proposed by the Applicant as a FUM which is acceptable. Section 5.2 of the SPC has also been updated with relevant information on the paediatric population based on all currently available data.

Pharmacodynamics

At the time of initial approval of tacrolimus, pharmacodynamic data were sparse. No new data on pharmacodynamics are presented with this application. Tacrolimus therapy is well established in clinical transplantation and dosing is individualised through therapeutic drug monitoring. Empirical therapeutic windows exist for blood concentrations in different clinical transplantation situations. Problems foreseen with this new administration form relate to dosing in relation to the approved administration forms.

- Mechanism of action

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

No dose-response studies were performed with the granule formulation. Since the development programme of the granule formulation is a partly based on the development programme of the capsule formulation, dose response studies with granules are not considered necessary.

- Main studies

The applicant has submitted tabular listings of altogether 120 clinical studies with tacrolimus, plus study synopses and study reports. Separate summaries of clinical efficacy for kidney transplantation, liver transplantation, heart transplantation and for other organ transplantation, plus a common safety summary for all organ transplantation have also been submitted.

Bioequivalence has not been shown between the granule formulation and the capsule formulation. According to the PK study 95-0-001, the granule formulation resulted in about 20 % greater means for C_{max} and AUC.

The following clinical studies were performed in **paediatric liver transplantation** with the granule formulation:

Study FG-506-01-08 was a phase I *de novo* open-label, non-comparative two-centre pilot study in pediatric liver transplant recipients below the age of 14. Of the 28 patients, 17 were evaluable for pharmacokinetic analyses

METHODS

Study Participants

Patients 15 years or younger undergoing primary liver transplantation were included in the study.

Treatments

Tacrolimus was started within 6 hours after completion of surgery, as a continous i. v. infusion with an initial dose of 0.045 mg/kg body weight/24 hours. After the initial period of intravenous therapy, tacrolimus was administered orally as fine granule formulation at a starting dose of 0.3 mg/kg/day divided into a twice daily dose regimen. Initial maximum dosage was 0.5 mg/kg/day. Target whole blood levels of tacrolimus were 5 to 15 ng/ml during the first month after transplantation and 5 to 10 ng/ml thereafter. Patients with postoperative renal impairment were not to commence tacrolimus therapy or to begin at a lower dose. Patients with early poor graft function were not to commence tacrolimus until significant improvement in liver function was observed. Anti-thymocyte globulin (ATG) was used for induction in these cases. Azathioprine was administered to all patients according to standard practice at each participating center. Standard corticosteroid protocol was used. Anti-rejection therapy with corticosteroids or ATG/OKT3 was given when needed.

Table 1. Assessment schedule in study FG-506-01-08.

Study drug exposure	Trough levels	Daily during the first two weeks of the study, on Days 21 and 28 (daily if hospitalised during this period), Weeks 6, 8 and 10, and Months 3, 6, 9, and 12 and as indicated
	Pharmacokinetic sampling	Intravenous tacrolimus dose, intravenous washout, first oral dose, and oral steady state (these data will be reported elsewhere)
Efficacy	Rejection episodes, graft and patient survival	Days 1, 7 and 14 (daily if hospitalised), on all subsequent study visits and on an ongoing basis as indicated.
	Liver biopsy	As clinically indicated
Safety	Adverse events (including infections)	Days 1, 7 and 14 (daily if hospitalised), Weeks 6, 8 and 10, and Months 3, 6, 9, and 12 and as indicated
	Microbiology	As clinically indicated
	Laboratory tests and physical examination	Day 0, Days 1, 5, 9, 14, 21, and 28, Weeks 6, 8 and 10, and Months 3, 6, 9, and 12
	Glomerular filtration rate	Day 0, Months 6 and 12
	Echocardiography	Days 0, 7 and 28 and Months 6 and 12
	Electrocardiography	Days 0 and 28, Months 3, 6 and 12, and as clinically indicated
	EBV and CMV monitoring	Days 0, 7 and 28, Months 2, 3, 6, 9, and 12 and as clinically indicated

The study protocol gives no details on how to prepare an oral suspension from the granules. Otherwise, study design was reasonable in this pilot study.

Objectives

The objective of this study was to assess the safety and efficacy of tacrolimus granules in children undergoing liver transplantation, to refine the dosing schedule in children and to compare dosing based on weight with dosing based on body surface area. No data are given in the study AR on dosing according to body surface area.

A pharmacokinetic (PK) assessment was undertaken to evaluate the dosing regimen for the fine granule formulation, without a switch to the capsule formulation.

Recruitment

The study was conducted between March 1996 and April 1998 in 2 European centres, including respectively 15 *(Catholic University of Leuven, Belgium)* and 13 patients *(Hopital Kremlin Bicetre, France).*

Statistical methods

Data were analysed using descriptive statistical methods. A sample size of 20 patients was planned in this pilot study.

RESULTS

Participant flow

Withdrawal rate was low, 6/28 patients.

Table 2. Patient disposition, study FG-506-01-08.

Reason for Withdrawal	Tacrolimus (N = 28) Number of Patients (%)
Adverse Event	3 (10.7)
Retransplantation	0 (0.0)
Death	2 (7.1)
Prohibited Medication Required	0 (0.0)
Suspension of Study Drug > 14 Days	0 (0.0)
Lack of Therapeutic Response	0 (0.0)
Withdrawal of Consent	0 (0.0)
Non-compliance	0 (0.0)
Lost to Follow-up	1 (3.6)
Total	6 (21.4)

Donor source

Graft quality was good.

Table 3. Donor characteristics, study FG-506-01-08.

Characteristic	Tacrolimus (N = 28) Number of Patients (%)/ Descriptive Statistics
Liver of Donor	
Whole Organ	12 (42.9)
Reduced Size (Partial Organ)	16 (57.1)
Total Ischaemic Time (hours)	
N	28
Mean	8.3
SD	3.9
Range	1.6 - 12.8
Assessment of Liver Prior To Reperfusion	
Very Good Organ	8 (28.6)
Good Organ	19 (67.9)
Fair Organ	1 (3.6)
Poor Organ	0 (0.0)
Living Related Donor Organ	
Yes	9 (32.1)
No	19 (67.9)

Baseline data

Table 4. Baseline demographics, study FG-506-01-08.

	Tacrolimus (N = 28)
Age in years, median (min-max)	3.1 (0.5 – 13.1)
Sex	
Male	13 (46%)
Female	15 (54%)
Ethnic group	
Caucasian	24 (86%)
Other	2 (7%)
Black	1 (4%)
Oriental	1 (4%)
Viral status at baseline	
HBV-positive	4 (14%)
HCV-positive	1 (4%)
HIV-positive	0 (0%)
Infection status at baseline	
No positive findings	16 (57%)
Bacterial	9 (32%)
Fungal	4 (14%)
Parasitical	2 (7%)
Primary diagnosis	
Biliary Atresia	22 (79%)
Cirrhosis	3 (11%)
Sclerosing cholangitis	1 (4%)
Other	2 (7%)
Type of transplant	
Whole organ	12 (43%)
Partial organ	16 (57%)

Intent-to-treat Population

Outcomes and estimation

Incidence of rejection was not higher than expected; all rejections were steroid-sensitive. Patient and graft survival were satisfying in this small study in small and severely ill children undergoing liver transplantation. Three patients (11 %) experienced graft loss; all three cases were due to patient's death.

Table 5. Incidence of rejection, study FG-506-01-08, ITT population.

	Number of Patients (%) (N = 28)
Acute rejection	6 (21%)
Corticosteroid-sensitive	6 (21%)
Tacrolimus-sensitive	1 (4%)
Spontaneously-resolving	0 (0%)
Corticosteroid-resistant	0 (0%)
Antibody-sensitive	0 (0%)
Refractory	0 (0%)
Chronic rejection	0 (0%)

Study FG-506-01-13 was a phase III de novo multi-centre, open-label, prospective, randomised comparative study in pediatric liver transplant recipients below the age of 16.

This study compared efficacy and safety between a regimen of tacrolimus plus corticosteroids and a regimen with ciclosporin (CsA- Neoral), azathioprine and corticosteroids.

METHODS

Study Participants

This study was of 12-months duration and included 185 patients.

Patients aged 16 or below and with a maximum weight of 40 kg and undergoing primary liver transplantation were included after informed consent.

Treatments

The recommended starting dose of tacrolimus was 0.3 mg/kg/day orally, divided into two equal doses. After the first trough level measurement, subsequent doses were adjusted to maintain the following target blood trough levels

- 15 ng/ml in the first two weeks (range 10 – 20 ng/ml)
- 12.5 ng/ml during week 3 and 4 (range 10 – 15 ng/ml)
- 10 ng/ml during month 2 and 3 (range 5 – 15 ng/ml)
- 8 ng/ml during month 2 and 3 (range 5 – 10 ng/ml)

Initial doses were administered via nasogastric tube. The sachets were emptied into a sterile container and mixed with a suitable amount of sterile water (maximum 50 ml) to produce a suspension which was drawn into a syringe and administered into the non-PVC nasogastric tube. The same quantity of sterile water was again drawn into the same syringe and sued to rinse the nasogastric tube and the sterile container. The gastric tube was clamped for 45 to 60 minutes after dosing.

The preparation of study drug suspension was made in line with the directions given in the proposed SPC for Modigraf.

CsA was administered orally at a starting dose of 10 mg/kg/day, divided into two doses. Doses were adjusted according to therapeutic drug monitoring (TDM) to achieve the following target blood trough levels:

- 300 ng/ml in the first two weeks (range 250 – 350 ng/ml)
- 250 ng/ml during weeks 3 to 12 (range 200 – 300 ng/ml)
- 150 – 200 ng/ml during months 4 to 12
- 100 -150 ng/ml thereafter

Corticosteroids were given according to the following schedule:

During surgery 10 mg/kg intravenously
Day 1 – 6 methylprednisolone iv 2 mg/kg/day
Day 7 – 13 prednisolone 1 mg/kg/day once daily p o
Day 14 – 20 prednisololone 0.75 mg/kg/day once daily p o
Day 21 – 28 prednisololone 0.5 mg/kg/day once daily p o
Month 2 – 3 prednisololone 0.25 mg/kg/day once daily p o
Thereafter passage to dosing on alternate days and/or attempt to taper off corticosteroids, according to local practice.

Azathioprine was administered only in the CsA group, at a dose of 1.5 mg/kg/day during the first three months after which it was administered according to local practice. Rejection treatment was either an increased dose of tac in the tac group and/or a full course of corticosteroids. Patients with corticosteroid resistant rejections were to be withdrawn from the study and given therapy according to the sites practice.

Objectives

The objective of the study was to investigate the safety and efficacy of a tacrolimus based regimen using the fine granule formulation in comparison to a cyclosporine Neoral based standard regimen in children receiving a primary liver transplant.

Outcomes/endpoints

The primary endpoint was the incidence and time of onset of acute rejection. Secondary efficacy endpoints were the incidence and time to onset of steroid-resistant rejection, patient and graft survival rate and the cumulative corticosteroid dose over time. The safety endpoint was the overall incidence of AEs.

Recruitment

The study was carried out in 10 transplant centres in 6 EU countries from October 1997 to December 2000.

Randomisation

Randomisation was to be performed directly before the first administration of study drug, usually within 6 hours post-transplantation. In case of renal impairment the randomisation could be delayed up to 24 hours post transplantation. Screening was done on day 0 (day of transplantation) and study visits were scheduled at days 1, 5, 9, 14, 21, 30; weeks 6, 8, 10, 12; months 6, 9 and 12.

Sample size

Sample size was calculated to be 200 patients which would allow a difference of 20 % in the frequency of acute rejections to be detected at the $\alpha = 0.05$ level with a power of at least 80 % (based on a rejection rate of 50 % after 12 months).

RESULTS

Participant flow

Compared to study FG506-01-08, a higher number of patients (35 % of the ITT population) discontinued study medication.

Table 6. Study discontinuation, study FG-506-01-13, ITT population, number of patients (%).

		Treatment Group		Total
		Tacrolimus	Cyclosporin-ME	
Randomised		93	92	185
Received no study treatment		1	2	3
Received incorrect study treatment		1	0	1
Completed		68	44	112
Withdrawals during study		21	43	64
Deaths, total		6	7	13
Died during the study		2	3	5
Died after withdrawal		4	4	8
Evaluable Population:	Intent-to-treat	91	90	181
	Efficacy	91	90	181

Baseline data

Table 7. Patient demographics and baseline characteristics, study FG-506-01-13, ITT population, number of patients (%).

Variable	Treatment Group	
	Tacrolimus N=91	Cyclosporin-ME N=90
Age in years (mean±SD, min-max)		
<3	0.6±0.8, <1-2	0.5±0.7, <1-2
≥3	7.3±3.9, 3-15	7.7±4.2, 3-16
Sex Male	46 (50.5)	48 (53.3)
Female	45 (49.5)	42 (46.7)
Height in cm (mean±SD, min-max)†	88.7±28.3, 60-167	87.7±26.9, 56-165
Weight in kg (mean±SD, min-max)†	14.6±10.3, 5-51	13.9±10.7, 3-60
Ethnic group Caucasian	75 (82.4)	80 (88.9)
Other	16 (17.6)	10 (11.1)
Viral status at baseline†		
CMV IgG positive	33/90 (36.7)	36/88 (40.9)
CMV IgM positive	8/81 (9.9)	8/77 (10.4)
EBV EA IgG	7/50 (14.0)	8/43 (18.6)
EBV PCR	5/58 (8.6)	8/56 (14.3)
EBV VCA IgA positive	1/6 (16.7)	0
EBV VCA IgG positive*	24/75 (32.0)	37/71 (52.1)
EBV VCA IgM positive	4/69 (5.8)	7/66 (10.6)
HBV positive	8/90 (8.9)	7/88 (8.0)
HCV positive	0	0
HIV positive	0	0
Bacterial status positive at baseline	15 (16.5)	10 (11.1)
Fungal status positive at baseline	11 (12.1)	7 (7.8)
Parasitical status positive at baseline	0	0
No bacterial, fungal or parasitical findings at baseline	69 (75.8)	75 (83.3)
Primary diagnosis		
Biliary atresia	54 (59.3)	44 (48.9)
Cirrhosis	16 (17.6)	25 (27.8)
Alagille syndrome	6 (6.6)	6 (6.7)
Metabolic disease	2 (2.2)	2 (2.2)
Sclerosing cholangitis	0	2 (2.2)
Other	13 (14.3)	11 (12.2)

Donor source

Fewer patients than in study FG-506-01-08 got their transplants from a living donor:

Table 8. Data on donor livers in study FG-506-01-13.

	Number of Patients (%)				
	Tacrolimus N=91		Ciclosporin-ME N=90		p-value
Assessment of Liver Prior to Reperfusion					
Very good	33	(36.7)	29	(34.5)	0.853+
Good	48	(53.3)	51	(60.7)	
Fair	8	(8.9)	4	(4.8)	
Poor	1	(1.1)	0	(0.0)	
Not Recorded	1		6		
Total Ischaemia Time (hours)					
N	82		85		
Mean	8.6		8.8		0.675~
SD	3.4		3.4		
Minimum	1.7		1.2		
Maximum	15.8		16.7		
Total Ischaemia Time Distribution					
<24 hours	82	(100.0)	85	(100.0)	
24-36 hours	0	(0.0)	0	(0.0)	
>36 hours	0	(0.0)	0	(0.0)	
Not Recorded	9		5		
Partial Liver Transplant					
Yes	61	(67.0)	65	(72.2)	0.448^
No	30	(33.0)	25	(27.8)	
Living Related Donor Organ					
Yes	10	(11.0)	11	(12.2)	0.796^
No	81	(89.0)	79	(87.8)	

Mean tacrolimus levels were comparable to those in study FG-506-01-08 and were mostly within target ranges.

Outcomes and estimation

More acute rejections occurred in both treatment groups in this study than in study FG-506-01-08. Altogether, more acute rejections and significantly more corticosteroid-resistant acute rejections occurred in the ciclosporine treatment group during the study. More graft losses and more deaths also occurred in this treatment group.

Table 9. Rejections, number of patients (%), study FG-506-01-13.

	Treatment Group		
	Tacrolimus N = 91	Cyclosporin-ME N = 90	p-value[§]
Acute Rejections	38 (41.8)	49 (54.4)	0.102
Untreated Acute Rejections	1 (1.1)	5 (5.6)	0.118
Tacrolimus-sensitive Acute Rejections	2 (2.2)	NA	NA
Corticosteroid-sensitive Acute Rejections	33 (36.3)	24 (26.7)	0.201
Corticosteroid-resistant Acute Rejections	5 (5.5)	24 (26.7)	<0.001
Other-basic immunosuppressant maintained	2 (2.2)	1 (1.1)	1.000
Other-basic immunosuppressant not maintained	1 (1.1)	5 (5.6)	0.118
Unresolved Acute Rejections	2 (2.2)	18 (20.0)	<0.001
Chronic Rejections	1 (1.1)	3 (3.3)	0.368
Suspected Acute Rejections	2 (2.2)	0	0.497

Intent-to-treat population
NA Not applicable
[†] Number of patients experiencing one or more episode
§ Fisher's exact test

Table 10. Summary of graft loss – number (%) of patients, study FG-506-01-13, ITT population.

	Treatment Group	
	Tacrolimus N = 91	Cyclosporin-ME N = 90
Retransplantation, no Death	1 (1.1)	7 (7.8)
Death, no Retransplantation	2 (2.2)	5 (5.6)
Retransplantation followed by Death	4 (4.4)	2 (2.2)
Total Retransplantations	5 (5.5)	9 (10.0)
Total deaths	6 (6.6)	7 (7.8)
Total Graft Loss	7 (7.7)	14 (15.6)
Graft Loss During Study	6 (6.6)	7 (7.8)
Graft Loss After Withdrawal	1 (1.1)	7 (7.8)

- Supportive studies

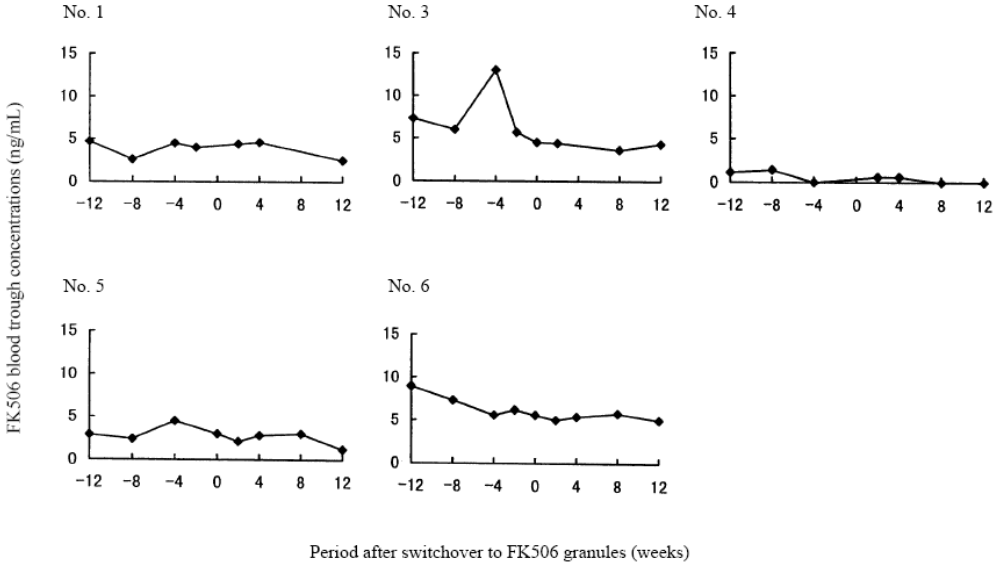
Supportive studies in liver transplantation

Study **FJ-0201** was a 4-week phase II study on the safety, efficacy, usefulness and PK of the granule formulation, performed in Japan in August 1995. Patients in this single centre study were switched over for a period of 4 weeks from tacrolimus capsules to granules, after a period of at least 4 weeks on capsules. Five patients who received partial living donor liver transplants were included but two of these 5 subjects were excluded due to GCP incompliance. Two of the remaining three patients were evaluable for PK analyses. One of the patients experienced a reversible rejection episode 22 days after switch. Two of the patients had impaired transplant function due to hepatitis. No PK comparison on the granule and capsule formulations can be made as PK parameters are given only after switch. An English translation of the synopsis of this study report was submitted.

An English translation of the paper on the report on the Japanese studies FJ-0202 and FJ-203 was also submitted. Study **FJ-0203** was a 12 week phase III open-label two-centre trial to study safety and efficacy in *de novo* liver transplant recipients. The study was started in January 1997 and included 8 children, aged between 9 months and 6 years. One patient was excluded from analyses due to AEs necessitating intravenous tacrolimus administration for a longer period of time.

Study **FJ-0202** was a switch-over study from capsules to granules in two Japanese centres. The study included 6 patients, of whom one was excluded from all analyses because of lack to fulfil inclusion criteria. Patients were from the age of three and a half years to 64 years. The period from transplantation until switch from tacrolimus capsules to granules was from 4 months to 5 years 9 months. The study was performed during 12 weeks from February 1997. No rejections occurred at the time of switchover from capsules to granules. Trough concentrations did not markedly change after switch.

Fig 1. Changes in tacrolimus blood trough concentration by each case at switchover, study FJ-0202.



Supportive studies in kidney transplantation

Study **FJ-0211** was an 8 week Japanese study on safety, efficacy, usefulness and PK and included 10 patients, aged 16 or below, of whom 9 were evaluable for PK analyses. In this single-centre phase III open-label, switch-over study, patients were switched from capsules to granules for at least 4 weeks on an mg to mg basis, at least 6 months after transplantation. Graft function remained stable in all patients. An English translation of the paper on the report on the two Japanese studies FJ-0212 and FJ-0213 was also submitted. Study **FJ-0213** included patients directly after kidney transplantation. Patients were administered tacrolimus granules for 12 weeks. All patients received corticosteroids and some patients also received azathioprine or mizoribine. Twenty-three patients were included in the study, 21 received study drug. Seventeen patients were eligible for analysis. Of these, 15 got living donor transplants and 2 got a cadaveric graft. Patients were aged 11.8 to 30.1 years. They got i. v. tacrolimus directly after transplantation and thereafter received tacrolimus granules for the rest of the study period. One patient (5.9 %) experienced graft loss due to rejection plus infection. Patient survival was 100 %. Rejection occurred in 41.2 % of the patients during the study period.

Study **FJ-0212** was a multicenter phase III *de novo* open-label two-centre switch-over study on safety and efficacy. Study duration was 12 weeks and the study included 22 patients in all ages from October 1996 to October 1998. Study patients had undergone kidney transplantation at least 6 months prior to study inclusion, had a stable transplant and had been on tacrolimus for at least 12 weeks. Patients were then switched to tacrolimus granules for a period of 12 weeks. Ten patients, aged 11 to 56 years, were included in the study. One of the patients required an increased dose of tacrolimus, from 8 to 10 mg daily, at the 4th week after the switchover. The remaining 9 patients did not require any dose adjustments after switch. No patient experienced an acute rejection at the time of switch.

In conclusion, the Japanese studies are uncontrolled and included few patients. The results from them are provided as translated synopses/papers that are difficult to evaluate. PK data are not structured in the same way as PK data from studies 95 - 0-001 and FG-506-01-08 and are not directly comparable. Taken together, data from these Japanese studies support the feasibility of treating patients with tacrolimus granules after liver or kidney transplantation and of switching from tacrolimus capsules to granules. The PK relationship between the two tacrolimus formulations is however not further clarified in these studies.

- Discussion on clinical efficacy

The applicant has shown that the tacrolimus formulation of fine granules is an appropriate formulation for immunosuppression after kidney, liver and heart transplantation in adults and children. As tacrolimus is an active substance with a narrow therapeutic margin any approved tacrolimus formulation should be of therapeutically equivalent value when used in the same individual. Optimal therapy in the clinical situation requires maintenance of appropriate systemic exposure (AUC) on an individual patient basis. Inter-individual variations in oral bioavailability are great, doses are guided by frequent therapeutic drug monitoring (TDM) using trough levels as surrogate markers of AUC. Clinical studies have shown tacrolimus granules formulation to therapeutically appropriate for the prophylaxis of rejection after allograft transplantation. In the bioequivalence study, the mean AUC of tacrolimus was 18 % greater with granules then with capsules (Prograf). No switch study from granules to capsules has been submitted by the applicant.

Clinical safety

- Patient exposure

Worldwide cumulative exposure to tacrolimus since the first marketing authorisation in 1994 is estimated at about 1.5 million patient-years altogether. During the most recent PSUR period April 2006 to March 2007, the exposure to tacrolimus was 229.000 patient years worldwide. Altogether 91 patients were randomised to the granule tacrolimus formulation in liver transplantation study FG-506-01-13 and 28 patients received tacrolimus granules in liver transplant study FG-506-01-08.

The granule formulation has been approved in Japan since 2001. The Summary of Clinical Safety does not specify post-marketing data for the granule formulation. However, safety data reported post-approval for this formulation in Japan has not markedly differed from safety data reported for Prograf capsules.

- Adverse events

The most common AEs (fever, infections and abnormal liver function tests) were seen more often in the children in these studies than in an adult liver transplant population.

- Serious adverse event/deaths/other significant events

<u>Deaths</u>

Two patients died during study FG-01-08; one due to cardiac arrest associated with hyperkalemia and the other one due to hemorrhagic collapses. Another patient died due to suspect intestinal volvulus following withdrawal from this study due to a lymphoma-like reaction.

Five patients died in study FG-01-13, 2 in the tacrolimus granules group and 3 in the CsA group. Causes of death were (1 case of each): cerebral oedema, multiorgan failure with disseminated intravascular coagulation, hemorrhagic shock, sepsis and sepsis + multiorgan failure. Four patients in each group died after study withdrawal (1 case each of cardiac arrest during retransplantation, graft failure, hyperphosphatemic coma, multiorgan failure, multiorgan failure secondary to surgical attempt of repair of massive biliary fistula, multiorgan failure due to adenovirus infection, sepsis + cardiac arrest and gastrointestinal haemorrhage secondary to gastric ulcer + aspiration pneumonia and sepsis).

<u>SAEs</u>
The most frequently reported SAEs (regardless of relationship to study drug) in the two studies of tacrolimus granules in liver transplantation are shown below.

Table 11. Most frequently reported SAEs, seen in ≥ 4 % of patients, in studies FG-506-01-08 and FG-506-01-13.

	FG-506-01-08	FG-506-01-13	
Adverse Event (COSTART term)	**Tacrolimus granules N=28**	**Tacrolimus granules N=91**	**Ciclosporin-ME N=90**
Fever	2 (7.1)	20 (22.0)	21 (23.3)
Liver function tests abnormal	0	17 (18.7)	15 (16.7)
Bile duct disorder	3 (10.7)	8 (8.8)	7 (7.8)
Infection	5 (17.9)	5 (5.5)	4 (4.4)
Sepsis	0	9 (9.9)	8 (8.9)
Gastroenteritis	1 (3.6)	8 (8.8)	2 (2.2)
Gastrointestinal hemorrhage	1 (3.6)	7 (7.7)	8 (8.9)
Diarrhea	1 (3.6)	6 (6.6)	9 (10.0)
EBV infection	1 (3.6)	6 (6.6)	2 (2.2)
Ascites	0	6 (6.6)	8 (8.9)
Kidney function abnormal	1 (3.6)	5 (5.5)	5 (5.6)
Thrombosis	2 (7.1)	4 (4.4)	2 (2.2)
Pleural effusion	0	5 (5.5)	5 (5.6)
Hypertension	0	5 (5.5)	3 (3.3)
Convulsion	0	5 (5.5)	2 (2.2)
CMV infection	1 (3.6)	4 (4.4)	11 (12.2)
Vomiting	1 (3.6)	4 (4.4)	7 (7.8)
Haemoperitoneum	3 (10.7)	2 (2.2)	0
Haemorrhage	3 (10.7)	0	2 (2.2)
Gamma glutamyltransferase increased	2 (7.1)	0	0
SGOT increased	2 (7.1)	0	0
SGPT increased	2 (7.1)	0	0

Intent-to-treat population; Number of patients (%)

- Laboratory findings

Nephrotoxicity is a well known adverse effect of tacrolimus. The glomerular filtration rate (GFR) decreased by month 6 compared to baseline and further decreased by month 12 in study FG-506-01-13. This was also true for patients in study FG-506-01-08. Liver function tests improved markedly after transplantation and approached normal values for study completers at month 12 after transplantation.

- Safety in special populations

Fever, liver function test abnormal and acidosis are more common in children than in adults, irrespective of immunosuppressive therapy, in the liver transplantation studies. It is not clear whether children are more susceptible than adults to cardiomyopathy as an adverse effect of tacrolimus. The figures for PTLD given by the applicant, 1.8 – 2.1 % in a paediatric transplant population, are comparable to those from other sources. There seems to be a relationship between the total immunosuppression and the risk of developing PTLD, rather than a risk specific for any single immunosuppressive agent.

The ADR profile for tacrolimus in elderly patients does not differ from that in the general population for tacrolimus.

No clinical studies have shown different ADR profiles for males and females.

Severe hepatic impairment may necessitate a reduction of the tacrolimus dose, as pointed out in the SPC.

Tacrolimus is not excreted by the kidneys so from an efficacy point of view, no dose adjustment is required in patients with impaired renal function. However, as tacrolimus is nephrotoxic, careful monitoring is recommended when tacrolimus is used in patients with impaired renal function.

- Safety related to drug-drug interactions and other interactions

Tacrolimus has many clinically important interactions. Interactions of clinical importance are those between tacrolimus and medicines with the potential to inhibit CYP3A4 and thus increase blood levels of tacrolimus ***or*** to induce CYP3A4 and thus decrease blood levels of tacrolimus. For instance, corticosteroids induce the CYP3A4 system and withdrawal of steroids can increase tacrolimus blood levels. Maintenance doses of steroids may reduce tacrolimus levels. The concomitant administration of CsA and tacrolimus is not recommended as the half life of CsA is prolonged by tacrolimus and as additive nephrotoxic effects can occur.

A class effect of immunosuppressives is their potential to affect the response to vaccination. Vaccination during treatment with tacrolimus may be less effective and the use of live attenuated vaccines should be avoided.

- Immunological events

In 1999, 30 case reports of food allergy were evaluated. Twenty-one of these were from the US, 23 were non-serious; all of the events were in paediatric liver transplant patients. The patients developed allergies to food ingredients. In all cases, the allergy was controlled by anti-allergic therapy and by avoiding exposure to allergens. Angioedema in 12 paediatric liver transplant recipients, aged 6 months to 2 years, under tacrolimus therapy was reported from a single French centre in 2003.

- Discontinuation due to adverse events

Two patients in study FG-506-01-08 withdrew from the study due to AEs: One patient was withdrawn on day 1 because of a duodenal perforation that made oral tacrolimus administration impossible and another patient was withdrawn from the study on day 1 because of an hepatic artery thrombosis with abdominal bleeding. In study FG-506-01-13, there were altogether 50 AEs resulting in withdrawal, 10 (11 %) in the tacrolimus group and 38 (38.9 %) in the CsA group. The main reason for withdrawal in this study was graft rejection. Graft rejection was the reason for withdrawal in 21 patients (23.3 %) in the CsA group and 2 patients (2.2 %) in the tacrolimus group. All but one patient in the CsA group who had experienced a graft rejection were transferred to tacrolimus therapy.

- Discussion on clinical safety

Adverse effects from tacrolimus as such are not expected to differ between granules and approved tacrolimus formulations

2.5 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.

Table Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
Important identified risks		
Hypertension Cardiac arrhythmias Neurological and visual disorders Diabetogenicity Electrolyte changes Hepatic and renal dysfunction Blood cell changes Coagulopathies	Routine pharmacovigilance Phase IV study (F506-CL-0404) in stable pediatric allograft recipients	Warning in Section 4.4 of the SPC Listed as an ADR in section 4.8 of the SPC
Ventricular hypertrophy Cardiomyopathies Prolonged QT interval	Routine pharmacovigilance Phase IV study (F506-CL-0404) in stable pediatric allograft recipients	Warning in Section 4.4 of the SPC Listed as an ADR in section 4.8 of the SPC
Serious infections and reactivation of pre-existing infections	Routine pharmacovigilance Phase IV study (F506-CL-0404) in stable pediatric allograft recipients	Warning in Section 4.4 of the SPC Listed as an ADR in section 4.8 of the SPC
Diarrhoea	Routine pharmacovigilance Phase IV study (F506-CL-0404) in stable pediatric allograft recipients	Warning in Section 4.4 of the SPC Listed as an ADR in section 4.8 of the SPC
Neoplasms	Routine pharmacovigilance Phase IV study (F506-CL-0404) in stable pediatric allograft recipients	Warning in Section 4.4 of the SPC Listed as an ADR in section 4.8 of the SPC
Galactose-intolerance	Routine pharmacovigilance Phase IV study (F506-CL-0404) in stable pediatric allograft recipients	Warning in Section 4.4 of the SPC

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
Pregnancy	Routine pharmacovigilance	Warning in Section 4.6 of the SPC
Lactation	Routine pharmacovigilance	Warning in Section 4.6 of the SPC
Important potential risks		
Exchangeability between granule and capsule formulations of tacrolimus	Routine pharmacovigilance Phase IV study (F506-CL-0404) in stable pediatric allograft recipients	Description in Section 4.2 of the SPC Warning in Section 4.4 of the SPC
Medication errors	Routine pharmacovigilance	Indications in Section 4.1 of the SPC Description in Section 4.2 of the SPC Warning in Section 4.4 of the SPC Description in Section 4.9 of the SPC

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.

2.6 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 toxicity of tacrolimus has previously been well established with the organs of toxicity identified. The currently proposed formulation would not be considered to result in any new toxicity concerns.

The potential environmental risk should be further addressed (FUM).

Efficacy

The applicant has shown that the tacrolimus formulation of fine granules is an appropriate formulation for immunosuppression after kidney and liver transplantation.

Safety

Adverse effects from tacrolimus as such are not expected to differ between granules and approved tacrolimus formulations. From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics

In the bioequivalence study, the mean AUC of tacrolimus was 18 % greater with granules then with capsules (Prograf). However, in keeping with clinical practice, switching from any oral formulation of tacrolimus requires frequent therapeutic drug monitoring (TDM) using trough levels as surrogate markers of AUC and readjustment of dose to ensure that similar systemic exposure (AUC) is maintained. Thus, having considered the safety concerns in the risk-management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed this issue.

- User consultation

The user testing report submitted is adequate and in accordance with current recommendations.

Risk-benefit assessment

Benefits

There is a clear value in a tacrolimus formulation that can be more easily administered to young children and to individuals having difficulties to swallow capsules. The applicant has shown that the tacrolimus formulation of fine granules is an appropriate formulation for immunosuppression after kidney, liver and heart transplantation. The 0.2 mg granule sachets also provide a possibility for more exact dosing of the drug.

Risks

Adverse effects from tacrolimus as such are not expected to differ between granules and approved tacrolimus formulations. A problem arises at the switch from tacrolimus capsules to granules or vice versa as bioequivalence has not been shown between the two formulations. In the pivotal bioequivalence study, administration of the granular formulation resulted in significantly greater mean C_{max} and AUC where the percent differences were 23 % and 18 %, respectively. The applicant advocates that a conversion from tacrolimus capsules to Modigraf granules, or vice versa, in stable allografts can be done on an mg:mg basis, irrespective of the non-bioequivalence of the two formulations. Considering the difference in exposure and the proposed 1:1 switch, there is a risk of too high or too low tacrolimus concentrations and subsequent unnecessary dose adjustments compared to if a dose correction constant was used. No relevant clinical conversion studies were performed in support of the application. Another risk with the product is that there may be problems with medication errors with the granular formulation.

Hence, a prospective study to give information on the frequencies of dose changes after conversions between Modigraf and Prograf and on occurrences of medication errors, has been proposed by the Rapporteurs as a follow-up measure (FUM). Clinical study F506-CL-0404, (monitoring safety and efficacy in stable paediatric allograft recipients) has been amended accordingly.

Balance

There is an unmet need for a paediatric formulation of tacrolimus. In terms of clinical efficacy and safety, the new formulation is essentially similar to the tacrolimus capsule formulation. The risk of too high or too low tacrolimus concentrations when converting from tacrolimus capsules to Modigraf granules, or vice versa, on a mg:mg basis has been thoroughly discussed. It is deemed that the risk of a transient period of time, if any, on an incorrect dose cannot preclude a recommendation for approval. This risk was addressed by a strict and informative SPC text on conversion. A phase IV study to monitor safety and efficacy in stable paediatric allograft recipients is suggested by the applicant as FUM. A text on medication errors has also been included in the SPC.

The overall risk-benefit ratio for Modigraf is considered favourable.

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

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- 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 Modigraf in the "Prophylaxis of transplant rejection in adult and paediatric, kidney, liver or heart allograft recipients. Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients" was favourable and therefore recommended the granting of the marketing authorisation.