CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210115Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA, 505(b)(1)
Application Number(s)	210,115
Priority or Standard	Standard
Submit Date(s)	July 26, 2017, September 15, 2017, November 15, 2017, December 05, 2017, January 24, 2018, April 16, 2018
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PDUFA Goal Date	May 26, 2018
Division/Office	DTOP/OAP
Reviewer Name(s)	Ergun Velidedeoglu, MD
Review Completion Date	April 22, 2018
Established/Proper Name	Tacrolimus
(Proposed) Trade Name	Prograf® Granules
Applicant	Astellas Pharma US, Inc.
Dosage Form(s)	for oral suspension
Applicant Proposed Dosing Regimen(s)	Starting dose of 0.15-0.20 mg/kg/day, in two divided doses, every 12 hours, titrated later to target 5-20 ng/mL trough concentrations for the first 12 months posttransplant
Applicant Proposed Indication(s)/Population(s)	Oral suspension for prevention of rejection in pediatric heart, kidney, or liver transplant recipients
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as proposed by the Applicant

Link to NDA submission (EDR Location): \\CDSESUB1\evsprod\NDA210115\210115.enx

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

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OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

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1. Executive Summary

1.1. Product Introduction

Tacrolimus is a macrolide immunosuppressant belonging to the calcineurin inhibitor (CNI) group of immunosuppressants produced by the fungus-like bacteria "*Streptomyces tsukubaensis*." Tacrolimus inhibits T-lymphocyte activation. Currently reviewed immediate-release tacrolimus for oral suspension (Prograf® Granules) is the 'for oral suspension' dosage form of tacrolimus which is the first 'for oral suspension' formulation to be marketed in US, suitable for administration to pediatric (and some adult) patients who cannot swallow capsules or tablets. The active moiety of Prograf®, 'tacrolimus' has been on the US market for 24 years (since 1994) in oral capsule and injection (for intravenous use) dosage forms and is extensively used as the mainstay of the immunosuppressive regimens in most transplant recipients not only for the approved indications but also off-label in all types of solid organ, tissue and cell transplantations. Tacrolimus for suspension has been approved and marketed outside of the US in 32 countries including Japan since 2001 with the tradename Prograf Granules® and Europe since 2009 with the tradename Modigraf®.

Tacrolimus was originally approved as an immediate-release oral capsule and injection formulations under the current proprietary name Prograf, in 1994 (NDA 50-708 for the capsules and NDA 50-709 for the injection form) for the prophylaxis of rejection in liver transplant recipients followed by the approval in kidney transplant recipients in 1997 and heart transplant recipients in 2006. In addition to Prograf, currently there are multiple generic tacrolimus immediate release capsule formulations lawfully marketed in US.

The current NDA 210,115 for tacrolimus as granules, in 0.2 mg and 1 mg packets for oral suspension submitted by Astellas is in response to a Postmarketing Requirement (PMR) under the Pediatric Research Equity Act (PREA) attached to the approval of Astagraf XL® (NDA 204,096 also submitted by Astellas) to develop an age-appropriate formulation to allow dosing for ages 1 to <5 years. Current NDA 210,115 proposes the use of immediate release tacrolimus granules in 0.2 mg and 1 mg packets for oral suspension for the prevention of rejection in *pediatric heart, kidney, or liver transplant recipients*.

Orphan Drug Designation was granted for tacrolimus for oral suspension on October 4, 2016, for the prevention of rejection in heart, kidney, or liver transplant in pediatric patients. The applicant is requesting a '*three-year exclusivity*' for a new condition of use of tacrolimus (*as tacrolimus for oral suspension which can be administered to pediatric patients who have difficulty swallowing capsules*) upon approval of the NDA.

NDA 210,115 is supported by two clinical efficacy and safety studies, FG-506-01-08 and FG-506-01-13; two pharmacokinetic studies, F506-CL-0403 (OPTION) and F506-CL-0404A (PROGRESSION); and a healthy subject bioequivalence study 95-0-001.

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NDA 210,115 fulfills the PMR under the PREA attached to the approval of Astagraf XL® (NDA 204-,096) to develop an age-appropriate formulation to allow for dosing for ages 1 to <5 years.

Per the Pregnancy and Lactation Labeling Rule (PLLR) legislation, the Prograf labeling is required to be updated in *Section 8 Use in Special Populations* to comply with PLLR. The currently proposed labeling by the applicant is compliant with PLLR. The nonclinical portion of the PLLR labeling is reviewed by the Pharmacology/Toxicology discipline, and discussed with the Clinical discipline. The findings, conclusions and recommended labeling revisions are summarized in the Pharmacology/Toxicology discipline NDA review (DARRTS April 13, 2018). In addition, this application includes clinical data on patients who were on tacrolimus during their pregnancy and outcomes of the pregnancies. These data are reviewed by the Medical Officer and corresponding recommended labeling for these data are included in the Human Data portion of the PLLR.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Study FG-506-01-13 is the only randomized controlled study conducted with tacrolimus for oral suspension, hence the main study in support of the current NDA 210,115. Studies FG-506-01-08 and F506-CL-0404A are single arm, noncomparative studies and provide supportive efficacy and safety data. Study F506-CL-0403 (OPTION) is a 14-day PK study and is not covered in this clinical review. Since this is a known molecular entity, one adequate and well controlled study is considered sufficient to demonstrate the efficacy and safety of this new formulation.

Study FG-506-01-13 demonstrates that in pediatric de novo liver transplant recipients, Prograf® (tacrolimus for oral suspension) based maintenance immunosuppressive treatment regimen results in fewer acute rejections, fewer deaths and fewer graft loses and favorable safety when compared to a cyclosporine based maintenance immunosuppressive regimen. These differences fail to reach statistical significance due to the relatively small sample size in the study. Demonstration of superiority is not required for approval; new drugs can be approved based on the demonstration of non-inferiority.[1] Single arm studies, FG-506-01-08 (conducted in pediatric de novo liver transplant recipients) and F506-CL-0404A (conducted in pediatric de novo liver, heart and kidney transplant recipients as an extension of the 14-day PK Study F506-CL-0403) demonstrate that a tacrolimus for oral suspension based immunosuppressive regimen results in rates of rejection, death and graft loses which are consistent with rates that are expected to be seen in these patient populations in today's clinical practice and support the efficacy and safety findings of the main Study FG-506-01-13.

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1 https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8&ved=2ahUKEwjVg4HF3_3aAhVDpFkKHaI4D2EQFjABegQIABA3&url=https%3A%2F%2Fwww.fda.gov%2Fdownloads%2FDrugs%2FGuidances%2FUCM202140.pdf&usg=AOvVaw0lcSInqpqpe_jKFTBwn4Hz

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NDA 210,115 fulfills the PMR under the PREA included in the approval letter of Astagraf XL® (NDA 204,096) to develop an age-appropriate formulation to allow for dosing for ages 1 to <5 years.

The applicant's '*proposed indication for use*' as included in box 15 of the FDA Form 365h is (b) (4). Currently approved indications for tacrolimus as included in the *Indications and Usage* section of the Prograf package insert are the prophylaxis of organ rejection in patients receiving allogeneic kidney transplants or liver transplants or heart transplants without specifying adult patients or pediatric patients for these indications. These indications will not be revised to make specific reference to adult or pediatric patients and the 'Indications and Usage' section of labeling will stay the same except for editorial changes.

The new information pertaining to the tacrolimus for oral suspension formulation including the starting dose and target trough levels for pediatric patients receiving liver transplants will be added to the 'Dosage and Administration' and other relevant sections of the package insert. No randomized controlled trials have been performed in pediatric heart or kidney transplant recipients with the granule formulation; however, DTOP considered adding the available PK data in pediatric heart or kidney transplant recipients from the PK study F506-CL-0403 (OPTION) to Section 12 of the PI (Table 17 of the PI) since tacrolimus is widely used off-label for these indications. DTOP also sought PERC's recommendation on the appropriateness of adding this PK data pertaining to pediatric heart and kidney transplant recipients to the Prograf PI. During the May 2, 2018 PERC meeting, PERC agreed with DTOP's decision to add this new PK data and recommended to consult the Division of Pediatric and Maternal Health (DPMH) to have DPMH's opinion whether the new indications of pediatric heart and kidney transplantations (including the starting doses and target trough levels) could be added to the Prograf labeling. As recommended by PERC, DTOP requested input from DPMH regarding section 8.4 of the Prograf labeling for this new dosage form and the rationale for extrapolation of efficacy from existing data in adults and pediatric liver transplant patients to pediatric kidney and heart transplants. DPMH agreed with DTOP that the efficacy of tacrolimus can be extrapolated from adult to pediatric patients because the pathophysiology, diagnosis, and management of allograft rejection are sufficiently similar between the two populations and there is sufficient pharmacokinetic and safety data (see table 1) to support dosing recommendations (DARRTS May 18, 2018). Therefore, the starting doses and the target trough levels for the pediatric liver, heart and kidney transplant recipients will be added to the Prograf PI along with appropriate changes to Section 8 of labeling.

I recommend approval of NDA 210,115 submitted for Prograf Granules (tacrolimus for oral suspension) for the prevention of rejection in pediatric heart, kidney, or liver transplant recipients.

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1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

As explained under the regulatory history, the active moiety of Prograf Granules (tacrolimus for oral suspension) has been on the US market for 24 years and has been used as the mainstay of the immunosuppressive regimens in most transplant recipients not only for the approved indications but off-label in all types of solid organ, tissue and cell transplantations. In NDA 210,115, the main Study FG-506-01-13 demonstrates that in pediatric de novo liver transplant recipients, Prograf® Granules (tacrolimus for oral suspension) based maintenance immunosuppressive treatment regimen results in fewer acute rejections, fewer deaths and fewer graft loses and favorable safety when compared to a cyclosporine based maintenance immunosuppressive regimen. Single arm studies, FG-506-01-08 (conducted in pediatric de novo liver transplant recipients) and F506-CL-0404A (conducted in pediatric *de novo* liver, heart and kidney transplant recipients) also support these findings.

Currently, there is not an age appropriate formulation of tacrolimus, available on the US market for pediatric patients and adult patients who are not able to swallow tacrolimus capsules. These patients are administered extemporaneously compounded oral liquid formulations of tacrolimus which have not gone through any product quality or clinical testing. Therefore, if approved, tacrolimus for oral suspension will fill a big void in the therapeutic armamentarium of pediatric (and adult) patients who are not able to swallow tacrolimus capsules.

All immunosuppressive therapies come at the expense of increased risk of infections and malignancies which also applies to tacrolimus as a CNI immunosuppressant. In all immunosuppressants, the risk of malignancies, infections and other adverse drug reactions are weighed against the benefit of maintaining the transplanted organ by preventing rejection. In this regard, tacrolimus for oral suspension demonstrated a favorable benefit/risk ratio in the clinical studies submitted in support of NDA 210,115, as anticipated based on the 24 years of U.S. postmarketing experience from other formulations of tacrolimus used in all types of solid organ and tissue transplantations.

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Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Evidence is explained above under Benefit-Risk assessment. Although there is always the possibility of discovering new adverse drug reactions after marketing with increased usage, currently there are no uncertainties.	I recommend approval of NDA 210,115 for Prograf Granules (tacrolimus for oral suspension) since this new formulation of tacrolimus demonstrated a favorable benefit/risk profile in pediatric transplant recipients for the studied indications.
Current Treatment Options	• See Section 2.1	See Benefit-Risk Integrated Assessment above
Benefit	• See Benefit-Risk Integrated Assessment above	See Benefit-Risk Integrated Assessment above
Risk and Risk Management	• See Benefit-Risk Integrated Assessment above	See Benefit-Risk Integrated Assessment above

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1.4. Patient Experience Data

Patient experience data were not submitted in this application.

2. Therapeutic Context

- Tacrolimus is a naturally occurring product with immunosuppressive and antifungal properties produced by the fungus-like bacteria *Streptomyces tsukubaensis*. Tacrolimus belongs to the calcineurin inhibitor (CNI) group of immunosuppressants. CNIs [mainly tacrolimus and cyclosporine (CsA)] form the backbone of triple drug maintenance immunosuppressive regimens consisting of a CNI, an antiproliferative (generally a mycophenolic acid product) and corticosteroids, utilized in most transplant recipients

2.1. Analysis of Current Treatment Options

The following products for use in kidney transplant recipients as induction, prevention, or treatment of acute rejection have been approved. The wording from the Indications and Usage sections of the package inserts are provided below.

2.2.1 Induction

Thymoglobulin® (rabbit-derived antithymocyte globulin)

Thymoglobulin® is indicated for the prophylaxis and treatment of acute rejection in patients receiving a kidney transplant. Thymoglobulin is to be used in conjunction with concomitant immunosuppression.

Simulect® (basiliximab)

Simulect® is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclosporine, USP (MODIFIED) and corticosteroids. The efficacy of Simulect® for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

Zenapax® (daclizumab)

Zenapax® is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplants. It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids. The efficacy of ZENAPAX for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

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Drugs used off-label for induction treatment

Campath® (alemtuzumab), Atgam® (anti-thymocyte globulin, Orthoclone OKT3® (muromomab-CD3) are used off-label as induction agents; all are indicated for the treatment of rejection (see below), except Campath® which is approved only for treatment of B-cell chronic lymphocytic leukemia (B-CLL).

2.2.2 Prevention of Rejection

Prograf® (tacrolimus) and generics for Prograf

Prograf is a calcineurin-inhibitor immunosuppressant indicated for prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants

Astagraf XL® (tacrolimus extended release capsules)

ASTAGRAF XL is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction.

Envarsus XR® (tacrolimus extended-release tablets)

Envarsus XR® is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations in combination with other immunosuppressants

Neoral® (cyclosporine) and generics for Neoral

Neoral® is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Neoral® has been used in combination with azathioprine and corticosteroids.

CellCept® (mycophenolate mofetil) and generics for CellCept

CellCept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.

Myfortic® (mycophenolic acid)

Myfortic® (mycophenolic acid) delayed-release tablets are indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

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Nulojix® (belatacept)

Nulojix® is a selective T-cell costimulation blocker (biologic) indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant. Use in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids

Rapamune® (sirolimus)

Rapamune (sirolimus) is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. Therapeutic drug monitoring is recommended for all patients receiving Rapamune.

Zortress® (everolimus)

Zortress® is an m-TOR inhibitor indicated for the prophylaxis of organ rejection in adult patients:

- Kidney transplant: at low-moderate immunologic risk. Use in combination with basiliximab, cyclosporine (reduced doses) and corticosteroids. (1.1)
- Liver transplant: Administer no earlier than 30 days post-transplant. Use in combination with tacrolimus (reduced doses) and corticosteroids.

Imuran® (azathioprine) and generics for Imuran

IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. It is also indicated for the management of active rheumatoid arthritis to reduce signs and symptoms. Renal Homotransplantation: IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. Experience with over 16,000 transplants shows a 5-year patient survival of 35% to 55%, but this is dependent on donor, match for HLA antigens, anti-donor or anti-B-cell alloantigen antibody, and other variables. The effect of IMURAN on these variables has not been tested in controlled trials.

Corticosteroids

No specific labeling regarding use in transplantation

2.2.3 Treatment of Rejection

ATGAM®

Lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution (Atgam®) is indicated for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection, it increases the frequency of resolution of the acute rejection episode. The drug has also been administered as an adjunct to other immunosuppressive therapy to delay the onset of the first rejection episode.

Orthoclone OKT3® (muromonab-CD3) Sterile Solution – murine monoclonal antibody
ORTHOCLONE OKT3 is indicated for the treatment of acute allograft rejection in renal transplant patients. ORTHOCLONE OKT3 is indicated for the treatment of steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.

Thymoglobulin® (Anti-Thymocyte Globulin (Rabbit))
Thymoglobulin® is indicated for the prophylaxis and treatment of acute rejection in patients receiving a kidney transplant. Thymoglobulin is to be used in conjunction with concomitant immunosuppression.

2.2. U.S. Regulatory Actions and Marketing History

Tacrolimus was originally approved in US as an immediate-release oral capsule formulation and injection formulation under the current proprietary name Prograf®, in 1994 (*NDA 50-708 for the capsules and NDA 50-709 for the injection form*) for the prophylaxis of rejection in liver transplant recipients followed by the approval for kidney transplant recipients in 1997 and heart transplant recipients in 2006. In addition to Prograf, currently there are multiple generic tacrolimus immediate release capsule formulations lawfully marketed in US.

The first extended release formulation of tacrolimus (Astagraf XL capsules) was approved by the FDA for the prophylaxis of organ rejection in kidney transplant patients on July 19, 2013 (NDA 204,096) followed by the approval of another extended release formulation, Envarsus-XR tablets on July 10, 2015 (NDA 206,406) to be used in kidney transplant patients converted from tacrolimus immediate-release formulations.

As evident from the regulatory history, the active moiety (tacrolimus) has been on the US market for 24 years and has been used as the mainstay of the immunosuppressive regimens in most transplant recipients not only for the approved indications but off-label in all types of solid organ, tissue and cell transplantations.[2]

2.3. Basis for the Current NDA Submission: Deferred requirement for development of an age appropriate formulation of tacrolimus

Currently, there is not an age appropriate formulation of tacrolimus, available on the US market for pediatric patients and adult patients who are not able to swallow tacrolimus capsules. These patients are administered extemporaneously compounded oral liquid formulations of tacrolimus.[3]

[2] Hart A, et.al. OPTN/SRTR 2016 Annual Data Report: Kidney. Am J Transplant. 2018 Jan;18 Suppl 1:18-113.
[3] Jacobson PA, Johnson CE, West NJ, Foster JA. Stability of tacrolimus in an extemporaneously compounded oral liquid. Am J Health Syst Pharm. 1997 15;54(2):178-80.

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Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) of 2003, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Orphan Designation and initial Pediatric Study Plan (iPSP):
It should be noted that NDA 210115 has received orphan designation on October 4, 2016. Following the pre-NDA meeting, on October 18, 2016, the applicant provided via e-mail a copy of the Orphan Designation letter issued by the FDA Office of Orphan Products Development (OOPD), which designated tacrolimus granules as an orphan product for the indication of "prevention of rejection in kidney, liver or heart transplant in pediatric patients." Per the OOPD letter, the orphan designation is based on a "plausible hypothesis that Prograf Granules may be clinically superior to the same drug that is already approved for the same indication". The Division confirmed that as a product with Orphan Designation, submission of an initial Pediatric Study Plan (iPSP) is not required as PREA does not apply to this product.

However, PREA applied to Astellas' s NDA 204096, as summarized below.

The July 19, 2013 Approval Letter of Astagraf XL capsules (NDA 204,096) submitted by the current applicant (*Astellas, who is also the applicant of the original Prograf NDAs 50-708 for the capsules and 50-709 for the injection form*) contained the following Post Marketing Requirement (PMR) which forms the basis for the current NDA submission:

> *"2061-1 Deferred requirement for development of an age appropriate formulation: Develop an age appropriate formulation to allow for dosing for ages 1 to <5 years.*
> *Final Report Submission: 12/2020"*

The reason for the deferral of this pediatric requirement at the time of NDA 204,096 approval was Astagraf-XL was ready for approval for use in adults and the studies in support of the safety and efficacy of the age appropriate formulation were not ready for submission.

The purpose of the current NDA submission is to fulfil the PMR 2061-1 included in the Astagraf XL capsules NDA 204,096 Approval Letter for developing an age appropriate formulation of tacrolimus to allow for dosing of pediatric patients 1 to <5 years of age.

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For completeness, it is noted that there was a second PMR 2061-2, which asked for evaluation of Astagraf XL in patients 5 to 16 years of age. Submission of the complete study report in response of this second PMR to NDA 204096 has been made and is under review at this time.

2.4. Summary of Presubmission/Submission Regulatory Activity

October 17, 2016 Pre-NDA Meeting
The applicant requested a pre-NDA meeting on August 16, 2016 to discuss the format and content of the upcoming NDA 210,115 submission. The meeting was granted and the applicant submitted the meeting package on September 15, 2016. Preliminary responses to the questions posted in the meeting package were sent to the applicant on October 11, 2016 and the pre-NDA meeting was held on October 17, 2016.

Highlights of the October 17, 2016 Pre-NDA Meeting:

1. The applicant proposed to cross-reference nonclinical data contained in previously submitted NDAs 50-708 Prograf capsules, 50-709 Prograf injection and 204,096 Astagraf XL and the Division agreed.

2. Studies conducted with tacrolimus for oral suspension to be included in the NDA for the new formulation as proposed by the applicant:
    a. Study FG-506-01- 13: A phase 3, 12-month, randomized, open-label parallel-group study to investigate the safety and efficacy of a tacrolimus granules-based regimen compared to a cyclosporine microemulsion (ME)-based regimen in 181 pediatric primary liver transplant recipients ≤ 16 years of age (*77% of patients were < 5 years of age*).
    b. Study FG-506-01-08: A phase 2, noncomparative pilot 12-month study to assess the safety, efficacy and pharmacokinetics of tacrolimus granules in 28 pediatric patients ≤ 15 years of age undergoing liver allograft transplantation [18 (64%) were < 5 years of age].
    c. Study 95-0-001: A phase 1, relative bioavailability (bioequivalence) study to compare tacrolimus immediate-release capsules (Prograf) and tacrolimus granules in 32 healthy adult subjects.
    d. Study F506-CL- 0403 (OPTION): A phase 4, 2-week, multicenter, open-label, pharmacokinetic study of tacrolimus granules in de novo kidney, liver and heart allograft recipients (in 52 pediatric patients ≤ 12 years).
    e. Study F506-CL-0404A (PROGRESSION): Pediatric patients who elected to could roll over into the long-term OPTION Study which is a phase 4, open-label study to evaluate the safety and efficacy of tacrolimus granules in

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47 pediatric transplant recipients. Overall, 33 (70.2%) patients were < 5 years of age. Treatment with study drug continued until commercial availability of Modigraf in the patients' respective countries (a minimum of 3 months; a maximum of 1 year).

Per the applicant, clinical safety and efficacy of tacrolimus for oral suspension in a pediatric liver transplant population were demonstrated in Study FG-506-01-13. Supportive pharmacokinetic data in pediatric liver transplant patients was obtained from Study FG-506-01-08, and in pediatric heart, liver and kidney transplant patients in the OPTION study (Study F506-CL-0403). The Division agreed with the applicant's proposal regarding the clinical studies to be included in the NDA submission.

The applicant also submitted a draft statistical analysis plan (SAP) describing the planned approach to analyze the data from pediatric patients < 5 years of age in studies FG-506-01-13 and FG-506-01-08 which the Division agreed.

Content and Format of the Proposed Labeling:
The Division requested the Applicant to submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56 and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (required for applications submitted on or after June 30, 2015) as well as Instructions for Use in preparation of the oral solution from the granules contained in the packets. The applicant also included a Patient Package Insert and Container/Carton labels with the application.

For further information on the meeting discussions see the Meeting Minutes dated November 16, 2016 in DARRTS.

2.5. Foreign Regulatory Actions and Marketing History

Tacrolimus for oral suspension (marketed as Modigraf® and Prograf Granules®) are approved in 32 countries. Prograf Granules has been marketed in Japan since 2001. Modigraf received marketing authorization from the European Commission in May 2009. Per the information in the NDA submission, Modigraf® and Prograf Granules® are indicated for kidney, liver, heart and other solid organ transplantations.

3. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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3.1. Office of Scientific Investigations (OSI)

The two main clinical non-US studies in support of the current NDA, studies FG-506- 01-08 and FG-506-01-13 were conducted by the Fujisawa Pharmaceutical Co. (predecessor of Astellas) and were completed in 1998 and 2000, respectively. Given there are no source data for these clinical studies available from the EU or Japan, OSI recommended not doing inspections of Astellas which currently has the case report forms (CRFs) which were submitted with the application but not the source data.

3.2. Product Quality

Please refer to the Product Quality NDA review.

3.3. Clinical Microbiology

Not Applicable

3.4. Nonclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology NDA review (DARRTS, April 13, 2018).

3.5. Clinical Pharmacology

Issues that pertain both to the Clinical and the Clinical Pharmacology disciplines are covered in the relevant sections of this clinical review.

Please refer to the Clinical Pharmacology NDA review for further information.

3.6. Devices and Companion Diagnostic Issues

N/A

3.7. Consumer Study Reviews

N/A

4. Sources of Clinical Data and Review Strategy

4.1. Table of Clinical Studies

Three clinical studies were submitted in support of the NDA 210,115 (Table 1) and are reviewed by the Clinical Reviewer are:

- **FG-506-01-13**: randomized controlled open-label two-arm study in pediatric *de novo* liver transplant recipients; will be referred to as '*Study 13*' in this review.

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- **FG-506-01-08**: noncomparative single-arm study in pediatric *de novo* liver transplant recipients; will be referred to as '*Study 08*' in this review.

- **F506-CL-0404A (PROGRESSION)**: non-comparative single-arm extension study of the PK study F506-CL-0403 (OPTION) in stable pediatric liver, kidney and heart transplant recipients; will be referred to as '*Study 04A*' in this review.

F506-CL-0403 (OPTION) is a PK study and will not be covered in this clinical review; however, it is included in Table 1 for completeness since Study F506-CL-0404 (PROGRESSION) is the extension phase of the OPTION Study.

Rewritten Clinical Study Reports (CSRs) by the Applicant:
Studies FG-506- 01-08 and FG-506-01-13 are old studies completed in 1998 and 2000, respectively. As stated by the applicant, FG-506- 01-08 and FG-506-01-13 clinical study reports (CSR) were rewritten to conform to the current standards. As part of the process, data were reconciled with patient case report forms (CRFs) for any inconsistencies with documentation of the process in the trial master file (TMF) for each study. The CSRs for Studies F506-CL-0403 and F506-CL-0404A were also rewritten per agreement with the FDA (Pre-NDA Meeting Minutes dated November 16, 2016) to include narratives for malignancies, infectious and cardiovascular SAEs, CMV and BK virus infections, study medication discontinuations and losses to follow-up.

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Table 1 List of Clinical Studies

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Duration/ Follow Up	No. of patients enrolled	Study Population
Controlled Studies to Support Efficacy and Safety						
FG-506-01-13	An Open Label, Randomized, Comparative, Multicenter Pediatric Clinical Trial of the Efficacy and Safety of Tacrolimus granules vs CsA-ME in Primary Liver Transplantation	Tac. granules: 0.3 mg/kg/day PO in 2 divided doses + CS vs CsA-ME/AZA + CS	Safety and efficacy of tacrolimus granules	12 months	Tac arm: 91 CsA arm: 90	Pediatric *de novo* liver recipients
Studies to Support Safety						
FG-506-01-08	A Two Center Clinical Pilot Study in Children with Tacrolimus Granule Formulation as Immunosuppressive Therapy in Liver Allograft Transplantation (noncomparative)	Tac. IV: 0.045 mg/kg as 24-h infusion for 12 h to 4 days: Tac. granules: 0.3 mg/kg/day PO in 2 divided doses	14-day PK followed by 12-month for safety and efficacy	12 months	28	Pediatric patients with *de novo* liver transplant
F506-CL-0403 (OPTION)*	A Multicenter, Open-label, Pharmacokinetic Study of Modigraf® (Tacrolimus Granules) in *de Novo* Pediatric Allograft Recipients	Tacrolimus granules: 0.3 mg/kg/day PO in 2 divided doses	2-week PK study	14 days	17 heart 20 liver 15 kidney	Pediatric *de novo* heart or liver or kidney recipients
F506-CL-0404 (PROGRESSION)	A Long-term, Open-label, Non-comparative Study to Evaluate the Safety and Efficacy of a Modigraf® Based Immunosuppression Regimen in Pediatric Allograft Recipients	Tacrolimus granules, daily dose equal to the dose at the end of F506-CL-0403	Safety and efficacy of tacrolimus granules	3 months to 1 year	18 liver, 8 kidney, 17 heart	Patients ≤ age 12 at enrolment in F506-CL-0403

* Study F506-CL-0403 (OPTION) is a PK study and will not be covered in this clinical review; however, it is included in Table 1 since the Study F506-CL-0404 (PROGRESSION) is the extension phase of the OPTION Study.

Reference ID: 4267221

4.2. Review Strategy

The three clinical studies submitted in support of the NDA 210,115 (FG-506-01-13, FG-506-01-08, and Study 506-CL-0404A) will be assessed in this clinical review. Among these three studies, only Study FG-506-01-13 is a randomized controlled study; hence, it is the main study in support of the efficacy and the safety of tacrolimus for oral suspension and will be reviewed first. Due to differences in the study designs and populations, the data from these three studies will not be pooled.

5. Review of Relevant Individual Trials Used to Support Efficacy

5.1. An Open Label, Randomized, Comparative, Multicenter Pediatric Clinical Trial Comparing the Efficacy and Safety of a Dual Regimen with Oral Tacrolimus (FK506) Versus a Triple Regimen With Oral Cyclosporine-Microemulsion in Primary Liver Allograft Transplantation (FG-506-01-13)

This non-US, multicenter study was conducted at 10 sites in a total of 6 countries including Belgium (1 site), France (2 sites), Germany (3 sites), Italy (1 site), Spain (2 sites) and the UK (1 site).

Study Initiation Date (Date of First Enrollment): June 02, 1997

Study Completion Date (Date of Last Evaluation): December 23, 2000

Date of Rewritten Clinical Study Report: April 25, 2017

5.1.1. Study Design (FG-506-01-13)

Overview and Objective

To investigate the safety and efficacy of a tacrolimus based regimen using a new formulation (granules) in comparison to a cyclosporine-microemulsion (CsA-ME) based standard regimen in children receiving a primary liver transplant.

Trial Design

This was an open-label, randomized, multicenter, pediatric, phase 3 study in primary liver allograft transplantation comparing a tacrolimus based dual drug immunosuppressive regimen (tacrolimus for oral suspension with low-dose corticosteroids) with a cyclosporine-ME based triple drug immunosuppressive regimen (CsA-ME with low-dose corticosteroids and azathioprine). Pediatric patients undergoing a primary liver allograft transplantation were enrolled into the study. Randomization

was to be performed directly before the first administration of study drug, usually within 6 hours posttransplantation. In case of postoperative renal impairment, the randomization could be delayed up to 24 hours posttransplantation. After the initial screening on day 0 (date of skin closure), patients were observed for efficacy and safety variables over a period of 12 months.

Rationale for Study Design

Per the protocol, the study design rationale was to obtain information on the efficacy and safety of the two different immunosuppressants (tacrolimus for oral suspension and CsA-ME) in pediatric liver transplant recipients. A comparative design with a 1:1 randomization was chosen. The study duration of 12 months covers both the early posttransplantation period and the phase of functional stabilization. The study duration also permitted the analysis of the effect of the immunosuppressive medication on the development of lymphoproliferative diseases.

Primary Endpoint

The primary endpoint was the incidence and time to first acute rejection.

The secondary endpoints were:

- Incidence and time to steroid-resistant acute rejection
- Patient and graft survival
- Cumulative concomitant immunosuppressive medication over time

Clinical Reviewer's Comment
Although the time to first rejection was the primary endpoint, and it was met, during the review of the application, the statistical and clinical reviewers also examined the more commonly used endpoint, where death, graft loss and loss to follow up are imputed as failure, as discussed below.

Definition of Rejection

- Acute rejections had to be confirmed by biopsy.
- Steroid-sensitive biopsy-proven acute rejections (BPARs) were BPARs that were treated with new or increasing corticosteroid medication only and resolved, irrespective of any study drug dose changes.
- Steroid-resistant BPARs are BPARs that did not resolve following treatment with corticosteroids. In case that a rejection episode was not treated with corticosteroids first but only with antibodies, it was considered steroid-resistant. Patients with steroid-resistant BPARs had to discontinue study drug.

Graft Loss

Graft loss was defined as retransplantation or death. The date of graft loss was the

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earliest date of any of these events.

Clinical Reviewer's Comment
Protocol specified primary and secondary endpoints and their definitions are appropriate for the pediatric *de novo* liver transplant patient population. The protocol mandated that patients with steroid-resistant BPARs had to discontinue study drug. In today's clinical practice, neither tacrolimus nor cyclosporine are discontinued in the case of a steroid resistant rejection; however, the target trough concentrations may be increased. These, protocol mandated, study drug discontinuations in the case of 'steroid resistant rejections' might have resulted in some unwarranted discontinuations in both arms of the study as will be discussed later.

Rationale for the tacrolimus and cyclosporine starting doses:

Per the applicant, the oral bioavailability of tacrolimus is comparable between adults and children (i.e., approximately 20% to 25%), but the clearance in children is approximately 2-fold higher than that in adults. Therefore, to achieve similar exposures, children would require approximately a 2-fold higher dose than adults. Thus, the first oral dose in pediatric liver transplant patients in this study was set at 0.3 mg/kg per day, approximately 2-fold higher relative to the approved starting dose for tacrolimus capsules in adult liver transplant patients.

The starting dose of CsA-ME in this study was based on the recommended starting dose as specified in the EU Summary of Product Characteristics for Neoral (CsA-ME) at the time of study conduct.

Subsequent doses of tacrolimus for oral suspension and CsA-ME were adjusted for each patient based on clinical evidence of toxicity and efficacy and to maintain target whole blood trough levels.

Clinical Reviewer's Comment
The applicant's justification for the protocol specified starting doses and the rationale for tacrolimus granules and CsA-ME are acceptable. However, as discussed later in this review due to the high starting dose (0.30 mg/kg), the tacrolimus trough levels during the first few days were high which prompted the investigators to reduce the doses. The CsA trough levels during the study in general were on the high side when compared to today's clinical practice. The high starting dose of tacrolimus and the relatively high CsA target trough levels in the study reflects the clinical practice in Europe and US during the late 1990's -2000, the time when this study was conducted. Since then, the clinical practice has evolved to use relatively lower starting doses of tacrolimus. The CsA use in liver transplantation has been considerably diminished like in other solid organ transplantations. Protocol specified target trough levels will be commented on later.

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Inclusion Criteria

1. Pediatric patients undergoing primary liver allograft transplantation (cadaveric or living related donor).
2. Male or female patients $\leq$ 16 years of age with a maximum weight of 40 kg
3. Written informed consent (IC) from the patient's parent or legal representative. In addition, if the patient could understand the concept of IC, the child's written IC was also obtained.

Exclusion Criteria

1. Patients undergoing liver-allograft retransplantation
2. Recipients of multiorgan transplants or previous organ transplants
3. Patients exhibiting symptoms of, or having any history of neoplastic diseases including leukemia. However, patients with primary liver carcinoma without metastases could be enrolled.
4. Patients in whom the administration of azathioprine was contraindicated.
5. ABO incompatible graft.
6. Patients with systemic infections requiring continued therapy at the time of study entry
7. Human immunodeficiency virus (HIV) positive recipient or donor
8. Patients who simultaneously participated in another investigational drug study or have participated within 28 days prior to the entry into this study
9. Patients with known sensitivity to tacrolimus, CsA-ME, HC0-60 (polyoxyl 60 hydrogenated castor oil) or structurally related compounds

Clinical Reviewer's Comment
Protocol specified inclusion/exclusion criteria are appropriate and acceptable.

Randomization

Immediately prior to administration of the first dose of study drug, patients who met the eligibility criteria and for whom IC was available, were randomly assigned to receive tacrolimus granules or CsA-ME using a 1:1 randomization schedule generated by the applicant's Data Operations department or its designee. A telephone-based computerized central randomization system was used. The random assignment was stratified within each clinic, by organ source (living vs cadaveric donor) and by patient age at time of randomization (< 3 vs ≥ 3 years of age).

Treatment Compliance

Forms were provided to the investigator or pharmacist to keep accurate records of all medications received from the applicant, dispensed to the patient, and returned by the patient. Treatment compliance was also to be monitored by blood trough level

assessments. Furthermore, the patients and their legal representatives were reminded to strictly follow the dosing recommendations.

Study treatments

Immediately prior to administration of the first dose of study drug (within 6 h posttransplantation or 24 h in case of postoperative renal impairment), patients were randomly assigned to receive either tacrolimus for oral suspension with low-dose corticosteroids or CsA-ME with low-dose corticosteroids and azathioprine as immunosuppressive therapy.

Tacrolimus dosage regimen:

Tacrolimus therapy was to commence as soon as possible after surgery but no longer than 6 h (24 h in case of postoperative renal impairment) after closure of the skin.

The planned initial daily dose for tacrolimus for oral suspension was 0.3 mg/kg per day administered via nasogastric or nasojejunal tube at 12-hour intervals. After the initial period of nasogastric or nasojejunal therapy, tacrolimus for oral suspension was to be administered orally at a starting dose of 0.3mg/kg/day, given in 2 doses (0.15 mg/kg twice daily).

The recommended target whole blood trough levels of tacrolimus were:

- 10 to 20 ng/mL during the first 2 weeks after transplantation,
- 10 to 15 ng/mL during weeks 3 and 4,
- 5 to 15 ng/mL during months 2 and 3 and
- 5 to 10 ng/mL thereafter.

Dose adjustments were to be made based on the patient's overall clinical status and trough concentrations. If adverse events related to tacrolimus were noted, the dose of tacrolimus was to be reduced by 20% or dosing was to be interrupted. Investigators were reminded that due to the long half-life of tacrolimus in blood (approximately 12 hours), a reduction in dose might not result in an immediate reduction in toxicity. If unacceptable toxicity persisted after dose reduction and/or interruption, tacrolimus treatment was to be discontinued. If toxicity led to interruption for more than 7 days (in case of renal impairment for more than 14 days), the patient was to be removed from the study.

Cyclosporine-ME dosage regimen:

CsA-ME therapy was to commence as soon as possible after surgery but no longer than 6 h (24 h in case of postoperative renal impairment) after closure of the skin. The planned initial daily dose for CsA-ME was 10 mg/kg per day orally, given in 2 doses (equals 5 mg/kg twice daily). Intravenous administration was to be conducted in addition to oral therapy when needed.

The recommended target whole blood trough levels of cyclosporine were 250 to 350

ng/mL within the first 2 weeks after transplantation, 200 to 300 ng/mL during weeks 3 to 12, 150 to 200 ng/mL during months 4 to 12 and 100 to 150 ng/mL thereafter. Dose adjustments were to be made based on the patient's overall clinical status and trough concentrations.

After a patient, had completed the 12-month study period or discontinued study drug, further immunosuppressive treatment of the patient was at the discretion of the investigator.

Clinical Reviewer's Comment
The label recommended tacrolimus target through level range for pediatric liver transplant recipients is 5-20 ng/mL during the first year following transplantation. The protocol specified target whole blood trough levels of tacrolimus are within the label recommended range. Per the Neoral® (CsA-ME) package insert, "If cyclosporine trough blood concentrations are used, the target range is the same for Neoral® as for Sandimmune®." However, Neoral® (CsA-ME) and Sandimmune® package inserts do not provide any recommended target trough levels since the methods and assays of concentration measurements had not been standardized at the time of labeling. Both the tacrolimus and cyclosporine target trough concentrations utilized in the protocol are compatible with the clinical practice.[4]

All patients in both groups were to receive corticosteroids as part of their maintenance regimen; azathioprine was to be administered to patients in the CsA-ME group only. This difference might have resulted in overimmunosuppression in the CsA-ME group compared to the tacrolimus group. As will be discussed later, this possible overimmunosuppression in the CsA group did not result in reduced rejection rates compared to the tacrolimus granules group.

Other immunosuppressive therapies:

For the corticosteroid treatment, patients in both treatment groups were to be administered 10 mg/kg methylprednisolone intravenously during surgery. Postoperative corticosteroid treatment consisted of intravenous methylprednisolone on days 1 to 6 (2 mg/kg per day) and once daily oral prednisolone thereafter. The dose of prednisolone was 1 mg/kg on days 7 to 13, 0.75 mg/kg on days 14 to 20, 0.5 mg/kg on days 21 to 28 and 0.25 mg/kg at months 2 to 3. Thereafter, prednisolone was to be taken every other day and/or tapered off, per local practice. Azathioprine was to be administered to patients in the CsA-ME group only.

Tacrolimus or CsA-ME dosing in case of concomitant disease:

[4] Jain A, Mazariegos G, Kashyap R, Green M, Gronsky C, Starzl TE, Fung J, Reyes J. Comparative long-term evaluation of tacrolimus and cyclosporine in pediatric liver transplantation. Transplantation. 2000;70(4):617-25.

In the event of EBV infection, the daily tacrolimus or CsA-ME dosage was to be reduced to 50% or as low as could be tolerated by the patient. If needed, additional treatment was to be given per local practice. To treat suspected PTLD, the dosage of tacrolimus for oral suspension or CsA-ME was to be reduced to as low as could be tolerated by the patient including temporary discontinuation. If needed, additional treatment was to be given per local practice. Treatment of established PTLD required discontinuation of tacrolimus or CsA-ME and surgery if needed. Patients with postoperative renal impairment were not to commence tacrolimus or CsA-ME therapy. The investigator could consider dose reduction for patients with renal impairment later in the study.

Acute rejections were treated with an increased dose of tacrolimus in the tacrolimus for oral suspension group and/or 1 full course of corticosteroids (total dose of 45 mg/kg methylprednisolone). Patients with acute rejections that did not respond to this corticosteroid treatment were to discontinue study drug and were to be treated per local practice.

Clinical Reviewer's Comment
Protocol specified changes in the dosing regimens of the CNIs (tacrolimus or CsA) in the case of PTLD or acute rejection episodes are appropriate and reflect the clinical practice.

Follow-up of patients who discontinued study drug

All patients who discontinued study drug were to be followed for serious adverse events (SAEs) for 28 days. An attempt was to be made to monitor all patients who discontinued study drug. These patients were to be followed up at a 12-month visit for patient and graft survival, actual immunosuppressive medication and SAEs. If a patient was discontinued from the study with an ongoing AE or an unresolved laboratory result that was significantly outside of the reference range, the investigator was to follow the patient until the condition stabilized or was no longer clinically significant.

Schedule of Assessments

All visits were calculated from the date of skin closure (day 0). After surgery, patients were observed daily for rejection episodes and AEs during hospitalization and at each outpatient visit throughout the study. Tacrolimus and cyclosporin trough levels were determined per the same schedule. At visits 1 to 6 (days 1, 5, 9, 14, 21 and 30), and visits 7 to 13 (week 6 to month 12) changes in tacrolimus or CsA-ME dosing and concomitant medication were recorded. If clinically indicated at any time, biopsy samples were taken to assess the rejection status of the patient.

Table 2 Schedule of Assessments (FG-506-01-13)

	Screening Visit (Day 0)	Study Phase							Follow-up Phase		
		Visits 1-4	Visit 5	Visit 6 (Day	Visit 7 (Week	Visit 8	Visit 9 (Week	Visit 10	Visit 11 (Month	Visit 12 (Month	Visit 13†

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		(Days 1, 5, 9, 14)	(Day 21)	28/ Month 1)	6)	(Week 8/ Month 2)	10)	(Week 12/ Month 3)	6)	9)	(Month 12)
Inclusion/exclusion criteria	X										
Written informed consent	X‡										
Medical history	X‡										
Donor data/recipient data	X‡										
Randomization details	X										
Surgical details	X										
Echocardiography	X	X§	X§	X§	X§	X§	X§	X	X	X§	X
Prestudy/concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Microbiology (bacterial, fungal, viral, parasitical)	X‡	X§	X§	X§	X§	X§	X§	X§	X§	X§	X§
EBV serology	X	X¶	X§	X	X	X	X	X††	X	X	X
EBV PCR measurements	X	X§	X§	X	X§	X§	X§	X	X	X§	X
Adverse events		X‡‡	X‡‡	X‡‡	X	X	X	X	X	X	X
Rejection episodes		X‡‡	X‡‡	X‡‡	X	X	X	X	X	X	X
Routine laboratory§§	X	X	X	X	X	X	X	X	X	X	X
Tacrolimus/cyclosporin trough levels		X‡‡	X‡‡	X‡‡	X	X	X	X	X	X	X
Liver biopsy		X§	X§	X§	X§	X§	X§	X§	X§	X§	X§
Pregnancy test	X¶¶										X¶¶

EBV: Epstein-Barr virus; EDTA: ethylenediaminetetraacetic acid; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ME: microemulsion; PCR: polymerase chain reaction
† Or at discontinuation of study drug
‡ Written informed consent, medical history, recipient data and viral status could be obtained/performed at the time of registration for waiting list. If needed for any reason, it should
have been repeated in due time before transplantation.
§ As clinically indicated
¶ At day 14
†† Every 6 weeks until month 6
‡‡ Daily while hospitalized, otherwise at visit
§§ Cholesterol, HDL and LDL only at screening and visits 6, 8, 10, 11, 12 and 13; EDTA-clearance only at screening and month 12
¶¶ For female patients of childbearing potential

Clinical Reviewer's Comment
The schedule of assessments is appropriate for the follow-up of pediatric *de novo* liver transplant recipients and reflects the clinical practice.

Monitoring for Infectious Disease

The patients' infection status was assessed at the screening visit to establish if any bacterial, parasitical, fungal or viral infections (cytomegalovirus [CMV], Epstein-Barr virus [EBV], human immunodeficiency virus [HIV], hepatitis B virus [HBV], hepatitis C virus [HCV]) were present. If an infection was suspected during the study, appropriate samples were to be taken for microbiological analysis and the results were entered in the CRF.

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Throughout the study, careful monitoring for new (serum Anti-EBV IgM antibodies and/or positive EBV-PCR in circulating lymphocytes in previously negative patients) or reactivated EBV infection (reappearance of IgM antibodies and/or positive EBV-PCR and/or positive culture with a compatible clinical context in patients previously immunized against EBV) was performed.

Management of PTLD

A diagnosis of suspected PTLD was based on proven EBV new infection or reinfection, unexplained clinical signs (any enlargement of tonsils, lymph nodes, spleen, any unexplained fever or abnormal liver enzymes, any tumor detected), significant increase of total serum gamma globulins, peak of oligo or monoclonal immunoglobulin and neutropenia (not mandatory) without abnormal B cell proliferation.

Schedule and Methods for Drug Concentration Measurements

Monitoring of tacrolimus blood levels was performed using local IMx analysis. Blood samples were taken in the morning before the first dose of tacrolimus or CsA-ME. Levels were assessed daily while the patient was hospitalized and routinely at the visits.

Statistical Analysis Plan

The sample size was calculated to be 200 patients (100 patients per arm). This would allow a difference of 20% in the frequency of acute rejection to be detected at the $\alpha = 0.05$ level with a power of at least 80% (based on acute rejection rate of 50% after 12 months). The ITT population consisted of all randomized patients that received at least 1 dose of study drug.

Efficacy Population
The efficacy population was to consist of all randomized patients with results attributed to the treatment group that they were randomized to and who received at least 1 dose of study drug. Patients who had displayed the following major protocol violations were to be excluded from the efficacy population:

- Patient was undergoing liver allograft re-transplantation
- Patient was a recipient of multi-organ transplant or previous organ transplant
- Patient or donor were HIV positive

All statistical testing was performed at the 5% level, unless otherwise indicated.

Protocol Amendments

The original protocol (Version 1.0) was dated 19 Mar 1997. Since then, 3 substantial amendments (dated 25 Jul 1997, 04 Dec 1997 and 05 Feb 1999) were made. Important changes in the substantial amendment 1, dated 25 Jul 1997, is summarized below.

- The method for the diagnosis, early detection and monitoring of Epstein-Barr virus (EBV) infection was found to be incorrect and was thus modified. It was specified that at least qualitative EBV polymerase chain reaction (PCR) was to be

performed and that donor blood was to be analyzed if available.

- Per the investigators' agreement, the definition of acute steroid-resistant rejection was modified to reference 1 course of steroids instead of 2 ("*an acute steroid resistant rejection was defined as an acute rejection not responding to 1 full course of steroids [total dose of 45 mg/kg methylprednisolone]*").
- The laboratory value for ethylenediaminetetraacetic acid (EDTA) clearance was amended to include a larger range of methods for estimation of the glomerular filtration rate.

Protocol amendment 2, dated 04 Dec 1997, was issued to clarify that for the post study treatment, patients would be switched from tacrolimus for oral suspension to 0.5 mg and 1.0 mg capsules of tacrolimus after the end of the study.

Protocol amendment 3, dated 05 Feb 1999, was issued to recommend prophylaxis treatment for EBV infection only for those patients who were EBV negative at baseline instead of all patients. This change resulted from investigators opinion that prophylaxis should only be administered to high risk patients. In addition, it extended the enrollment period from 18 to 28 months.

5.1.2. Study Results (FG-506-01-13)

Compliance with Good Clinical Practices

This study was performed in compliance with Good Clinical Practice (GCP).

Financial Disclosures

Study FG-506-01-13 was conducted between October 1998 and December 2000 in 10 centers in Belgium, France, Germany, Italy, Spain, and the UK. The two studies were sponsored by Fujisawa GmbH (Munich). The applicant, Astellas, has taken the necessary steps to retrieve financial certification and disclosure information by contacting the principal study investigators retrospectively. Astellas attempted to deliver financial disclosure requests to all FG-506-01-13 principal investigators. Financial disclosures were received from all but the following two FG-506-01-13 principal investigators:

- (b) (6)
-

All FG-506-01-13 principal investigators from whom financial disclosure information was received certified no financial arrangements, payments, or interests requiring disclosure under 21 CFR 54.4(a)(3).

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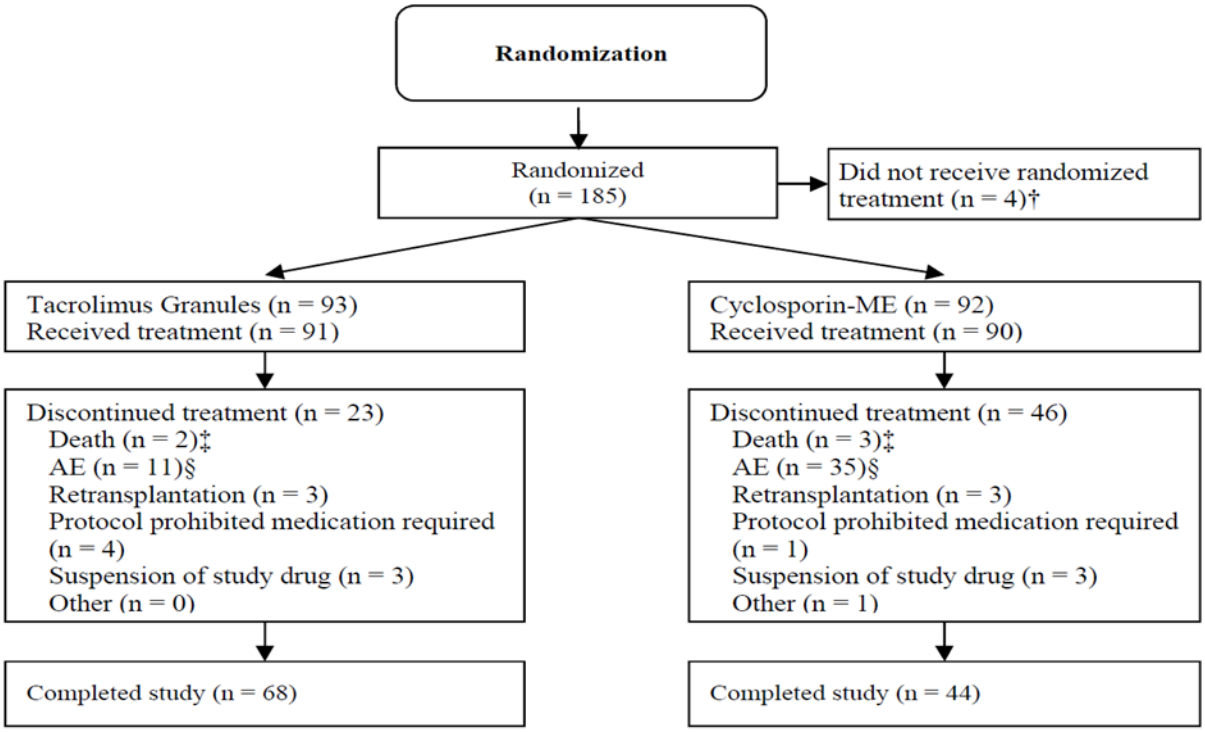
Patient Disposition

Figure 1 Patient Disposition (FG-506-01-13)
(Copied from Figure 1 in the Clinical Study Report)



† Three patients (1 randomized to tacrolimus granules and 2 randomized to cyclosporin-ME) did not receive treatment. One additional patient was randomized to tacrolimus granules but received cyclosporin-ME and discontinued after the first dose. No further data were collected for this patient.
‡ An additional 11 patients (5 tacrolimus granules, 6 cyclosporin-ME) died after they discontinued from the study.
§ Reason for discontinuation on the Study Completion CRF was "AE."

Table 3 Patient Disposition by Age Groups (FG-506-01-13)
(ITT population)
(Table generated by the FDA Biostatistics Reviewer Hongling Zhou)

	Tacrolimus for oral suspension			**Cyclosporine ME**		
	Total N=91 (100%)	<5 Y N=70 (100%)	≥5 Y N=21 (100%)	Total N=90 (100%)	<5 Y N=70 (100%)	≥5 Y N=20 (100%)
Completed study/treatment	**68 (74.7)**	**53(75.7)**	**15(71.4)**	**44 (48.9)**	**32(45.7)**	**12(60)**

Discontinued study treatment	**23 (25.3)**	**17(24.3)**	**6(28.6)**	**46 (51.1)**	**38(54.3)**	**8(40)**
Adverse Event	11 (12.1)	7(10)	4(19.0)	35 (38.9)	31(44.3)	4(20)
Retransplantation	3(3.3)	3(4.3)	0	3(3.3)	2(2.9)	1(5)
Protocol prohibited medication required	4 (4.4)	2(2.9)	2(9.5)	1 (1.1)	0	1(5)
Suspension of study drug	3(3.3)	3(4.3)	0	3(3.3)	2(2.9)	1(5)
Death	2 (2.2)	2(2.9)	0	3 (3.3)	3(4.3)	0
Other	0	0	0	1 (1.1)	0	1(5)

Table 4 Discontinuations of Study Drug Over Time (FG-506-01-13)
(ITT population)
(Copied from Table 2 in the Clinical Study Report)

Time of Study Drug Discontinuation	Number of Patients, n (%)			
	Tacrolimus Granules n = 91		Cyclosporin-ME n = 90	
	Discontinued Study Drug	Remained on Study Drug	Discontinued Study Drug	Remained on Study Drug
Weeks 1-2	5 (5.5)	86 (94.5)	17 (18.9)	73 (81.1)
Weeks 3-4	6 (6.6)	80 (87.9)	9 (10.0)	64 (71.1)
Months 2-3	3 (3.3)	77 (84.6)	11 (12.2)	53 (58.9)
Months 4-6	8 (8.8)	69 (75.8)	4 (4.4)	49 (54.5)
Months 7-9	1 (1.1)	68 (74.7)	4 (4.4)	45 (50.0)
Months 10-12	0	68 (74.7)	1 (1.1)	44 (48.9)
Total	23	68	46	44

Clinical Reviewer's Comment
The younger age group (<5 Y) constitute the majority of patients in both groups. The discontinuation rate due to AEs is more than twice as high in the CsA-ME group compared to the tacrolimus granules group (25.3% vs 51.1%). The very high discontinuation rate in the CsA-ME group may have resulted in relative under- or overrepresentation of the safety and efficacy events in this treatment group depending on the rates of these events in the tacrolimus for oral suspension group since most patients who discontinued the CsA-ME treatment were switched over to tacrolimus based immunosuppression per the patient narratives. The CsA-ME discontinuation rate is higher than would be expected throughout the study period (Table 4), and a careful analysis was done to look for possible explanations. The discontinuation rates for tacrolimus are closer to what is seen in adult studies of tacrolimus.

Protocol Violations/Deviations
A total of 4 patients (2 tacrolimus granules, 2 CsA-ME) entered the study despite not

satisfying an entry criterion (they did not meet inclusion criterion 3). One patient received the wrong treatment (CsA-ME instead of tacrolimus granules) and was not included in the ITT population.

Demographic Characteristics

Recipients:
Demographic characteristics were generally comparable between the tacrolimus for oral suspension and the CsA-ME groups. The mean age was 3.5 years in the tacrolimus granules group and 3.5 years in the CsA-ME group (Table 5). The mean weight was 14.6 kg in the tacrolimus granules group and 13.9 kg in the cyclosporin-ME group. In both the tacrolimus granules and CsA-ME groups, most patients were < 5 years of age (76.9% and 77.8%, respectively). The proportion of patients < 1 year of age was 34.1% in the tacrolimus granules group and 42.2% in the CsA-ME group.

Donors:
In both the tacrolimus for oral suspension and the CsA-ME groups, most donors were male (62.9% and 56.8%, respectively) and Caucasian (84.9% and 85.9%, respectively). The mean age was 16.9 years in the tacrolimus granules group and 17.8 years in the CsA-ME group.

Table 5 Recipient Demographics and baseline Characteristics (FG-506-01-13)

Parameter Category/Statistics	**Tacrolimus for oral suspension n = 91** n (%)	**Cyclosporine-ME n = 90** n (%)
Sex		
Male	46 (50.5)	48 (53.3)
Female	45 (49.5)	42 (46.7)
Age (years)		
Mean (SD)	3.5 (3.9)	3.4 (4.2)
Median	1.9	1.5
Range	0.3-15.0	0.1-16.0
Age Group		
≥ 5 years	21 (23.1%)	20 (22.2%)
< 5 years	70 (76.9)	70 (77.8)
< 1 years	31 (34.1)	38 (42.2)
Race		
White	75 (82.4)	80 (88.9)
Black or African American	6 (6.6)	2 (2.2)
Unknown	12 (14.0)	12 (14.1)
Missing	5	5
Recipient weight, kg Mean (SD)	14.58 (10.30)	13.86 (10.74)

Reference ID: 4267221

Recipient height, cm Mean (SD)	88.7 (28.3)	87.7 (26.9)
Living related donor		
Yes	10 (11.0)	11 (12.2)
No	81 (89.0)	79 (87.8)

Clinical Reviewer's Comment
Both treatment groups are balanced in terms of donor/recipient age, gender, race and other characteristics. Approximately 11-12% of transplantations in both treatment groups were performed using partial liver grafts from living related donors.

Demographics and Other Baseline Characteristics by Age Subgroup

Category ≥ 5 Years

Recipients

The tacrolimus granules and CsA-ME groups included 21 and 20 patients ≥ 5 years of age, respectively. Among patients ≥ 5 years of age, male patients made up approximately half of patients (52.4%) in the tacrolimus granules group and the majority (75.0%) in the CsA-ME group. In both the tacrolimus granules and CsA-ME groups, most patients ≥ 5 years of age was Caucasian (76.2% and 90.0%, respectively). The mean weight was 29. 9 kg in the tacrolimus granules group and 30 kg in the CsA-ME group.

Donors

In both the tacrolimus granules and CsA-ME groups, donors for recipients ≥ 5 years of age were mostly male (70.0% and 55.0%, respectively) and Caucasian (94.4% and 84.2%, respectively). The mean age of donors for recipients ≥ 5 years was 18.84 years in the tacrolimus granules group and 14.77 years in the CsA-ME group.

Category < 5 Years

Recipients

The tacrolimus granules and CsA-ME groups each included 70 patients <5 years of age. Among patients < 5 years of age, male patients constituted half of patients in both groups (52.4% in the tacrolimus granules group and 47.1% in the CsA-ME group). In both the tacrolimus granules and the CsA-ME groups, the majority of patients < 5 years of age were Caucasian (84.3% and 88.6%, respectively). The mean weight was 9.99 kg in the tacrolimus granules group and 9.19 kg in the CsA-ME group.

Donors

In both the tacrolimus granules and CsA-ME groups, donors for recipients < 5 years of age were mostly male (60.9% and 57.4%, respectively) and Caucasian (82.4% and 86.4%, respectively). The mean age of donors for recipients < 5 years was 16.2 years in the tacrolimus granules group and 18.6 years in the CsA-ME group.

Clinical Reviewer's Comment
In terms of baseline donor and recipient characteristics, both the *'< 5 years of age*' and the *'≥ 5 years of age*' subgroups were generally balanced across the treatment arms with a few exceptions:
Among patients ≥ 5 years of age, in the CsA-ME group, the donors were relatively younger (14.7 vs 18.8) and there were relatively more male recipients (75.0% vs 52.4%) compared to the tacrolimus granules group. As will be discussed later, the preponderance of male recipients in the CsA-ME ≥ 5 years of age subgroup may have worked in favor of the CsA-ME group since there were unexpectedly high rejection rates among female recipients treated with CsA-ME compared to female recipients treated with tacrolimus granules.

Table 6 Primary Diagnosis (FG-506-01-13 ITT Population)

Primary Diagnosis Category/Subcategory	Number of Patients, n (%)	
	Tacrolimus for oral suspension n = 91	Cyclosporine-ME n = 90
Alagille syndrome	6 (6.6)	6 (6.7)
Biliary atresia	54 (59.3)	44 (48.9)
Metabolic disease	2 (2.2)	2 (2.2)
Other	13 (14.3)	11 (12.2)
Sclerosing cholangitis	0	2 (2.2)
Cirrhosis (total)	16 (17.6)	25 (27.8)
Alpha-1-antitrypsin	4 (4.4)	2 (2.2)
Autoimmune	0	3 (3.3)
Byler's disease	3 (3.3)	10 (11.1)
Cryptogenic	2 (2.2)	4 (4.4)
Other	7 (7.7)	6 (6.7)

Clinical Reviewer's Comment
Both treatment groups are generally balanced in terms primary disease as the cause of liver failure (Table 6).

Recipient and Donor Blood Type and Viral Status
Most patients in the tacrolimus for oral suspension and CsA-ME groups received their transplant from a donor with identical blood group (75 [82.4%] and 75 [83.3%] patients, respectively). Rhesus factor mismatch occurred in 21 (23.6%) patients in the tacrolimus granules group and 24 (27.0%) of patients in the CsA-ME group. The HLA type was not recorded for 48 patients in the tacrolimus granules group and 54 patients in the CsA-ME group.

The majority of patients in the tacrolimus for oral suspension and CsA-ME groups matched their donors in negative status for HBV, HCV and HIV: 80 (87.9%) and 81 (90.0%) patients,

respectively, were HBV-negative and had received a transplant from an HBV-negative donor; 85 (93.4%) and 88 (97.8%) patients, respectively, were HCV negative and had received a transplant from an HCV-negative donor; and 83 (91.2%) and 83 (92.2%) patients, respectively, were HIV-negative and had received a transplant from an HIV-negative donor (Table 7).

Regarding CMV status, approximately equal proportions of patients in the tacrolimus for oral suspension and CsA-ME groups matched their donors in terms of CMV status. In the tacrolimus for oral suspension and CsA-ME groups, 29 (31.9%) and 31 (34.4%) patients, respectively, were CMV-negative and received organs from CMV-negative donors; 21 (23.1%) and 25 (27.8%) patients, respectively, were CMV-positive and received organs from CMV-positive donors. However, 29 (31.9%) and 22 (24.4%) patients, respectively, were CMV-negative and received organs from CMV-positive donors.

At baseline, the proportions of EBV-negative patients with an EBV-positive donor and of EBV-negative patients who had a donor with unknown EBV status were higher in the tacrolimus granules group (20.9% and 29.7%, respectively) than in the CsA-ME group (12.2% and 15.6%, respectively) [Table 7]. At baseline among patients < 1 year of age, the proportions of EBV-negative patients with an EBV-positive donor and of EBV-negative patients who had a donor with unknown EBV status were higher in the tacrolimus granules group (22.6% and 45.2%, respectively) than in the CsA-ME group (18.4% and 18.4%, respectively)

Table 7 EBV and HIV Viral Status at Baseline (FG-506-01-13 ITT Population)

Parameter	Category/Statistic	Number of Patients, n (%)	
		Tacrolimus for oral suspension n	Cyclosporine-ME n = 90
EBV Status (Recipient/Donor)	Positive/Positive	6 (6.6)	16 (17.8)
	Positive/Negative	3 (3.3)	12 (13.3)
	Positive/Unknown	23 (25.3)	23 (25.6)
	Negative/Positive	19 (20.9)	11 (12.2)
	Negative/Negative	11 (12.1)	12 (13.3)
	Negative/Unknown	27 (29.7)	14 (15.6)
	Unknown/Positive	0	1 (1.1)
	Unknown/Negative	0	0
	Unknown/Unknown	2 (2.2)	1 (1.1)
HIV Status (Recipient/Donor)	Positive/Positive	0	0
	Positive/Negative	0	0
	Positive/Unknown	0	0
	Negative/Positive	0	0
	Negative/Negative	83 (91.2)	83 (92.2)
	Negative/Unknown	2 (2.2)	0
	Unknown/Positive	0	0
	Unknown/Negative	6 (6.6)	7 (7.8)
	Unknown/Unknown	0	0

Reference ID: 4267221

Clinical Reviewer's Comment
In general, the proportions of EBV-negative patients with an EBV-positive donor or with a donor with unknown EBV status were higher in the tacrolimus for oral suspension group compared to the CsA-ME group which was more pronounced among patients < 1 year of age. These imbalances may have disadvantaged the tacrolimus granules group in terms of post-transplant lymphoproliferative disease (PTLD) risk since EBV seronegativity especially when combined with a EBV (+) donor is a risk factor for PTLD. There were no HIV (+) recipients and no HIV (+) donors in the study; however, in a few donors and recipients, the HIV status was unknown.

In both the tacrolimus for oral suspension and CsA-ME groups, most patients received partial liver transplants (61 [67.0%] and 65 [72.2%] patients, respectively). The total ischemia time, which was recorded for 82 patients in the tacrolimus for oral suspension group and 85 patients in the CsA-ME group, was less than 20 hours. The mean (SD) total ischemia time was similar in the tacrolimus for oral suspension and CsA-ME groups (8.6 [3.4] hours and 8.8 [3.4] hours, respectively).

Study Drug Exposure, Treatment Compliance and Concomitant Medications
Patients in the tacrolimus for oral suspension group received a dual immunosuppressive treatment regimen consisting of tacrolimus for oral suspension and corticosteroid. Patients in the CsA-ME group received a triple immunosuppressive treatment regimen consisting of CsA-ME, corticosteroid and azathioprine.
All 181 patients received either tacrolimus for oral suspension or CsA-ME in oral form. There were 1/91 (1.1 %) instance of intravenous tacrolimus therapy and 42/90 (46.7%) instances of intravenous CsA-ME therapy during the study. A summary of total daily dose of study drugs over time is presented in Table 8.

Table 8 Total Daily Doses of Study Drugs (FG-506-01-13 ITT Population)

(Table reproduced from the Study Report Table 6)

Visit	Total Daily Dose (mg/kg) administered as BID					
	Tacrolimus for oral suspension			Cyclosporin-ME		
	n	Mean (SD)	Median	n	Mean (SD)	Median
First dose†	91	0.26 (0.09)	0.29	89	12.32 (4.21)	12.10
Day 1	91	0.23 (0.10)	0.27	89	11.35 (4.32)	10.41
Day 3	90	0.18 (0.14)	0.14	85	14.63 (10.30)	11.67
Day 7	89	0.24 (0.18)	0.22	81	19.12 (13.91)	15.00
Day 14	88	0.30 (0.19)	0.25	75	17.72 (13.54)	15.00
Month 1	81	0.34 (0.22)	0.30	63	15.75 (15.74)	12.73
Month 3	77	0.31 (0.19)	0.27	55	11.57 (5.97)	11.05
Month 6	71	0.25 (0.18)	0.20	49	10.98 (6.27)	10.20

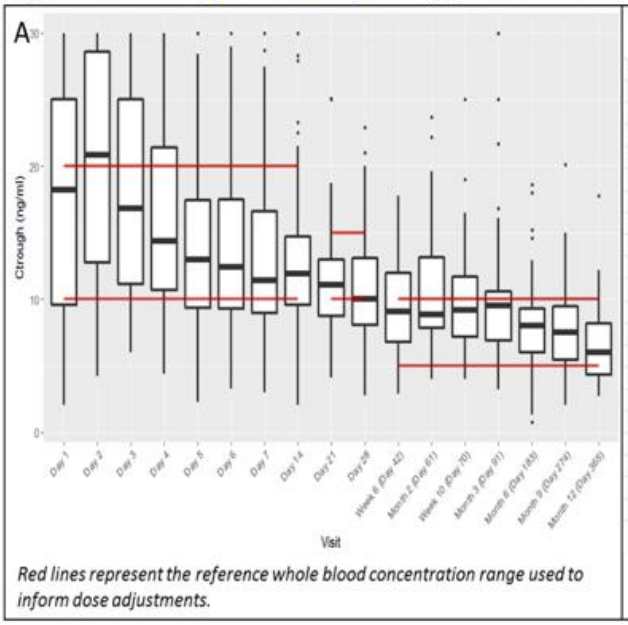
Reference ID: 4267221

Month 9	68	0.19 (0.12)	0.17	45	9.22 (3.37)	9.00
Month 12	58	0.18 (0.11)	0.16	39	8.65 (2.83)	8.33

† Initial daily starting dose of randomized study drug is defined as the total daily dose on the first day with morning and evening dose. One patient randomized to CsA-ME received only 1 dose of study drug; therefore, not included in the summary of initial daily starting dose.

Figure 2 Tacrolimus Trough Levels (ng/mL) (FG-506-01-13)
(Provided by Clinical Pharmacology Reviewer Dr. Abhay Joshi)

Figure 4: Box Plots (A) and Summary Table (B) for the Observed Trough Concentrations of Tacrolimus in Study FG-506-01-13



B

	Trough Con. (mg/mL)									
Percentile	LL	UL	P10	P25	***P50***	P75	P90	N	TargetTc_LL	TargetTc_UL
Visit										
Day 1	2.05	30	5.55	9.6	***18.2***	25	30	76	10	20
Day 2	4.2	30	8.6	12.78	***20.85***	28.57	30	88	10	20
Day 3	6	30	8.85	11.12	***16.8***	25	30	86	10	20
Day 4	4.4	30	7.55	10.67	***14.35***	21.4	30	86	10	20
Day 5	2.3	30	6.75	9.35	***12.95***	17.43	23.25	86	10	20
Day 6	3.3	30	6.54	9.3	***12.4***	17.5	24.28	85	10	20
Day 7	3	30	6.2	8.95	***11.4***	16.62	22.21	82	10	20
Day 14	2.05	30	6.92	9.55	***11.9***	14.7	19.1	87	10	15
Day 21	4.1	25.1	6.94	8.75	***11.1***	13	16.96	75	10	15
Day 28	2.8	22.9	6.52	8.05	***10***	13.07	16.76	72	5	10
Week 6 (Day 42)	2.9	17.8	5.3	6.8	***9.1***	12	14.36	69	5	10
Month 2 (Day 61)	4	23.7	5.69	7.82	***8.85***	13.15	14.97	74	5	10
Week 10 (Day 70)	4	25	6.2	7.2	***9.2***	11.7	13.6	61	5	10
Month 3 (Day 91)	3.2	30	5.24	6.9	***9.5***	10.6	15.42	65	5	10
Month 6 (Day 183)	0.75	18.6	4.51	6.03	***8***	9.3	11.59	62	5	10
Month 9 (Day 274)	2.05	20.1	4.46	5.45	***7.5***	9.45	11.17	60	5	10
Month 12 (Day 365)	2.7	17.8	3.5	4.35	***6***	8.2	10	51	5	10

Table 9 Trough Levels (ng/mL) (FG-506-01-13 ITT Population)
(Table reproduced from the Study Report Table 7)

Visit	**Daily Trough (ng/mL)**			
	Tacrolimus		**Cyclosporin**	
	n	**Mean (SD)**	**n**	**Mean (SD)**
Day 1	76	17.7 (8.9)	73	187.1 (180.2)
Day 7	82	13.0 (6.4)	80	280.2 (124.0)
Day 14	87	12.8 (5.4)	75	265.1 (115.3)
Month 1	72	10.7 (4.1)	54	271.0 (127.9)
Month 3	65	9.9 (4.7)	45	198.3 (87.2)
Month 6	62	8.1 (3.3)	45	159.6 (68.9)

Month 9	60	7.7 (3.2)	37	153.5 (73.6)
Month 12	51	6.6 (2.9)	29	143.5 (68.3)

Clinical Reviewer's Comment
Tacrolimus trough levels (Figure 2 and Table 9) throughout the study period were generally within the protocol specified range (*10 to 20 ng/mL during the first 2 weeks after transplantation, 10 to 15 ng/mL during weeks 3 and 4, 5 to 15 ng/mL during months 2 and 3 and 5 to 10 ng/mL thereafter*).

Cyclosporine trough levels throughout the study period (Table 8) are within the protocol specified target range (*250 to 350 ng/mL within the first 2 weeks after transplantation, 200 to 300 ng/mL during weeks 3 to 12, 150 to 200 ng/mL during months 4 to 12*) but somewhat on the high side compared to today's clinical practice[5]; however, they are in line with the clinical practice at the time when this study was conducted. It is important to keep in mind that CsA-ME patients received triple drug therapy including azathioprine unlike the tacrolimus patients who received dual drug therapy when making comparative efficacy and safety assessments.

Table 10 Daily Doses of Corticosteroid and Azathioprine (FG-506-01-13 ITT Population)

Visit	Treatment Groups								
	Tacrolimus for oral suspension			Cyclosporin-ME					
	Daily Dose of Corticosteroid (mg/kg)			Daily Dose of Corticosteroid (mg/kg)			Daily Dose of Azathioprine (mg/kg)		
	n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median
Week 1	91	3.19 (0.97)	3.03	89	3.36 (1.73)	3.14	86	1.47 (0.27)	1.50
Week 2	89	1.19 (0.87)	1.09	82	1.07 (0.38)	1.05	80	1.48 (0.26)	1.50
Week 4	83	0.79 (0.68)	0.64	69	0.77 (0.34)	0.69	66	1.46 (0.30)	1.51
Month 3	77	0.39 (0.26)	0.31	59	0.36 (0.19)	0.31	49	1.30 (0.35)	1.34
Months 4-6	71	0.28 (0.16)	0.26	45	0.28 (0.16)	0.26	32	1.19 (0.45)	1.23
Months 7-9	56	0.24 (0.16)	0.20	33	0.26 (0.17)	0.24	19	1.16 (0.47)	1.29
Months 10-12	50	0.21 (0.15)	0.18	31	0.21 (0.10)	0.20	17	1.09 (0.37)	1.15

Clinical Reviewer's Comment
Following the initial high doses of corticosteroids at the time of transplant surgery, in both treatment groups, the mean daily dose of corticosteroids and in the CsA-ME group, the mean daily dose of azathioprine decreased over time (Table 10) as expected.

Common prior medications included ursodeoxycholic acid, diuretics (spironolactone and

[5] Spada M, Riva S, Maggiore G, Cintorino D, Gridelli B. Pediatric liver transplantation. World J Gastroenterol. 2009;15(6):648-74.

furosemide) and gastrointestinal medications (ranitidine and lactulose). In general, prior medication usage was similar in the 2 treatment groups. Common concomitant medications included gastrointestinal medications (ranitidine), anti-infective medication (acyclovir, amphotericin and nystatin) and diuretics (furosemide). The number of patients receiving the most common medications was similar in both treatment groups.

Efficacy Results of Study FG-506-01-13

Key efficacy findings (incidence rates) including results broken down by age groups as calculated by the FDA Biostatistics Reviewer Dr. Hongling Zhou are included in Table 11 below.

Table 11 Efficacy Results by Treatment Group at 12 Months

(Table generated by the FDA Biostatistics Reviewer Hongling Zhou)

Endpoints	**Tacrolimus Granules**	**Cyclosporine-ME**	**Risk Difference (95% CI) (tacrolimus granules – Cyclosporine-ME)**
ITT Population			
	N=91	N=90	
AR	39* (42.9%)	49 (54.4%)	-11.6% (-26.1%, 2,9%)
BPAR	40* (44.0%)	49 (54.4%)	-10.5% (-25.0%,4.0%)
Death	6 (6.6%)	7 (7.8%)	-1.2% (-8.7%, 6.3%)
Graft loss	7 (7.7%)	13 (14.4%)	-6.8% (-15.8%, 2.3%)
Graft loss excluding death	1 (1.1%)	6(6.7%)	
BPAR/GL/D	46 (50.5)	55 (61.1%)	-10.6% (-24.9%, 3.8%)
Unknown status	2 (2.2%)	0	2.2% (-2.1%, 8.3%)
BPAR/GL/D/LTFU	48 (52.7%)	55(61.1%)	-8.4% (-22.7%, 6.0%)
< 5 years of age			
	N=70	N=70	
AR	31*(44.3%)	40 (57.1%)	-12.9% (-29.3%, 3.6%)
BPAR	32* (45.7%)	40 (57.1%)	-11.4% (-27.9%, 5.0%)
Death	5 (7.1%)	7 (10%)	-2.9% (-12.1%, 6.4%)
Graft loss	6(8.6%)	12(17.1%)	-8.6% (-19.6%, 2.4%)
BPAR/GL/D	37 (52.9%)	45 (64.3%)	-11.4% (-27.6%, 4.8%)
Unknown status	2 (2.2%)	0	2.2% (-2.1%, 8.3%)
≥ 5 years of age			
	N=21	N=20	
AR	8 (38.1)	9 (45)	-6.9% (-37.0%, 23.2%)
BPAR	8 (38.1)	9 (45)	-6.9% (-37.0%, 23.2%)
Death	1 (4.8)	0	4.8% (-12.4%,24.3%)

Graft loss	1 (4.8)	1 (5)	-0.2% (-20.6%, 19.9%)
BPAR/GL/D	9 (42.9)	10 (50)	-7.1% (-37.6%, 23.3%)

* Patient (b) (6) had a biopsy done for determination of PTLD (not a diagnosed AR) that revealed a BPAR. The patient was marked as an event for BPAR but not AR.
Source: Biostatistics Reviewer Analysis

As included in Table 10, AR, BPAR, death (D), graft loss (GL) and the BPAR/GL/D composite incidence rates at 12 months are all numerically lower in the tacrolimus for oral suspension group compared to the CsA-ME group with similar trends in the two age groups (< 5 and ≥ 5 years of age).

Clinical Reviewer's Comment

(b) (4)

(b) (4) For further information about the applicant's proposal to summarize the efficacy results (b) (4) see Biostatistics review of NDA 210,115. Incidence rate comparisons across the treatment groups in Table 10 (b) (4) (b) (4) will be included in the Prograf package insert.

All the confidence intervals (CI) of the differences between the incidence rates of the efficacy events across the treatment groups cross over (include) zero (0). Therefore, the differences do not reach statistical significance. It is likely that the differences would reach statistical significance if the sample size had been larger.

Patient Survival and Gender Effect

The rates of patient survival at 12 months were 93.4% and 92.2%, in the tacrolimus for oral suspension and CsA-ME groups respectively. Gender breakdown of the deaths observed during the study are in Table 12.

Table 12 Deaths by Gender FG-506-01-13

	Tacrolimus	Cyclosporin-ME
All Deaths	6 (6.6%)	7 (7.8%)
Male	3/46 (6.5%)	2/48 (4.2%)

Female	3/45 (6.7%)	5/42 (11.9%)

Clinical Reviewer's Comment
Most of the deaths were observed in the < 5 years of age group. Overall, the proportion of deaths across the treatment groups is balanced (6.6% and 7.8%). However, in the gender subgroup analyses, the highest death rate was observed in the CsA-ME females (11.9%) which is almost twice as high compared to tacrolimus females (6.7%). Since these are small numbers the percentages may dramatically change by one or two death events in any of the treatment groups and must be interpreted with caution. The numerically higher number of deaths among the CsA females relative to the deaths among the tacrolimus females may be at least partially explained by the relatively more intense immunosuppression in the CsA-ME arm with higher than expected CsA trough levels throughout the study and with azathioprine which the tacrolimus arm did not include. This relatively more intense immunosuppression in the CsA-ME arm might have affected females more than the males for currently unknown reasons possibly contributing to more female deaths and more graft loses as discussed below in this subgroup. However, the possibility that these differences might have occurred by chance or due to unknown reasons cannot be ruled out in this relatively small study. See the safety assessment section of this review for further information and comments on the deaths.

Graft Survival
The rate of graft survival at 12 months were 92.3% and 85.4%, in the tacrolimus granules and CsA-ME groups respectively. When we exclude graft loses due to deaths, 1 (1.1%) patient lost a graft in the tacrolimus granules group compared to 6 (6.7%) patients in the CsA-ME group.

Graft Loss and Gender Effect
There were more death censored graft loses in the CsA-ME group [6/90 (6.7%)] compared to the tacrolimus granules group [1/91 (1.1%)] barely missing statistical significance [95% CI -13.0%, 0.2%] (Table 13). This difference was primarily driven by the 4 graft losses (9.5%) among the CsA-ME females compared to 0 graft loses among the tacrolimus for oral suspension females reaching statistical significance [95% CI (-22.8%, -0.9%)].

Table 13 Death Censored Graft Loses by Gender FG-506-01-13

	Tacrolimus for oral suspension N=91	Cyclosporine-ME N=90	95% CI of the difference
All Graft loses	1/91 (1.1%)	6/90 (6.7%)	-5.6% (-13.0%, 0.2%)
Male	1/46 (2.2%)	2/48 (4.2%)	-2.0% (-12.9%, 8.5%)
Female	0/45 (0)	4/42 (9.5%)	-9.5% (-22.8%, -0.9%)

Clinical Reviewer's Comment
Statistically significant higher graft loss rate among the CsA females compared to tacrolimus females is similar to the observation of a numerically higher death rate in the CsA-ME females

compared to tacrolimus females without reaching statistical significance. Based on the information in the patient narratives it is unlikely that the 4 graft loses that occurred among CsA females and tipped the balance in favor of the tacrolimus group are caused by cyclosporine. All 4 graft loses occurred early on (within the first 12 days in 3 patients and on Day 30 in the 4th patient) following the transplantation surgery. The graft loses occurred in connection with the following events in the 4 patients: iatrogenic colon perforation during transplantation; hepatic artery thrombosis on D8; primary nonfunction and portal vein thrombosis on D4. Therefore, although the imbalance in graft loses in the female subpopulation reaches statistical significance there seems to be no apparent direct causality association with the study treatment.

Protocol Specified Primary Endpoint and Gender Effect

Per the protocol, acute rejection was defined as a diagnosed acute rejection with histologic confirmation (BPAR). Table 14 shows the gender subgroup analysis of the BPAR events. The difference between the acute rejection rates across the two groups in favor of the tacrolimus granules group, was primarily driven by the unexpectedly high acute rejection rate observed among the female patients treated with CsA-ME.

Table 14 Incidence of Biopsy Confirmed Acute Rejection in 12 Months (FG-506-01-13)
(Reproduced from Tables 12.3.1.1 and 12.3.1.5 in CSR)

	Tacrolimus	Cyclosporine-ME
Overall*	40/91 (44.0%)	49/90 (54.4%)
Male**	21/46 (45.7%)	19/48 (39.6%)
Female***	18/45 (40.0%)	30/42 (71.4%)

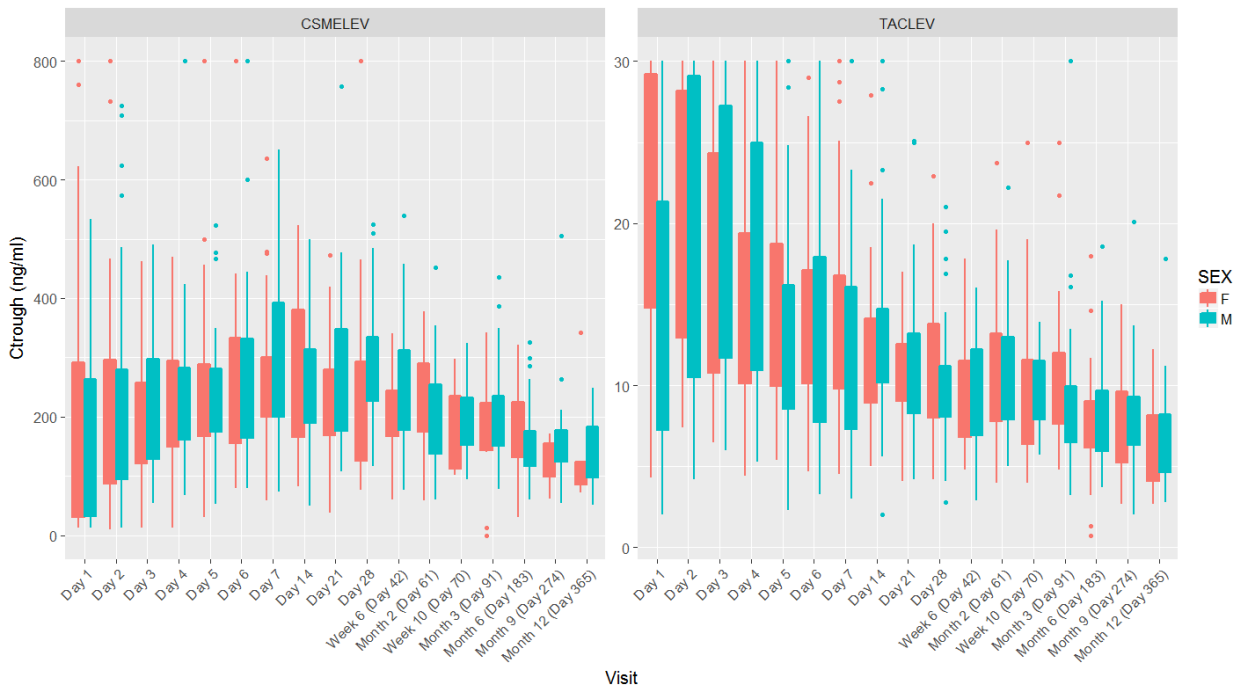
*P= 0.182
**P = 0.677
***P= 0.005

Clinical Reviewer's Comment
In Study FG-506-01-13, the incidence of biopsy proven acute rejection (BPAR) at 12 months (primary endpoint) was 44.0% in the tacrolimus group compared to 54.4% in the CsA-ME group with a 10.5 % [-25.0, 4.0] difference that did not reach statistical significance probably due to the small study size. This difference is primarily driven by the significantly high incidence of BPAR in female patients of the CsA group (71.4%) [compared to 40.0% BPAR rate in female patients of the tacrolimus group (p=0.005)]. In the male patient subgroup, an opposite trend was observed with a higher incidence of acute rejection in patients treated with tacrolimus (45.7%) compared to patients treated with CsA (39.6%), the difference not statistically significant. Except for the outlier subgroup of female CsA patients, the 12-month incidence

rates of BPAR are similar in the remaining gender based subgroups ranging from 39.6 % to 45.7 % which are within the expected range for this patient population.

As discussed earlier, the increased mortality among the female CsA-ME patients may possibly be the result of over-immunosuppression in the CsA-ME group. Therefore, it is paradoxical to see increased acute rejection rates in the same subpopulation (CsA-ME females) despite possible over-immunosuppression. The reason(s) for the higher than expected incidence of acute rejection concomitant with increased graft losses and mortality in the female patients of the CsA group is not clear. However, as further discussed under the safety analysis of Study FG-506-01-13, there seems to be little association if any, between the study treatments and the death events in both arms of the study. Therefore, the slightly higher number of deaths among the CsA females might have occurred by chance. It is also possible that female CsA patients were biopsied more frequently hence diagnosed with rejection more frequently in this open label study for reasons not entirely clear.

In order to rule out any possible increased (or decreased) CsA exposure in female patients compared to male patients, the observed trough levels were analyzed by the Clinical Pharmacology Reviewer Dr. Abhay Joshi. The graphs below showing the observed trough levels for both CsA and tacrolimus throughout the study period broken down by gender do not suggest any increased CsA exposure among female patients or any other CNI exposure imbalance among the gender based subgroups.



Reference ID: 4267221

It is also possible that the observed imbalances in terms of the efficacy events discussed above may be at least partially related to baseline conditions despite randomization in this relatively small study.

Primary Efficacy Variable by Age Subgroup

Category < 5 Years
The tacrolimus granules and CsA-ME groups each included 70 patients < 5 years of age. Among patients < 5 years of age the incidence of BPAR at 12 months was lower in the tacrolimus granules group compared to the CsA-ME group (45.7% and 57.1%, respectively), with a difference of -11.4% (-27.9%, 5.0%).

Category ≥ 5 Years
The tacrolimus granules and CsA-ME groups included 21 and 20 patients ≥ 5 years of age, respectively. Among patients ≥ 5 years of age, the incidence of BPAR at 12 months was lower in the tacrolimus granules group compared to the CsA-ME group (38.1% and 45.0%, respectively), with a difference of -6.9% (-37.0%, 23.2%).

Primary Efficacy Variable by Race

Caucasian
The tacrolimus granules and CsA-ME groups included 75 and 80 Caucasian patients, respectively. Among Caucasian patients, the incidence of BPAR at 12 months was lower in the tacrolimus granules group compared to the CsA-ME group (44.0% and 52.5%, respectively), with a nonsignificant difference of -8.5 (95% CI: -24.2, 7.2; P = 0.336, Fisher's exact test).

Non-Caucasian (Black, Oriental and Other)
The tacrolimus granules and CsA-ME groups included 15 and 10 non-Caucasian patients, respectively. Among non-Caucasian patients, the incidence of BPAR at 12 months was lower in the tacrolimus granules group compared to the CsA-ME group (33.3% and 70.0%, respectively), with a nonsignificant difference of -36.7 (95% CI: -73.8, 0.4; P = 0.111, Fisher's exact test).

Clinical Reviewer's Comment
In all subgroup analyses based on gender, age group and race, the overall trend of increased BPAR (without reaching statistical significance) in the CsA-ME group compared to the tacrolimus granules group is replicated except for the male subpopulation. As explained earlier, in the male patient subgroup, an opposite trend was observed with a higher incidence of acute rejection in patients treated with tacrolimus (45.7%) compared to patients treated with CsA (39.6%) which is statistically nonsignificant. In fact, although this trend is in the opposite direction when compared with other subgroup analyses based on race or age group in which tacrolimus patients experienced less rejection events compared to CsA patients, it is in line with the assumption that CsA-ME group may be over-immunosuppressed compared to the

tacrolimus granules group due to the presence of azathioprine in the regimen. As stated earlier, it is not clear why the female patients displayed an opposite trend compared to male patients.

5.2. A Two Centre Clinical Pilot Study in Children with Tacrolimus (FK506) Fine Granule Formulation As Immunosuppressive Therapy in Liver Allograft Transplantation (FG-506-01-08)

5.2.1. Study Design (FG-506-01-08)

Overview and Objective

The objective of this study was to assess the safety and efficacy of tacrolimus granules in children undergoing liver allograft transplantation, to refine the current dosing schedule in children and to compare dosing based on weight with dosing based on body surface area. A pharmacokinetics assessment was undertaken to help to evaluate the dosing regimen for tacrolimus granules; these data are presented in a separate pharmacokinetic study report [FG-506-01-08-R-PK-1].

Trial Design

This was a 12-month, open-label, phase 2, noncomparative single arm, pilot study conducted at 2 European sites to assess the safety and efficacy of tacrolimus granules in pediatric patients undergoing liver transplantation. The intention was to recruit a total of 20 patients. Treatment was to begin within 6 hours of skin closure and consisted of tacrolimus, corticosteroids and azathioprine. Assessments were performed on day 0 (baseline or screening visit, i.e., the day of skin closure), days 1, 5, 9, 14, 21 and 28; weeks 6, 8 and 10; and months 3, 6, 9 and 12. Patients were assessed for allograft rejection, patient and graft survival, and for adverse events on days 1 through 14 (daily if hospitalized), on all subsequent study visits and on an ongoing basis as indicated. Liver biopsies were performed when clinically indicated. Since no inferential statistics were planned, a sample size of 20 patients, who were also to provide pharmacokinetic profiles, was adequate for investigating the efficacy and safety of tacrolimus granules in this pilot study.

Clinical Reviewer's Comment
Since Study FG-506-01-08 is a small non-comparative study, the results provide only supportive evidence for safety and efficacy of tacrolimus granules in pediatric liver transplant recipients.

Study Endpoints

Patient and graft survival were to be assessed at months 3 and 12 and rejection episodes were to be assessed on days 1, 5, 9 and 14 (daily if hospitalized), on all subsequent study visits and

Reference ID: 4267221

on an ongoing basis as indicated. Graft failure was defined as occurring if a patient died or required retransplantation.

Inclusion Criteria
1. The patient had undergone primary liver allograft transplantation.
2. The patient was 15 years of age or younger.
3. The patient's parent or legal representative had given written IC to participate in the study.

Exclusion Criteria
1. The patient had undergone previous liver allograft transplantation.
2. The patient had undergone any previous organ transplantation or was to receive a multi-organ transplant.
3. The patient exhibited symptoms or had a history of malignancy including leukemia.
4. The patient had gross renal impairment prior to transplant (i.e., eGFR < 60 mL/min/1.73 m2 or less than half the lower limit of the normal range for age at the particular site).
5. The patient had received an organ from an ABO incompatible donor.
6. The patient had uncontrolled severe extrahepatic infection including fulminant or subfulminant viral hepatitis, fulminant Wilson's disease, or fulminant ischemic hepatic necrosis with biliary atresia.
7. The patient was known to have human immunodeficiency virus (HIV) or hepatitis B virus (HBV) positive serology.
8. The patient had active collagen-vascular disease.
9. The patient had a stage IV B hepatic encephalopathy, was comatose or unresponsive to noxious stimuli and had an abnormal ECG or fulminant liver disease irrespective of the presence of asterixis.
10. The patient had received any unapproved investigational agent within 28 days prior to entry into the study.
11. The patient had a known sensitivity to tacrolimus, polyoxyethylene hydrogenated castor oil 60 or structurally related compounds.
12. The patient had received treatment with disallowed immunosuppressive agents (e.g., cyclosporine).
13. The patient was a sexually active female, was pregnant or lactating or of childbearing potential and did not use adequate contraceptive measures.

Treatments
Treatment consisted of tacrolimus in combination with azathioprine and corticosteroids.
Tacrolimus dose regimen:
Tacrolimus therapy was to commence as soon as possible after surgery but no later than 6 h after closure of the skin. An initial dose of 0.045 mg/kg per 24-h was to be administered as a continuous intravenous infusion for 12 h to 4 days. After the initial period of intravenous

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therapy, tacrolimus was to be administered orally for a duration of 12 months. Oral dosing was to commence no sooner than 12 h after stopping intravenous infusion. The planned starting dose was 0.3 mg/kg per day divided into a twice-daily dose regimen. The maximum initial dose was 0.5 mg/kg per day. Recommended target whole blood levels of tacrolimus were 5 to 15 ng/mL during the first month after transplantation and 5 to l0 ng/mL thereafter.

Other immunosuppressive therapies:
Patients were to be administered azathioprine and corticosteroid immunosuppressive therapy according to standard practice at each participating site, as well as antirejection therapy with corticosteroids or ATG/murine monoclonal anti-CD3 antibody (OKT3)

Overview of Schedule of Procedures
After surgery, patients were to be observed daily for rejection episodes and AEs during hospitalization and at each outpatient visit throughout the study (Table 15). Tacrolimus trough levels were to be determined according to the same schedule. At visits 1 to 6 (days 1, 5, 9, 14, 21 and 28), and visits 7 to 13 (week 6 to month 12) changes in tacrolimus dosing and concomitant immunosuppression therapy were to be recorded. If clinically indicated at any time, biopsy samples were to be taken to assess the rejection status of the patient. Patients who discontinued study drug were to be followed up at the month 12 visit for rejection episodes, immunosuppressive regimen, SAEs and patient and graft survival. SAEs in all patients were to be monitored for a minimum of 12 months.

Table 15 Schedule of Assessments (Study FG-506-01-08)

Visit		**Study Phase**							**Follow-up Phase**			**Open Extension**
	Section A	**Section B**			**Section C**				**Section D**			**Section E‡‡‡**
Day, Week, Month	Screening Day 0	Visits 1 to 4, Days 1, 5, 9, 14	Visit 5, Day 21	Visit 6, Day 28, Month 1	Visit 7, Week 6	Visit 8, Week 8, Month 2	Visit 9, Week 10	Visit 10, Week 12, Month 3	Visit 11, Month 6	Visit 12, Month 9	Visit 13, Month 12†	Yearly Intervals
Written, Informed Consent	X‡											
Medical History	X‡											
Surgical Details, Donor Data/Recipient Data	X‡											
Viral and Parasite Titers	X‡											
ECG	X	X§	X§	X	X§	X§	X§	X	X	X§	X	X§
Echocardiography	X	X¶	X§	X	X§	X§	X§	X§	X	X§	X	X§
EBV and CMV Monitoring	X	X¶	X§	X	X§	X	X§	X	X	X	X	X§
PCR – EBV Measurements	X	X††	X§	X	X§	X	X§	X	X	X	X	X§
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X

Physical Examination and Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Microbiology	X‡	X§	X§	X§	X§	X§	X§	X§	X§	X§	X§	X§
Biochemistry/Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X‡‡										X‡‡	X‡‡
Liver Biopsy		X§	X§	X§	X§	X§	X§	X§	X§	X§	X§	X§
eGFR	X	X§	X§	X§	X§	X§	X§	X§	X	X§	X	X§
Tacrolimus PK Sampling		X§§		X§§								
Tacrolimus Trough Levels		X¶¶	X†† †	X†††	X	X	X	X	X	X	X	X
AEs/Rejection Episodes		X†††	X	X	X	X	X	X	X	X	X	X

AE: adverse event; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ECG: Electrocardiogram; eGFR: estimated glomerular filtration rate; PCR: polymerase chain reaction
† Or at discontinuation of study drug
‡ Informed consent, medical history, donor/recipient data and microbiology could be performed in advance when the patient was on the transplantation waiting list.
§ Whenever clinically indicated
¶ Day 7
†† Day 14
‡‡ For female patients of childbearing potential
§§ One profile during intravenous and washout, one profile during the first oral dose, and one profile during steady state at last day of hospitalization.
¶¶ Daily
††† Daily if hospitalized, otherwise weekly
‡‡‡ Data related to long-term monitoring of patients in the open-extension phase are not available.

Statistical Analysis Plan

The data were to be analyzed using descriptive statistical methods. Time dependent variables were to be analyzed by the Kaplan-Meier method. For continuous variables, descriptive statistics such as the number of patients, mean, SD, median, minimum and maximum were to be used. Categorical data were to be summarized by number of observations, frequency and percentage (where appropriate). Subgroup analyses for key efficacy and safety variables were to be performed by age group (≥ 3 years and < 3 years; the age cut-off was subsequently changed to 5 years.

5.2.2. Study Results (FG-506-01-08)

Compliance with Good Clinical Practices

This study was performed in compliance with Good Clinical Practice (GCP).

Financial Disclosure

FG-506-01-08 was conducted between March 1996 and April 1998 in Belgium and France. Financial disclosures were successfully collected from the principal study investigators for FG-506-01-08, all of whom reported no financial arrangements, payments, or interests requiring disclosure under 21 CFR 54.4(a)(3).

Reference ID: 4267221

Patient Disposition

A total of 28 patients were enrolled and most these patients (22/28, 78.6%) completed the study. Three deaths were reported and 4 patients discontinued the study drug, of which 3 were due to AEs and 1 patient was lost to follow-up (Table 16). The 4 study drug discontinuations and 2 deaths while on study drug all occurred in the first 6 months of starting treatment. One of the patients who discontinued due to an AE in month 3 subsequently died in month 9.

Table 16 Patient Disposition (Study FG-506-01-08)

Parameter	Tacrolimus, n (%)
Enrolled	28 (100)
Completed	22 (78.6)
Total deaths	3 (10.7)
During study†	2 (7.1)
After withdrawal‡	1 (3.6)
Withdrawn§	4 (14.3)
AEs	3 (10.7)
Lost to follow-up	1 (3.6)

† While on study drug.
‡ After study drug discontinuation.
§ Discontinued study drug for reasons other than death.

Protocol Violations/Deviations

A single patient who violated exclusion criterion 7 was enrolled in the study.

Demographic Characteristics

Most patients were ≥ 1 year of age (21/28, 75.0%) and most were < 5 years (18/28, 64.3%). A single patient was ≥ 12 years of age (3.6%), almost half of the patients were < 2 years of age (12/28, 42.9%). Majority of the patients were Caucasian (24/28, 85.7%). Most donors were male (17/28, 63.0%).

Other Baseline Characteristics

The most common primary diagnosis was biliary atresia (22/28, 78.6%) and more than half of the patients (16/28, 57.1%) received a partial liver transplant. Mean total ischemic time was 8.3 hours and the total duration of ischemia was < 24 h in all patients.

The recipient and donor baseline characteristics for microbiological status showed that most recipients and donors were HBV, hepatitis C virus (HCV) and HIV negative (23/28, 22/28 and 24/28, respectively). Many donors were CMV and EBV positive (13/28 and 11/28, respectively). Less than half of the recipients had a positive bacterial status at baseline (10/28, 35.7%) and very few recipients had positive fungal and parasitical status (4/28 and 2/28, respectively).

Reference ID: 4267221

Clinical Reviewer's Comment
The baseline characteristics of patients in Study FG-506-01-08 are representative of a typical pediatric *de novo* liver transplant patient population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Tacrolimus Dosing
All 28 patients who enrolled in the study received intravenous tacrolimus administration and 26 (92.9%) received oral tacrolimus for oral suspension. Two patients did not receive oral dosing due to early study drug discontinuation because of AEs. A single patient received intravenous tacrolimus infusion for 6 days (days 0 to 5), while all other patients received intravenous dosing as planned, ranging from 1 to 4 days. The median daily dose ranged from 0.010 to 0.040 mg/kg and the initial median intravenous dose (1st visit) was 0.046 mg/kg per 24 h. Oral tacrolimus therapy was administered for a duration of 12 months. The initial median oral dose (1st visit) by body weight was 0.30 mg/kg per day. The median daily oral dose was 0.23 to 0.30 mg/kg during week 1 and 0.15 mg/kg and 0.14 mg/kg during months 9 and 12.

Tacrolimus whole blood trough levels (Table 17) decreased over time, with median concentrations in the target range of 5 to 15 ng/mL by day 3 when most patients completed intravenous infusion and were initiated on oral tacrolimus granules, and 6.4 ng/mL and 6.1 ng/mL during months 9 and 12.

Clinical Reviewer's Comment
Study FG-506-01-08 enrolled relatively younger patients compared to the comparative Study FG-506-01-13 and utilized initial IV dosing during the first few days following transplantation unlike Study FG-506-01-13, in which the patients started receiving the oral granule formulation of tacrolimus right after the transplant surgery except for one patient.

Table 17 Tacrolimus Whole Blood Trough Levels (Study FG-506-01-08)

	Tacrolimus Trough Levels (ng/mL)			
Visit	**n**	**Mean**	**SD**	**Median**
Day 2	2	37.90	18.24	37.90
Day 7	24	14.80	8.53	13.35
Day 21	26	10.65	5.76	9.75
Week 6	24	10.91	3.10	11.00
Month 2	24	9.89	3.75	9.95
Month 3	21	9.46	3.39	9.60
Month 6	21	7.79	3.20	7.50
Month 9	16	6.79	3.04	6.35

Month 12	17	6.49	2.51	6.10

Clinical Reviewer's Comment
The mean tacrolimus whole blood trough levels observed in Study FG-506-01-08 are similar to the levels observed in the comparative Study FG-506-01-13 (Table 8). However, unlike in Study FG-506-01-13, all patient received azathioprine in addition to tacrolimus which probably resulted in relatively increased immunosuppression when compared to the tacrolimus patients in Study FG-506-01-13.

Azathioprine, OKT3 and ALG/ATG

All 28 (100.0%) patients received azathioprine treatment at some point during the study. None of the patients received antirejection therapy with OKT3. One patient received ALG/ATG for a duration of 5 days due to interruption of the primary immunosuppressant

Corticosteroids
The total duration of oral corticosteroid administration was 12 months (median of 356 days). The median oral dose administered during the study decreased over time by a factor of more than 4-fold from 0.86 mg/kg in month 1 to 0.2 mg/kg in months 10 to 12.

Prior and Concomitant Medications
The most common prior medications were ursodeoxycholic acid, spironolactone, amphotericin B, phytomenadione and rifampicin. Regarding concomitant medication, nearly all patients took either acyclovir, amphotericin B or bactrim at some point during the study. Most patients also took ursodeoxycholic acid, dipyridamole, nifedipine and ranitidine.

Efficacy Results of Study FG-506-01-08

Patient and Graft Survival
Graft and patient survival were both 89.3% at 12 months. Three patient deaths (3/28, 10.7%) occurred due to AEs and were also considered as graft losses in the graft survival analysis. Of the 3 patients who died, 2 (20.0%) were ≥ 5 years of age and 1 (5.6%) patient was < 5 years. In patients < 1 year of age, no deaths or graft losses were reported. Two patients died during study drug administration and 1 patient died after study drug discontinuation. The 2 patients who died while on study drug were ≥ 5 years of age while the patient who died after study drug discontinuation was < 5 years.

Clinical Reviewer's Comment
Graft and patient survival rate of 89.3% at 12 months is an acceptable result in this small study and does not raise any red flags.

Rejection
Acute rejection, which was confirmed by biopsy (biopsy proven acute rejection [BPAR]) was reported in 6 (21.4%) patients, with 3 rejections each noted in patients ≥ 5 and < 5 years of age (30.0% and 16.7%, respectively) (Table 18). In patients < 1 year of age, a single acute

rejection (BPAR) was reported (14.3%). No chronic rejections were reported.

Table 18 Efficacy Outcomes (Study FG-506-01-08)

Outcome	Tacrolimus, n (%)			
	Total n = 28	≥ 5 Years n = 10	< 5 Years n = 18	< 1 Year n = 7
Acute Rejection	6 (21.4)	3 (30.0)	3 (16.7)	1 (14.3)
Biopsy Proven Acute Rejection	6 (21.4)	3 (30.0)	3 (16.7)	1 (14.3)
Death	3 (10.7)	2 (20.0)	1 (5.6)	0
Graft Loss	3 (10.7)	2 (20.0)	1 (5.6)	0

Clinical Reviewer's Comment
The 12 month BPAR rate of 21.4% is quite low for this patient population and is probably a sign of over-immunosuppression considering that all patients received azathioprine in addition to tacrolimus and corticosteroids. This low rate of BPAR may also explain the mortality rate of 10.7 % which is acceptable but could have been lower. Among the three patients who died in the study, two were male and one was female.

5.3. A Long-term, Open-label, Non-comparative Study to Evaluate the Safety and Efficacy of a Modigraf® Based Immunosuppression Regimen in Paediatric Solid Allograft Recipients (PROGRESSION STUDY, F506-CL-0404)

5.3.1. Study Design (F506-CL-0404)

Overview and Objective
Study F506-CL-0404 is an extension study of the 14-day PK Study F506-CL-0403 conducted in de novo recipients of heart, liver or kidney transplants. The objective of the study was to monitor the safety and efficacy of Modigraf® (tacrolimus for oral suspension)) in stable pediatric allograft (liver, kidney or heart) recipients.

Trial Design
This was a multicenter, open-label, single arm study. Pediatric patients who had undergone liver, kidney or heart transplantation and met the inclusion criteria and complying with the exclusion criteria prior to initiation of tacrolimus therapy were enrolled. All patients had previously participated in Study F506-CL-0403.

Clinical Reviewer's Comment

Reference ID: 4267221

Study F506-CL-0404 is an extension study of Study F506-CL-0403. Fourteen-day PK Study F506-CL-0403 enrolled pediatric patients undergoing liver, kidney or heart transplantation. Therefore, patients enrolled in Study F506-CL-0404 were approximately two weeks out from their transplantation surgery (Table 19) and continued their prescribed doses of tacrolimus for oral suspension adjusted per the target trough levels.

Patients began the study on the same dose regimen as they received at the end of the F506-CL-0403 study. Subsequent Modigraf (tacrolimus for oral suspension) doses were adjusted based on clinical evidence of efficacy and occurrence of adverse events and taking into consideration the recommended whole blood trough level range of 5-20 ng/ml.

Patients were enrolled in the study for a maximum period of 1 year or until commercial availability of Modigraf in the patient's country (whichever occurred first). If, however, commercial availability occurred before the 3-month visit, patients were to continue in the study and complete their end of study visit (Part A) (ESVA) at that visit. This ensured a minimum of 3 months safety and efficacy data per patient. If there was no commercial availability of Modigraf in the patient's country after 1 year, Astellas was to continue to provide Modigraf outside of the study until commercial availability or until the patient was converted to a twice-a-day commercial Prograf capsules regimen. Patient visits took place at months 1, 2 and 3 and every 3 months thereafter until the ESVA after 12 months (latest possible time, minimum after 3 months). Following the ESVA, patients were converted to commercial Modigraf.

Study Population

Pediatric patients who had undergone liver, kidney or heart transplantation and met the inclusion and complying with the exclusion criteria prior to initiation of tacrolimus therapy were enrolled. Patients were enrolled in the study for a maximum period of 1 year or until commercial availability of Modigraf in the patient's country (in this case, a minimum of 3 months safety and efficacy data per patient was ensured).

Inclusion Criteria

A patient was eligible for the study if all the following applied:

1. Patient was ≤ 12 years of age at enrolment into Study F506-CL-0403.
2. Patient received at least 1 dose of Modigraf in the F506-CL-0403 study.
3. In the opinion of the patient's investigating physician, the patient was to benefit from further treatment with Modigraf.
4. The patient's parent(s) or their legal representative(s) had been fully informed and had given written informed consent to participate in the study. The patient had given assent where applicable.

Exclusion Criteria

As all patients included in this study conformed to the exclusion criteria in Study F506-CL-0403, no specific exclusion criteria were relevant for this study.

Treatments
Patients were treated with a Modigraf (tacrolimus for oral suspension))-based immunosuppressive regimen. There were no study specific prohibitions for concomitant medications. Per the Study F506-CL-0403 protocol (*the precursor study for the current Study F506-CL-0404*) "monoclonal antibodies, polyclonal antibodies (thymoglobulin), mycophenolate mofetil /Cellcept® and steroids were permitted to be used as concomitant immunosuppressive medications." Tacrolimus granules for oral suspension were available (b) (4) containing either 0.2 mg or 1 mg tacrolimus granules per (b) (4).

The first dose of Modigraf for each individual patient was identical to the final dose at the end of Study F506-CL-0403 for respective patient. Where the total daily dose was not divisible by 0.2 (that being the smallest (b) (4) size), the dose was rounded up or down by 0.1 mg. For example, if the total daily dose was equal to 3.3 mg (derived from 11 kg multiplied by 0.3 mg), then the dose was rounded up to 3.4 mg or down to 3.2 mg. Where it was not possible to divide the daily dose exactly, the higher dose was given in the morning.

The first dose of Modigraf was to be administered on the morning of day 1. Subsequent oral tacrolimus doses were adjusted by the investigator based on clinical evidence of efficacy and occurrence of AEs and observing the recommended whole blood trough level range of 5 to 20 ng/ml.

Study Endpoints
The efficacy of Modigraf was described from the following parameters:

- Rejection episodes:
- Acute rejection episodes;
- Biopsy-proven acute rejection (BPAR) episodes;
- Severity of BPAR.
- Patient and graft survival:
- Death and reason for death;
- Graft loss.

A BPAR episode was defined as any acute rejection episode confirmed by biopsy.

Figure 3 Flow Chart (**F506-CL-0404**)

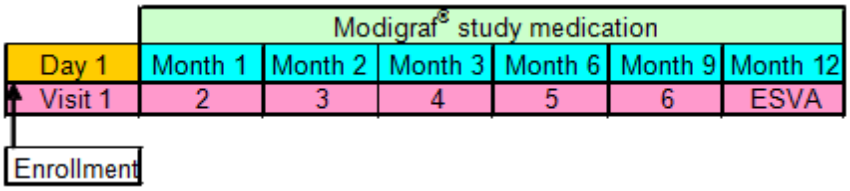


Table 19 Schedule of Assessments (F506-CL-0404)

Visit	Baseline Visit 1	Visit 2	Visit 3	Visit 4, 5, 6	ESVA¶
Day	Day 1 (± 7 days)	Month 1 (± 7 days)	Month 2 (± 7 days)	Month 3, 6 9 (± 1 month)	Month 12†† (± 1 month)
Informed Consent†	X				
Inclusion/Exclusion Criteria	X				
Allocation of Patient Number and Enrollment	X				
Patient Data‡	X				
Primary Diagnosis/Secondary Diagnosis	X				
Medical History/Prestudy Medication§	X				
Physical Examination	X	X	X	X	X
Vital Signs (Pulse, BP, Oral Temperature)	X	X	X	X	X
Body Weight	X	X	X	X	X
Biochemistry/Hematology	X	X	X	X	X
Ongoing Data Collection:					
Modigraf Dosing (Twice a Day)					
Rejection Episodes					
Recording of Dose Changes					
Tacrolimus whole Blood Trough Levels¶					
AEs					
Concomitant Medication					
Hospitalization					

BP: blood pressure; CMV: cytomegalovirus; EBV: Epstein-Barr virus; ESVA: end of study visit (Part A); HBV: hepatitis B virus; HCV: hepatitis C virus; HLA: human leukocyte antigen.
† Informed consent for F506-CL-0404A was to be obtained prior to Visit 1.
‡ Patient data include: date of birth (or age), sex, height, race, reason for the patient's organ failure, transplant date, previous transplants, viral status (HBV, HCV, CMV, EBV) and date, ABO blood type, HLA main types.
§ Medical history from Study F506-CL-0403 was merged into the database for this study. All AEs from Study F506-CL-0403 were to be entered into this study as medical history.
¶ Tacrolimus trough level specimens were to be drawn immediately before dosing in the morning.
†† Patients who discontinued prematurely were to complete all ESVA procedures at their final visit and were to be followed for safety as appropriate by each Investigator.

Statistical Analysis Plan

For continuous variables, descriptive statistics which included the number of patients, mean, standard deviation, median, minimum and maximum were provided. Frequencies and percentages were displayed for categorical data. Percentages by categories were based on the number of patients with no missing data.

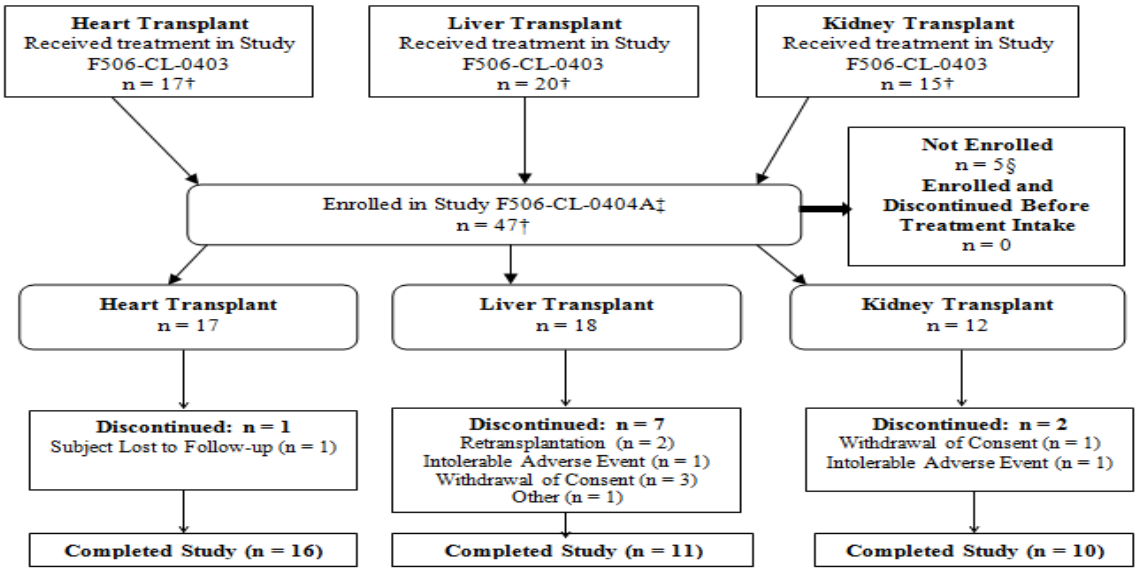
Analyses were performed separately by type of organ transplant (liver, kidney and heart transplant). All analyses were presented for the overall population and also by age group at the time of transplantation (age group < 5 years and ≥ 5 years). Date of first dose of Modigraf administered was used as reference starting date.

5.3.2. Study Results (F506-CL-0404)

Compliance with Good Clinical Practices
This study was performed in compliance with Good Clinical Practice (GCP).

Patient Disposition
All 47 enrolled patients took at least 1 dose of Modigraf study drug and were included in the Safety Analysis Set (SAF). The SAF was used for all analyses in this study (Figure 4).

Figure 4 Patient Disposition (Study F506-CL-0404)



† Data from Clinical Study Report F506-CL-0403.
‡ Patients were considered enrolled in Study F506-CL-0404A once the informed consent for this study had been completed.
§ Five patients who received treatment in Study F506-CL-0403 were not enrolled in this extension Study F506-CL-0404A; 3 of 5 patients discontinued Study F506-CL-0403 (2 withdrew consent and 1 started prohibited concomitant medication) and 2 of 5 patients completed Study F506-CL-0403.

Protocol Violations/Deviations
Overall, protocol deviations were reported in 11 (23.4%) patients. The most frequent protocol deviations were PD3 (received wrong treatment or incorrect dose).

Demographic Characteristics

Overall, most patients in the SAF were male (68.1%), white (97.9%) and < 5 years (70.2%). The mean age at enrollment was 4.2 years. The mean weight was 14.54 kg. Most patients were in the subgroups of age ≥ 2 years to ≤ 11 years (children) and ≥ 28 days to ≤ 23 months (infants and toddlers) at transplantation (61.7% and 36.2%, respectively).

Overall, 51.1% of donors in the SAF were male. The mean age was 5.2 years in the heart transplant group, 2.3 years in the liver transplant group and 5.4 years in the kidney transplant group (Table 20).

Table 20 Summary of Demographics and Baseline Characteristics

(Study F506-CL-0404)

Parameter Category/ Statistics	Heart Transplant (n = 17)	Liver Transplant (n = 18)	Kidney Transplant (n = 12)	Total (n = 47)
Sex, n (%) (Recipient)				
Male	13 (76.5%)	10 (55.6%)	9 (75.0%)	32 (68.1%)
Female	4 (23.5%)	8 (44.4%)	3 (25.0%)	15 (31.9%)
Sex, n (%) (Donor)				
Male	8 (47.1%)	8 (44.4%)	8 (66.7%)	24 (51.1%)
Female	8 (47.1%)	10 (55.6%)	4 (33.3%)	22 (46.8%)
Missing	1 (5.9%)	0	0	1 (2.1%)
Race, n (%) (Recipient)				
White	17 (100.0%)	18 (100.0%)	11 (91.7%)	46 (97.9%)
Black or African American	0	0	0	0
Asian	0	0	1 (8.3%)	1 (2.1%)
Other	0	0	0	0
Recipient Age at Transplantation (Years)				
n	17	18	12	47
Mean (SD)	5.2 (4.1)	2.3 (2.8)	5.3 (3.0)	4.1 (3.6)
Recipient Age at Enrollment (Years)				
n	17	18	12	47
Mean (SD)	5.3 (4.1)	2.3 (2.8)	5.4 (3.0)	4.2 (3.6)
Recipient Age at Transplantation subgroup				
< 5 years	9 (52.9%)	16 (88.9%)	8 (66.7%)	33 (70.2%)
≥ 5 years	8 (47.1%)	2 (11.1%)	4 (33.3%)	14 (29.8%)
Recipient Age at Transplantation subgroup				
≥ 28 days to ≤ 23 months (Infants and Toddlers)	5 (29.4%)	12 (66.7%)	0	17 (36.2%)
≥ 2 years to ≤ 11 years (Children)	11 (64.7%)	6 (33.3%)	12 (100.0%)	29 (61.7%)
≥ 12 years to ≤ 17 years (Adolescents)	1 (5.9%)	0	0	1 (2.1%)
Donor Age (Years)				
n	10	5	3	18
Mean (SD)	7.0 (4.5)	39.8 (8.3)	20.3 (20.3)	18.3 (16.9)
Time Since Transplantation (Day)				
n	17	18	12	47
Mean (SD)	15.6 (1.3)	14.7 (3.3)	17.8 (10.6)	15.8 (5.7)

† Time since transplantation was defined as (date of first dose in the study) - (date of transplantation) + 1.

Tacrolimus Exposure

Overall, the mean (SD) duration of exposure was higher in patients with kidney transplant than in patients with heart or liver transplant (226.5 [141.6] days vs 98.5 [38.9] days and 73.6 [38.8] days, respectively). Most of the patients (45 [95.7%]) had their dose adjusted during the study. Overall, increases and decreases of dose had a similar incidence.

The mean (SD) trough levels of tacrolimus are shown in Table 21.

Table 21 Tacrolimus Mean Trough Levels (ng/mL) by Visit (Study F506-CL-0404)

Statistics	Heart Transplant (n = 17)	Liver Transplant (n = 18)	Kidney Transplant (n = 12)
Overall			
n	17	18	11
Mean (SD)	9.9 (1.7)	10.8 (3.6)	7.0 (1.5)
Day 1			
n	8	15	9
Mean (SD)	8.7 (2.4)	11.7 (4.6)	11.71 (3.6)
Month 1			
n	17	18	11
Mean (SD)	11.7 (5.1)	9.8 (3.3)	7.1 (2.4)
Month 2			
n	16	12	11
Mean (SD)	9.80 (4.0)	9.15 (2.3)	5.65 (1.6)
Month 3			
n	15	11	11
Mean (SD)	9.29 (3.2)	12.82 (12)	6.50 (2)

Clinical Reviewer's Comment
Since there were no restrictions on concomitant immunosuppressant usage in this study as explained earlier, any comparative assessments of tacrolimus trough levels must be made with caution. For any particular patient, the presence or absence of any concomitant immunosuppressants in the regimen might have affected the targeted tacrolimus trough levels for that patient, hence the group means.

Efficacy Results of Study F506-CL-0404

Patient and Graft Survival
There were no deaths. Patients with liver transplant experienced graft losses in this extension study. A 6.5-year-old male patient experienced graft loss due to transplant failure after hepatic artery thrombosis 12 days after being enrolled in this extension study while receiving tacrolimus granules. A 4-year-old female patient experienced graft loss due to portal vein thrombosis 2 days after being enrolled in this extension study.

Clinical Reviewer's Comment
Pediatric liver transplantation performed with either deceased or living donors demands a refined surgical technique because of the small caliber of the vascular and biliary structures. The transplantation of partial liver grafts involves additional technical difficulties because it uses short vascular pedicles, which are more likely to cause postoperative vascular complications.[6] Additionally, biliary atresia, the leading indication for transplantation in children, is associated with portal vein sclerosis, which can result in added difficulties during vascular reconstruction in this population. (*The patient who was diagnosed with portal vein thrombosis in the study did not have biliary atresia, but hepatocellular carcinoma which also might increase thrombotic risk due to hypercoagulability*[7].) Hepatic artery thrombosis (HAT) is a major cause of retransplantation in the pediatric population.[8] Children have been reported to be at greater risk for HAT when compared to adults due to small arterial size. Therefore, it is not unusual to see these vascular complications in pediatric liver transplant recipients especially during the early postoperative period. The possible contribution of tacrolimus to these thrombotic events cannot be ruled out.[9]

Acute Rejection
Overall, 9 patients experienced one acute rejection episode. In the heart transplant group, 5 (29.4%) patients had rejections with 2 classified as a BPAR. In the liver transplant group 3 (16.7%) patients had rejections and all were classified as BPAR. In the kidney transplant group, 1 patient had a rejection without biopsy confirmation.

Clinical Reviewer's Comment
There were no deaths in this study and the safety events including the two graft loses in the liver transplant recipients due to vascular thromboses are among the expected complications in this pediatric study. The observed acute rejection rates for all three different types of organ transplantations are within the expected ranges.

6. Integrated Review of Effectiveness

[6] Neto et.al. Analysis of factors associated with portal vein thrombosis in pediatric living donor liver transplant recipients. Liver Transpl. 2014 Oct;20(10):1157-67
[7] Martinelli et.al. Thrombosis after liver transplantation for hepatocellular carcinoma. PLoS One. 2017 Oct 26;12(10)
[8] Kivela et.al. Late Hepatic Artery Thrombosis After Pediatric Liver Transplantation: A Cross-Sectional Study of 34 Patients. Liver Transpl. 2014 May;20(5):591-600.
[9] Takahashi et.al. Recurrence of hepatic artery thrombosis following acute tacrolimus overdose in pediatric liver transplant recipient. Pediatr Transplant. 2005 Dec;9(6):809-12.

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6.1. Assessment of Efficacy Across Trials

Efficacy of tacrolimus granules is discussed under individual study assessments above. Pooling of data will not be performed as explained earlier. Study FG-506-01-13 demonstrates that in pediatric *de novo* liver transplant recipients, Prograf® Granules (tacrolimus) for oral suspension based maintenance immunosuppressive treatment regimen results in fewer acute rejections, fewer deaths and fewer graft loses and favorable safety when compared to a cyclosporine based maintenance immunosuppressive regimen. These differences fail to reach statistical significance due to the relatively small sample size in the study. Single arm studies, FG-506-01-08 (conducted in pediatric *de novo* liver transplant recipients) and F506-CL-0404A (conducted in pediatric de novo liver, heart and kidney transplant recipients as an extension of the 14-day PK Study F506-CL-0403) demonstrate that a tacrolimus for oral suspension based immunosuppressive regimen results in rates of rejection, death and graft loses which are to be expected in these patient populations in today's clinical practice and support the efficacy and safety findings of the main Study FG-506-01-13.Tacrolimus has been on the US market for 24 years and there is considerable experience gained both for efficacy and safety in different transplant populations. Tacrolimus is part of the immunosuppressive regimen in most transplant patients both for the labeled and off-label organ transplantations.

6.2. Additional Efficacy Considerations

6.2.1. Considerations on Benefit in the Postmarket Setting

The safety and efficacy of tacrolimus granules as assessed in the trials submitted in support of NDA 210,115 is in line with the results of the trials that supported the approval of the capsule formulation both in adults and pediatric patients. The availability of an age appropriate (granule) pediatric formulation for the ≤ 5-year age group and also for patients who cannot swallow capsules will be of great benefit to transplant patients. The availability of the granule formulation with demonstrated efficacy, safety and stability will ensure continued reliable immunosuppression in patients who cannot swallow the capsules when compared to the currently administered extemporaneously compounded liquid formulations of tacrolimus to these patients.

7. Review of Safety

7.1. Safety Review Approach

Similar to the review of efficacy, the three clinical studies (Study FG-506-01-08, Study FG-506-01-13 and Study F506-CL-0404A) will be reviewed separately for the assessment of safety. Among these three, only Study FG-506-01-13 is a controlled study, hence it is the main study in

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support of the efficacy and the safety of Prograf granules. Due to major differences in the study designs and populations, the data from these three studies will not be pooled.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

Prior to the US approval in 1994, tacrolimus was first approved for marketing in Japan on April 2, 1993. Currently tacrolimus is marketed in 104 countries globally and extensively used as part of the maintenance immunosuppression in transplant patients.

During the conduct of the three clinical studies submitted in support of NDA 210,115 the tacrolimus exposures are as follows:

Study FG-506-01-13:

A total of 185 patients were randomized to receive treatment following screening, 93 in the tacrolimus group and 92 in the CsA-ME group. A total of 181 patients were included in the intent-to-treat population (91 tacrolimus and 90 CsA-ME), with 112 patients completing the 12-month treatment period as planned (68 tacrolimus and 44 CsA-ME). For the mean daily doses of tacrolimus and cyclosporine throughout the study see Table 8.

Study FG-506-01-08

All 28 (100.0%) patients who were enrolled in the study received intravenous tacrolimus administration and 26 (92.9%) received oral administration. Two patients did not receive oral dosing due to study drug discontinuation as a result of adverse events (AEs) that were unrelated to study drug. The median daily dose ranged from 0.010 to 0.040 mg/kg.

Study F506-CL-0404A

Out of 52 patients who were transplanted and received treatment in Study F506-CL-0403, 47 were enrolled (33 children < 5 years and 14 children ≥ 5 years with informed consent) in the extension Study F506-CL-0404A. From the 47 patients who received treatment, 10 (21.3%) patients discontinued the study. Overall, the mean (SD) duration of exposure was higher in patients with kidney transplant than in patients with heart or liver transplant (226.5 [141.6] days vs 98.5 [38.9] days and 73.6 [38.8] days, respectively).

7.2.2. Adequacy of the safety database:

Tacrolimus has been on the US market since 1994 with extensive use in transplant patients providing considerable assurance of safety and efficacy. The extent of the safety data and assessments of safety for the new granule formulation of tacrolimus as included in the current

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NDA 210,115 submission is adequate and acceptable.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

No issues are identified.

7.3.2. Categorization of Adverse Events

No issues are identified.

7.3.3. Routine Clinical Tests

No issues are identified. Routine clinical tests were performed in compliance with the routine care of transplant patients and data adequately collected and reported in the CSRs.

7.4. Safety Results

7.4.1. Deaths

Study FG-506-01-13
Among all randomized subjects, 5 patients (2 tacrolimus granules, 3 CsA-ME) died while on study drug and 11 patients (5 tacrolimus granules, 6 CsA-ME) died after they discontinued study drug. An additional 3 patients (1 tacrolimus granules, 2 CsA-ME) died after the 12-month visit. An additional 3 patients (1 tacrolimus granules, 2 CsA-ME) died after the 12-month visit (Table 23).

Table 22 Deaths (FG-506-01-13 All Randomized Subjects)

	Primary Cause of Death (Investigator assessment)	Day of Death	Last Dose Day
Tacrolimus granules			
≥ 5 Years			
1	Abdominal bleeding	0*	Not dosed
2	Graft failure	28	27
3	Primary liver carcinoma	398†	31
< 5 years			
4	Sepsis	13	10
5	Disseminat. Intr-vasc. Coag.mult.org.fai/Gastrointestinal hemorrhage	16	13
6	Multiorgan failure	37	9
7	Sepsis-cardiac arrest	131	1
8	Hyperphosphatemic coma	194	3
Cyclosporine-ME			
≥ 5 Years			

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	No deaths were reported.		
< 5 years			
1	Hyperkalemia*	0*	Not dosed
2	Cerebral edema	1	1
3	Cardiac shock *	1*	Not dosed
4	Hemorrhagic shock	8	7
5	Sepsis, multiple organ failure, adenovirus infection	29	9
6	Multiorgan failure secondary to surgical attempt of repair of biliary massive fistula	85	3
7	Sepsis, multi organ failure	148	148
8	Cardiac arrest during hepatic retransplantation	232	156
9	Severe gastro-intestinal hemorrhage secondary to a gastric ulcer, aspiration pneumonia and sepsis	257	211
10	Sepsis; suspected recurrence of mitochondrial myopathy	473†	68
11	Obstructive cardiomyopathy hypertrophic with acute respiratory distress	576†	37

*Did not receive the study drug; therefore, not included in the ITT population for the analysis of efficacy
† Died after the 12-month visit

Clinical Reviewer's Comment

As included in Table 23, 8 deaths in the tacrolimus granules group and 11 deaths in the CsA-ME group were reported in Study FG-506-01-13. Of these total deaths, 6/8 in the tacrolimus granules group and 7/11 in the CsA-ME group are included in the efficacy analysis as discussed in Section 6 of this review. In the tacrolimus granules group one patient (b) (6) died before receiving the study drug (outside the ITT population definition) and another patient (b) (6) died outside the study period. Of the remaining 6 patients, 3 (b) (6) in Table 22) died within the first 30 days after transplantation decreasing the possibility of any causality associations between the deaths and the treatment regimen. Patients (b) (6) died after the initial 30 days following transplantation; however, all three patients received the study treatment less than 10 days again making it difficult to make any attributions to the study treatment as the cause of deaths.

In the CsA-ME group, two patients (b) (6) died before receiving the study drug (outside the ITT population definition) and two other patients (b) (6) died outside the study period for a total of four patients who were consequently excluded from the analysis of efficacy. Of the remaining seven patients, two patients (b) (6) died within the first 30 days following transplantation and patient (b) (6) received study treatment for 9 days only. Therefore, it is not likely that the study treatment might have played any major role in these deaths. Patient (b) (6) died on Day 85; however, received the study treatment for 3 days only. The remaining 3 patients (b) (6) died more than 3 months following transplantation and all received the

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study treatment more than 3 months. Therefore, it is possible that the study treatment may have a causality association with the death of these patients.

Numerically there are more deaths in the CsA group compared to the tacrolimus group which may be associated with possible over-immunosuppression in this group; however, in this small study the difference is not statistically significant and any conclusions favoring one treatment group over the other in terms of mortality cannot be made. The rates and reasons for deaths in both treatment groups are as expected in this patient population.

Study FG-506-01-08

In this single arm study, two patients died during study drug administration portion of the study and 1 patient died after completion and study drug discontinuation (Table 24). The 2 patients who died while on study drug were ≥ 5 years of age while the patient who died after study drug discontinuation was < 5 years. None of the patients who died were < 1 year of age.

Table 23 Deaths (FG-506-01-08 ITT Population)

Primary Cause of Death/ COSTART Preferred Term	Day of Death	Last Dose Day
≥ 5 Years		
Cardiac arrest due to hyperkalemia/hyperkalemia	32	28
Hemorrhagic collapsus/shock	25	25
< 5 Years		
Suspected volvulus intestinal problem/lymphoma like reaction	243	68
< 1 Year		
No deaths were reported.		

Clinical Reviewer's Comment

In this single arm study, two patients died during study period and 1 patient died after the study drug discontinuation. The rate and reasons for deaths are as expected in this patient population.

Study F506-CL-0404A

There were no deaths in this study.

7.4.2. Serious Adverse Events

Study FG-506-01-13

The incidence of nonfatal SAEs was comparable between the treatment groups; nonfatal

SAEs were reported for 76 (83.5%) patients in the tacrolimus granules group and 69 (76.7%) patients in the CsA-ME group. The most common (≥ 10% of patients in either treatment group) SAEs in the tacrolimus granules and CsA-ME groups were fever (20 [22.0%] and 21 [23.3%] patients, respectively), liver function tests abnormal (17 [18.7%] and 15 [16.7%] patients, respectively), CMV infection (4 [4.4%] and 11 [12.2%] patients, respectively) and diarrhea (6 [6.6%] and 9 [10.0%] patients, respectively). (Table 25)

Table 24 Serious Adverse Events (≥ 5% in Either Treatment Group) (Study FG-506-01-13)

COSTART System Organ Class Preferred Term	**Number of Patients, n (%)**	
	Tacrolimus Granules n = 91	**Cyclosporin-ME n = 90**
Any SAE	**76 (83.5)**	**69 (76.7)**
Body as a Whole	**40 (44.0)**	**48 (53.3)**
Fever	20 (22.0)	21 (23.3)
Sepsis	9 (9.9)	8 (8.9)
CMV infection	4 (4.4)	11 (12.2)
Ascites	6 (6.6)	8 (8.9)
Infection	5 (5.5)	4 (4.4)
EBV infection	6 (6.6)	2 (2.2)
Cardiovascular System	**17 (18.7)**	**17 (18.9)**
Hypertension	5 (5.5)	3 (3.3)
Digestive System	**50 (54.9)**	**41 (45.6)**
Liver function tests abnormal	17 (18.7)	15 (16.7)
Bile duct disorder	8 (8.8)	7 (7.8)
Diarrhea	6 (6.6)	9 (10.0)
Gastrointestinal hemorrhage	7 (7.7)	8 (8.9)
Vomiting	4 (4.4)	7 (7.8)
Gastroenteritis	8 (8.8)	2 (2.2)
Nervous System	**8 (8.8)**	**6 (6.7)**
Convulsion	5 (5.5)	2 (2.2)
Respiratory System	**15 (16.5)**	**11 (12.2)**
Pleural effusion	5 (5.5)	5 (5.6)
Urogenital System	**10 (11.0)**	**7 (7.8)**
Kidney function abnormal	5 (5.5)	5 (5.6)

Clinical Reviewer's Comment
Due to the high study medication discontinuation rate in the CsA-ME group (51%) it is not possible to make very accurate safety assessments. In general the SAEs are balanced across the treatment groups.

Study FG-506-01-08

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A total of 22 (78.6%) patients reported SAEs. Infection reported in 5 (17.9%) patients and hemoperitoneum, hemorrhage and bile duct disorder reported in 3 (10.7%) patients each were the most commonly reported SAEs, followed by fever, thrombosis and increased levels of GGT, SGOT (AST) and SGPT (ALT) in 2 (7.1%) patients each. (Table 26)

Table 25 Common (≥ 2 Patients Overall) SAEs (FG-506-01-08)

System Organ Class Preferred Term	Tacrolimus, n (%)			
	Total n = 28	≥ 5 Years n = 10	< 5 Years n = 18	< 1 Year n = 7
Any SAE	**22 (78.6)**	**7 (70.0)**	**15 (83.3)**	**6 (85.7)**
Body as a Whole	**13 (46.4)**	**4 (40.0)**	**9 (50.0)**	**4 (57.1)**
Infection	5 (17.9)	1 (10.0)	4 (22.2)	3 (42.9)
Hemoperitoneum	3 (10.7)	1 (10.0)	2 (11.1)	1 (14.3)
Fever	2 (7.1)	0	2 (11.1)	0
Cardiovascular System	**9 (32.1)**	**3 (30.0)**	**6 (33.3)**	**1 (14.3)**
Hemorrhage	3 (10.7)	0	3 (16.7)	1 (14.3)
Thrombosis	2 (7.1)	2 (20.0)	0	0
Digestive System	**11 (39.3)**	**5 (50.0)**	**6 (33.3)**	**2 (28.6)**
Bile duct disorder	3 (10.7)	1 (10.0)	2 (11.1)	2 (28.6)
Metabolic and Nutritional Disorder	**4 (14.3)**	**1 (10.0)**	**3 (16.7)**	**2 (28.6)**
GGT increased	2 (7.1)	0	2 (11.1)	1 (14.3)
SGOT increased	2 (7.1)	0	2 (11.1)	1 (14.3)
SGPT increased	2 (7.1)	0	2 (11.1)	1 (14.3)
Respiratory System	**2 (7.1)**	**0**	**2 (11.1)**	**1 (14.3)**
Skin and Appendages	**2 (7.1)**	**1 (10.0)**	**1 (5.6)**	**0**
Urogenital System	**2 (7.1)**	**2 (20.0)**	**0**	**0**

Clinical Reviewer's Comment
The types and rates of SAEs observed in Study FG-506-01-08 across all age groups are as expected in this patient population.

Study F506-CL-0404A
Overall, a total of 62 SAEs were reported by 26 (55.3%) patients (12 events by 8 [47.1%] patients with heart transplant, 18 events by 9 [50.0%] patients with liver transplant and 32 events by 9 [75.0%] patients with kidney transplant). Most commonly reported SAEs were infections and infestations (11 [23.4%] patients) followed by investigations and respiratory, thoracic and mediastinal disorders (4 [8.5%] patients each). (Table 27)

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Table 26 Incidence of Serious Adverse Events (F506-CL-0404A)

Preferred Term	Number of Patients, n (%)		
	Treatment		
	Heart Transplant n = 17	Liver Transplant n = 18	Kidney Transplant n = 12
Overall	**8 (47.1%)**	**9 (50.0%)**	**9 (75.0%)**
Infections and Infestations	**5 (29.4%)**	**1 (5.6%)**	**5 (41.7%)**
Gastroenteritis	2 (11.8%)	1 (5.6%)	1 (8.3%)
Lower respiratory tract infection	0	0	2 (16.7%)
Urinary tract infection	0	0	2 (16.7%)
Bacterial sepsis	0	0	1 (8.3%)
Cytomegalovirus infection	0	0	1 (8.3%)
Gastroenteritis clostridial	1 (5.9%)	0	0
Gastroenteritis norovirus	0	0	1 (8.3%)
Gastroenteritis viral	0	0	1 (8.3%)
Gastrointestinal protozoal infection	1 (5.9%)	0	0
Postoperative wound infection	1 (5.9%)	0	0
Respiratory tract infection	1 (5.9%)	0	0
Urinary tract infection bacterial	0	0	1 (8.3%)
Investigations	**0**	**1 (5.6%)**	**3 (25.0%)**
Blood creatinine increased	0	0	1 (8.3%)
Body temperature increased	0	0	1 (8.3%)
Hepatic enzyme increased	0	1 (5.6%)	0
Transaminases increased	0	0	1 (8.3%)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**3 (16.7%)**	**1 (8.3%)**
Pleural effusion	0	2 (11.1%)	0
Lung consolidation	0	1 (5.6%)	0
Pulmonary oedema	0	0	1 (8.3%)
Respiratory failure	0	1 (5.6%)	0
Blood and Lymphatic System Disorders	**3 (17.6%)**	**0**	**0**
Neutropenia	2 (11.8%)	0	0
Febrile neutropenia	1 (5.9%)	0	0
General Disorders and Administration Site Conditions	**1 (5.9%)**	**1 (5.6%)**	**1 (8.3%)**
Pyrexia	1 (5.9%)	1 (5.6%)	0
Drug interaction	0	0	1 (8.3%)
Injury, Poisoning and Procedural Complications	**0**	**3 (16.7%)**	**0**

Biliary anastomosis complication	0	1 (5.6%)	0
Complications of transplanted liver	0	1 (5.6%)	0
Gastrointestinal anastomotic leak	0	1 (5.6%)	0
Tibia fracture	0	1 (5.6%)	0
Cardiac Disorders	**1 (5.9%)**	**1 (5.6%)**	**0**
Cardiac hypertrophy	0	1 (5.6%)	0
Supraventricular tachycardia	0	1 (5.6%)	0
Tachycardia	1 (5.9%)	0	0
Gastrointestinal Disorders	0	1 (5.6%)	1 (8.3%)
Intra-abdominal haemorrhage	0	1 (5.6%)	1 (8.3%)
Hepatobiliary Disorders	0	2 (11.1%)	0
Cholangitis	0	1 (5.6%)	0
Hepatic vein thrombosis	0	1 (5.6%)	0
Liver disorder	0	1 (5.6%)	0
Metabolism and Nutrition Disorders	**0**	**0**	**2 (16.7%)**
Acidosis	0	0	1 (8.3%)
Dehydration	0	0	1 (8.3%)
Hyponatraemia	0	0	1 (8.3%)
Nervous System Disorders	0	1 (5.6%)	1 (8.3%)
Convulsion	0	1 (5.6%)	0
Neurotoxicity	0	0	1 (8.3%)
Renal and Urinary Disorders	**1 (5.9%)**	**0**	**1 (8.3%)**
Oliguria	0	0	1 (8.3%)
Renal impairment	1 (5.9%)	0	0
Social circumstances	0	0	1 (8.3%)
Treatment noncompliance	0	0	1 (8.3%)
Surgical and Medical Procedures	**0**	**0**	**1 (8.3%)**
Central venous catheter removal	0	0	1 (8.3%)

Clinical Reviewer's Comment
The types and rates of SAEs observed in F506-CL-0404A for different types of organ transplants are as expected in this patient population.

7.4.3. Common Adverse Events and Dropouts and/or Discontinuations Due to Adverse Events

Study FG-506-01-13

A total of 11 (12.1%) patients in the tacrolimus granules group and 13 (14.4%) patients in the CsA-ME group experienced AEs leading to discontinuation of study drug.

Table 27 Adverse Reactions Occurring in > 10% of Patients (FG-506-01-13)

	PROGRAF granules (N = 91)	Cyclosporine (N = 90)
Body as a Whole		
Fever	46%	51%
Infection	25%	29%
Sepsis	22%	20%
CMV Infection	15%	24%
EBV Infection	26%	11%
Ascites	17%	20%
Peritonitis	12%	7%
Cardiovascular System		
Hypertension	39%	47%
Digestive System		
Liver Function Tests Abnormal	37%	28%
Diarrhea	26%	26%
Vomiting	15%	13%
Gastrointestinal Hemorrhage	11%	12%
Bile Duct Disorder	12%	8%
Gastroenteritis	12%	4%
Hemic and Lymphatic System		
Anemia	29%	19%
Metabolic and Nutritional Disorders		
Hypomagnesemia	40%	29%
Acidosis	26%	17%
Hyperkalemia	12%	10%
Respiratory System		
Pleural Effusion	22%	19%
Bronchitis	11%	8%
Urogenital System		
Kidney Function Abnormal	13%	14%

Clinical Reviewer's Comment
Due to the high study medication discontinuation rate in the CsA-ME group (51%) it is not possible to make very accurate safety assessments. In general, the AEs are balanced across the treatment groups. (Table 28)

Table 28 Common Adverse Events (≥ 10%) in Different Age Groups (FG-506-01-13)

	Number of Patients, n (%)

System Organ Class Preferred Term	Tacrolimus Granules			Cyclosporine-ME		
	≥ 5 Years n = 21	< 5 Years n = 70	< 1 Year n = 31	≥ 5 Years n = 20	< 5 Years n = 70	< 1 Year n = 38
Any AE	**20 (95.2)**	**69 (98.6)**	**31 (100.0)**	**18 (90.0)**	**70 (100.0)**	**38 (100.0)**
Body as a Whole	**15 (71.4)**	**63 (90.0)**	**28 (90.3)**	**15 (75.0)**	**62 (88.6)**	**32 (84.2)**
Fever	4 (19.0)	38 (54.3)	18 (58.1)	8 (40.0)	38 (54.3)	18 (47.4)
Infection	2 (9.5)	21 (30.0)	6 (19.4)	2 (10.0)	24 (34.3)	15 (39.5)
CMV infection	1 (4.8)	13 (18.6)	4 (12.9)	2 (10.0)	20 (28.6)	10 (26.3)
Sepsis	3 (14.3)	17 (24.3)	10 (32.3)	4 (20.0)	14 (20.0)	7 (18.4)
EBV infection	2 (9.5)	22 (31.4)	10 (32.3)	2 (10.0)	8 (11.4)	4 (10.5)
Ascites	2 (9.5)	13 (18.6)	6 (19.4)	4 (20.0)	14 (20.0)	8 (21.1)
Peritonitis	5 (23.8)	6 (8.6)	5 (16.1)	0	6 (8.6)	2 (5.3)
Lab test abnormal	0	3 (4.3)	0	0	8 (11.4)	4 (10.5)
Flu syndrome	2 (9.5)	4 (5.7)	2 (6.5)	2 (10.0)	1 (1.4)	0
Surgical complication	1 (4.8)	2 (2.9)	1 (3.2)	2 (10.0)	4 (5.7)	2 (5.3)
Cardiovascular System	**10 (47.6)**	**40 (57.1)**	**18 (58.1)**	**9 (45.0)**	**44 (62.9)**	**23 (60.5)**
Hypertension	8 (38.1)	27 (38.6)	13 (41.9)	6 (30.0)	36 (51.4)	18 (47.4)
Cardiomegaly	4 (19.0)	2 (2.9)	1 (3.2)	1 (5.0)	1 (1.4)	1 (2.6)
Digestive System	**15 (71.4)**	**58 (82.9)**	**26 (83.9)**	**12 (60.0)**	**51 (72.9)**	**29 (76.3)**
Liver function tests abnormal	4 (19.0)	30 (42.9)	9 (29.0)	3 (15.0)	22 (31.4)	15 (39.5)
Diarrhea	4 (19.0)	20 (28.6)	9 (29.0)	4 (20.0)	19 (27.1)	11 (28.9)
Vomiting	1 (4.8)	13 (18.6)	6 (19.4)	1 (5.0)	11 (15.7)	5 (13.2)
Gastrointestinal hemorrhage	2 (9.5)	8 (11.4)	1 (3.2)	2 (10.0)	9 (12.9)	5 (13.2)
Bile duct disorder	4 (19.0)	7 (10.0)	3 (9.7)	0	7 (10.0)	4 (10.5)
Gastroenteritis	1 (4.8)	10 (14.3)	6 (19.4)	0	4 (5.7)	2 (5.3)
Cholangitis	1 (4.8)	5 (7.1)	3 (9.7)	2 (10.0)	6 (8.6)	5 (13.2)
Liver damage	1 (4.8)	6 (8.6)	4 (12.9)	1 (5.0)	3 (4.3)	2 (5.3)
Hepatic failure	2 (9.5)	4 (5.7)	1 (3.2)	2 (10.0)	3 (4.3)	1 (2.6)
Gum hyperplasia	1 (4.8)	0	0	2 (10.0)	6 (8.6)	3 (7.9)
Constipation	0	1 (1.4)	0	2 (10.0)	0	0
Endocrine System	**4 (19.0)**	**2 (2.9)**	**1 (3.2)**	**3 (15.0)**	**0**	**0**
Cushings syndrome	4 (19.0)	2 (2.9)	1 (3.2)	3 (15.0)	0	0
Hemic and Lymphatic System	**8 (38.1)**	**37 (52.9)**	**20 (64.5)**	**6 (30.0)**	**25 (35.7)**	**14 (36.8)**
Anemia	3 (14.3)	23 (32.9)	14 (45.2)	1 (5.0)	16 (22.9)	10 (26.3)
Leukopenia	0	9 (12.9)	5 (16.1)	3 (15.0)	3 (4.3)	2 (5.3)
Leukocytosis	1 (4.8)	3 (4.3)	2 (6.5)	3 (15.0)	3 (4.3%	0
Thrombocytopenia	3 (14.3)	1 (1.4)	2 (6.5)	1 (5.0)	2 (2.9)	1 (2.6)
Metabolic and Nutritional Disorders	**14 (66.7)**	**41 (58.6)**	**17 (54.8)**	**10 (50.0)**	**34 (48.6)**	**20 (52.6)**
Hypomagnesemia	8 (38.1)	28 (40.0)	13 (41.9)	7 (35.0)	19 (27.1)	8 (21.1)
Acidosis	4 (19.0)	20 (28.6)	11 (35.5)	2 (10.0)	13 (18.6)	8 (21.1)
Hyperkalemia	4 (19.0)	7 (10.0)	4 (12.9)	3 (15.0)	6 (8.6)	4 (10.5)
Hypokalemia	0	7 (10.0)	3 (9.7)	0	3 (4.3)	2 (5.3)
Diabetes mellitus	2 (9.5)	0	0	2 (10.0)	0	0
Creatinine increased	1 (4.8)	2 (2.9)	0	2 (10.0)	1 (1.4)	0
Hyperglycemia	3 (14.3)	2 (2.9)	0	1 (5.0)	2 (2.9)	1 (2.6)
Nervous System	**7 (33.3)**	**11 (15.7)**	**3 (9.7)**	**5 (25.0)**	**10 (14.3)**	**6 (15.8)**
Tremor	3 (14.3)	0	0	3 (15.0)	0	0
Anxiety	0	2 (2.9)	0	3 (15.0)	0	0
Respiratory System	**11 (52.4)**	**35 (50.0)**	**17 (54.8)**	**5 (25.0)**	**32 (45.7)**	**19 (50.0)**
Pleural effusion	6 (28.6)	14 (20.0)	5 (16.1)	3 (15.0)	14 (20.0)	8 (21.1)
Bronchitis	2 (9.5)	8 (11.4)	3 (9.7)	0	7 (10.0)	4 (10.5)
Pharyngitis	1 (4.8)	8 (11.4)	4 (12.9)	0	6 (8.6)	3 (7.9)
Pneumonia	1 (4.8)	5 (7.1)	4 (12.9)	0	4 (5.7)	3 (7.9)

Asthma	1 (4.8)	5 (7.1)	4 (12.9)	0	3 (4.3)	0
Skin and Appendages	**3 (14.3)**	**13 (18.6)**	**5 (16.1)**	**6 (30.0)**	**24 (34.3)**	**12 (31.6)**
Hirsutism	0	1 (1.4)	1 (3.2)	4 (20.0)	21 (30.0)	10 (26.3)
Urogenital System	**8 (38.1)**	**19 (27.1)**	**9 (29.0)**	**6 (30.0)**	**16 (22.9)**	**10 (26.3)**
Kidney function abnormal	6 (28.6)	6 (8.6)	4 (12.9)	4 (20.0)	9 (12.9)	4 (10.5)
Urinary tract infection	0	3 (4.3)	2 (6.5)	1 (5.0)	4 (5.7)	4 (10.5)

Clinical Reviewer's Comment
In general, the AEs are reported with similar frequencies across different age groups in both arms except for endocrine system and nervous system disorders which were reported in the ≥ 5 years age groups more frequently. See Glucose Metabolism Disorders in Section 7.4.4 of this review.

Table 29 AEs Resulting in Discontinuation (All Randomized Subjects, (FG-506-01-13)
(Table reproduced from Table 15 in the CSR)

AEs Resulting in Discontinuation† COSTART Preferred Term	Last Dose Day	Onset/ Stop Day	Outcome
Tacrolimus granules			
≥ 5 Years			
Anemia	61	53/Ongoing	Not recovered/not resolved
Lung edema	162	151/Ongoing	Not recovered/not resolved
Drug level increased	3	3/5	Recovered/resolved
< 5 Years			
EBV infection	172	163/Ongoing	Not recovered/not resolved
Allergic reaction	265	265/269	Recovered/resolved
Hepatic failure	115	110/Ongoing	Not recovered/not resolved
Hepatic failure	9	15/17	Recovered/resolved
Liver function tests abnormal	27	22/27	Recovered/resolved
Bilirubinemia			
Lymphoma like reaction	168	143/Ongoing	Not recovered/not resolved
Lymphoma like reaction	367	224/248	Recovered/resolved
Diarrhea	96	94/104	Recovered/resolved
Lymphoma like reaction		94/Ongoing	Not recovered/not resolved
Intestinal obstruction		128/128	Recovered/resolved
Cyclosporin-ME			
≥ 5 Years			
Fever	18	5/7	Recovered/resolved
Hyperglycemia	21	5/Ongoing	Not recovered/not resolved

Ascites	202	13/38	Recovered/resolved
< 5 Years			
Drug level decreased	71	25/71	Recovered/resolved
Drug level decreased	35	14/Ongoing	Not recovered/not resolved
Drug level decreased	10	6/Ongoing	Not recovered/not resolved
Drug level decreased	11	4/Ongoing	Not recovered/not resolved
Liver function tests abnormal	166	157/Ongoing	Not recovered/not resolved
EBV infection		166/Ongoing	
Diarrhea	314	298/315	Recovered/resolved
Liver function tests abnormal	85	69/111	Recovered/resolved
Convulsion	68	49/Ongoing	Not recovered/not resolved
Hirsutism	85	55/Ongoing	Not recovered/not resolved
Fever	39	0/Ongoing	Not recovered/not resolved
Diarrhea		2/Ongoing	Not recovered/not resolved
Vomiting		2/Ongoing	Not recovered/not resolved

† On the AE CRF, change in study drug was "discontinued."

Clinical Reviewer's Comment

The study medication discontinuation rate is twice as high in the CsA-ME group compared to the tacrolimus granules group (51% vs 25%) as discussed under patient disposition. The rate of discontinuation due to AEs is 38.9% (n=31) in the CsA-ME group compared to 12.1% (n=11) in the tacrolimus group which is three times high.

In the CSR, the applicant states that "A total of 11 (12.1%) patients in the tacrolimus granules group and 13 (14.4%) patients in the cyclosporin-ME group experienced AEs leading to discontinuation of study drug (i.e., change in study drug was "discontinued" on the AE." However, Figure 1 of the CSR shows the number of patients who discontinued due to AEs in the CsA group as 35. An explanation from the applicant regarding this discrepancy was requested on April 3, 2018. In their April 16, 2018 response, the applicant stated that Figure 1 in the CSR was created using the data from the CRFs and reflects all discontinuations including acute rejections and graft loses; however, Table 15 was created using the AE reporting forms which do not include acute rejections and graft loses as adverse events resulting in this discrepancy.

It is important to note that many patients in the CsA group discontinued due to reasons which probably are not justified such as "drug level decreased or diarrhea."

Reference ID: 4267221

Study FG-506-01-08

The most frequently reported AEs during the 12-month study period were fever and infection in 16 (57.1%) patients each, diarrhea in 15 (53.6%) patients and hypertension and bile duct disorder in 13 (46.4%) patients each. A single patient experienced hyperglycemia and there were no reports of diabetes mellitus.

In addition to the 2 study drug discontinuations due to death, 3 patients had AEs that led to discontinuation of study drug, one of whom subsequently died. Among the three discontinuations not due to death, two were on day 1 of the study prior to oral tacrolimus dosing and the 3rd discontinuation was on study day 68. All 3 patients who discontinued study drug were < 5 years of age. No patients < 1 year of age discontinued study drug (Table 31).

Table 30 AEs Resulting in Discontinuation (Study FG-506-01-08 ITT)

AEs Resulting in Discontinuation COSTART Preferred Term	Last Dose Day	Onset/ Stop Day	Outcome
≥ 5 Years			
No AEs resulting in discontinuation were reported.			
< 5 Years			
GI perforation	Not dosed	-1/Ongoing	Not recovered
Hemoperitoneum, Arterial thrombosis	Not dosed	1/Ongoing, 1/1	Not recovered/ Recovered
Lymphoma like reaction	68	52/Ongoing	Not recovered
< 1 Year			
No AEs resulting in discontinuation were reported.			

Study F506-CL-0404A

Overall, 43 (91.5%) patients reported at least one AE. The highest incidence of AEs was in the kidney transplant group (12 [100.0%] patients) followed by the liver transplant group (16 [94.1%] patients) and the heart transplant group (15 [83.3%] patients). In the total study population, the SOCs for which AEs were most commonly reported were infections and infestations (27 [57.4%] patients) and gastrointestinal disorders (25 [53.2%] patients). The most commonly reported TEAEs were vomiting (15 [31.9%] patients) followed by diarrhea (14 [29.8%] patients), hypomagnesemia (11 [23.4%] patients) and hypertension (10 [21.3%] patients).

Overall 3 (6.4%) patients reported a AE resulting in discontinuation. One patient with liver transplant experienced 3 drug-related AEs of hemolytic anemia, cardiac hypertrophy and supraventricular tachycardia leading to permanent discontinuation of study drug. Two patients with kidney transplant experienced 1 drug-related AE of treatment noncompliance and nephropathy toxic leading to permanent discontinuation of study drug.

Reference ID: 4267221

Clinical Reviewer's Comment
The AEs reported in Study F506-CL-0404A are as expected in this patient population.

7.4.4. Significant Adverse Events

Study FG-506-01-13
Infections
Infections were reported for 80 (87.9%) patients in the tacrolimus granules group and 74 (82.2%) patients in the CsA-ME group (Table 32). The incidence of infections of unknown etiology or not confirmed was 61.5% in the tacrolimus granules group and 38.9% in the CsA- ME group. None of the patients experienced a BK infection.

Table 31 Incidence of Infections (Study FG-506-01-13)

Infection Type	Tacrolimus Granules n = 91 n (%)	Cyclosporine-ME n = 90 n (%)
Any infection	**80 (87.9)**	**74 (82.2)**
Bacterial	50 (54.9)	59 (65.6)
Fungal	18 (19.8)	16 (17.8)
Other	0	1 (1.1)
Protozoal	3 (3.3)	0
Unknown or not confirmed	56 (61.5)	35 (38.9)
Viral	44 (48.4)	35 (38.9)

Table 32 Common AEs Reported as Infections (≥ 2% in Either Group) (Study FG-506-01-13)

System Organ Class Preferred Term	Number of Patients, n (%)	
	Tacrolimus Granules n = 91	Cyclosporin-ME n = 90
Any AE identified as infection	**80 (87.9)**	**74 (82.2)**
Body as a Whole	**70 (76.9)**	**70 (77.8)**
Infection	22 (24.2)	26 (28.9)
Fever	22 (24.2)	25 (27.8)
Sepsis	20 (22.0)	17 (18.9)
CMV infection	14 (15.4)	22 (24.4)
EBV infection	24 (26.4)	10 (11.1)
Peritonitis	11 (12.1)	6 (6.7)
Flu syndrome	6 (6.6)	3 (3.3)
Injection site reaction	3 (3.3)	4 (4.4)
Lab test abnormal	2 (2.2)	4 (4.4)
Moniliasis	2 (2.2)	3 (3.3)
Abscess	3 (3.3)	0

Digestive System	**30 (33.0)**	**26 (28.9)**
Diarrhea	12 (13.2)	11 (12.2)
Gastroenteritis	9 (9.9)	4 (4.4)
Cholangitis	5 (5.5)	7 (7.8)
Oral moniliasis	3 (3.3)	2 (2.2)
Gastrointestinal moniliasis	1 (1.1)	2 (2.2)
Liver function tests abnormal	1 (1.1)	2 (2.2)
Vomiting	0	3 (3.3)
Ileus	2 (2.2)	0
Hemic and Lymphatic System	**0**	**4 (4.4)**
Leukocytosis	0	2 (2.2)
Respiratory System	**32 (35.2)**	**18 (20.0)**
Bronchitis	10 (11.0)	7 (7.8)
Pharyngitis	9 (9.9)	5 (5.6)
Pneumonia	6 (6.6)	3 (3.3)
Rhinitis	7 (7.7)	1 (1.1)
Respiratory moniliasis	3 (3.3)	1 (1.1)
Skin and Appendages	**8 (8.8)**	**4 (4.4)**
Herpes simplex	4 (4.4)	3 (3.3)
Herpes zoster	2 (2.2)	1 (1.1)
Special Senses	**8 (8.8)**	**0**
Otitis media	7 (7.7)	0
Conjunctivitis	2 (2.2)	0
Urogenital System	**3 (3.3)**	**5 (5.6)**
Urinary tract infection	3 (3.3)	5 (5.6)

Clinical Reviewer's Comment
The incidences of infections were generally comparable between the treatment groups. Due to high discontinuation rate in the CsA-ME group (51%) the comparisons may not be very accurate.

Nephrological Disorders
The incidence of AEs classified as nephrological disorders was comparable between the tacrolimus granules and cyclosporin-ME groups (29 [31.9%] and 26 [28.9%] patients, respectively). Of these AEs, the most common event group was "kidney function abnormal", which was reported for similar numbers of patients in the tacrolimus granules and CsA-ME groups (12 [13.2%] and 13 [14.4%] patients, respectively).

Glucose Metabolism Disorders
The incidence of AEs classified as glucose metabolism disorders was and comparable between the tacrolimus granules and CsA-ME groups (10 [11.0%] and 8 [8.9%] patients, respectively) (Table 34). The incidences of hyperglycemia, hypoglycemia or diabetes mellitus were comparable between the treatment groups. The use of concurrent antidiabetic medication was similar between the treatment groups. Among patients without pre-existing diabetes, a similar number of patients developed diabetes during the study. In the tacrolimus granules and CsA-

Reference ID: 4267221

ME groups, the proportion of patients without pre-existing diabetes that received long-term treatment was the same (2.2% [2/91] and 2.2% [2/89], respectively).

Table 33 Glucose Metabolism Disorders (≥ 2% in Either Treatment Group) (Study FG-506-01-13)

System Organ Class Preferred Term	Number of Patients, n (%)	
	Tacrolimus Granules n = 91	Cyclosporine-ME n = 90
Any AE classified as glucose metabolism disorders	**10 (11.0)**	**8 (8.9)**
Metabolic and Nutritional Disorders	**10 (11.0)**	**8 (8.9)**
Hyperglycemia	5 (5.5)	3 (3.3)
Hypoglycemia	2 (2.2)	3 (3.3)
Diabetes mellitus	2 (2.2)	2 (2.2)

Neurological Disorders

The incidence of AEs classified as neurological disorders was comparable between the tacrolimus granules and CsA-ME groups (18 [19.8%] and 19 [21.1%] patients, respectively) (Table 35). No treatment differences were noted for the AEs classified as neurological disorders except for neuropathy, which was reported by 2 (2.2%) patients in the tacrolimus granules group and by none in the cyclosporin-ME group.

Table 34 Neurological Disorders (≥ 2% in Either Treatment Group) (Study FG-506-01-13)

System Organ Class Preferred Term	Number of Patients, n (%)	
	Tacrolimus Granules n = 91	Cyclosporine-ME n = 90
Any AE classified as neurological disorders	**18 (19.8)**	**19 (21.1)**
Nervous System	**18 (19.8)**	**18 (20.0)**
Convulsion	6 (6.6)	4 (4.4)
Agitation	3 (3.3)	3 (3.3)
Tremor	3 (3.3)	3 (3.3)
Anxiety	2 (2.2)	3 (3.3)
Neuropathy	2 (2.2)	0

Clinical Reviewer's Comment

Based on the published literature tacrolimus may cause more glucose metabolism disorders and tremor compared to cyclosporine. In Study FG-506-01-13, the incidence rates of these events were generally comparable across the treatment groups except for neuropathy which was reported in the tacrolimus group only (2 cases). In general, the incidences of glucose

metabolism disorders were low in both treatment groups which may at least partially be due to the young age of the patients enrolled.

Cardiovascular Events

The overall incidence of AEs classified as cardiovascular events was 47.3% (43/91) in the tacrolimus granules group and 50.0% (45/90) in the cyclosporin-ME group (Table 36). The most common cardiovascular event was hypertension, which was reported for similar numbers of patients in the tacrolimus granules and CsA-ME groups (34 [37.4%] and 41 [45.6%] patients, respectively). Serious cardiovascular events were experienced by 9 patients (9.8%) in the tacrolimus granules group and 5 patients (5.5%) in the CsA-ME group.

Table 35 Cardiovascular Events (≥ 2% in Either Treatment Group) (Study FG-506-01-13)

System Organ Class Preferred Term	Number of Patients, n (%)	
	Tacrolimus Granules n = 91	Cyclosporine-ME n = 90
Overall	**43 (47.3)**	**45 (50.0)**
Cardiovascular System	**43 (47.3)**	**44 (48.9)**
Hypertension	34 (37.4)	41 (45.6)
Cardiomegaly	6 (6.6)	2 (2.2)
Bradycardia	3 (3.3)	3 (3.3)
Hypotension	3 (3.3)	2 (2.2)
Pericardial effusion	2 (2.2)	1 (1.1)
Tachycardia	2 (2.2)	1 (1.1)
Cardiomyopathy	2 (2.2)	0

The number of patients receiving antihypertensive medications at any time during the study was comparable between the tacrolimus granules and CsA-ME groups (74 [81.3%] and 73 [81.1%] patients, respectively). In both treatment groups, the number of patients receiving antihypertensive medications decreased at the end of the study. In the tacrolimus granules and CsA-ME groups, few patients received antihyperlipidemic medications at any time during the study (3 [3.3%] and 5 [5.6%] patients, respectively).

Clinical Reviewer's Comment

In general, cardiovascular events are balanced across the treatment groups. However, cardiomyopathy was reported only in the tacrolimus group (n=2) and there were more cardiomegaly cases in the tacrolimus group (n=6) then in the CsA-ME group (n=2).

Malignancies

AEs classified as malignancy events were experienced by 5 patients in the tacrolimus granules group (1 gastrointestinal carcinoma and 4 lymphoma like reaction) and by none in the cyclosporin-ME group (Table 37). Lymphoma like reaction can be related to EBV

infection. All 4 patients who had lymphoma like reaction were EBV negative at baseline and all received prophylactic acyclovir. For these patients, 2 donors were EBV positive, 1 donor was EBV negative and information on EBV status was unavailable for 1 donor.

Table 36 Malignancies (Study FG-506-01-13)

System Organ Class Preferred Term	Number of Patients, n (%)	
	Tacrolimus Granules n = 91	Cyclosporine-ME n = 90
Overall	**5 (5.5)**	**0**
Digestive System	**1 (1.1)**	**0**
Gastrointestinal carcinoma	1 (1.1)	0
Hemic and Lymphatic System	**4 (4.4)**	**0**
Lymphoma like reaction	4 (4.4)	0

Post-Transplant Lymphoproliferative Disorder (PTLD)
Suspected PTLD was reported for 2 patients in the tacrolimus granules group and 1 patient in the CsA-ME group (Table 38). Established PTLD was reported for 3 patients in the tacrolimus granules group and none in the cyclosporin-ME group.

Table 37 PTLD (Study FG-506-01-13)

System Organ Class Preferred Term	Number of Patients, n (%)	
	Tacrolimus Granules n = 5	Cyclosporine-ME n = 1
Established PTLD	3 (60.0)	0
Suspected PTLD	2 (40.0)	1 (100.0)

All 6 patients with suspected or established PTLD were EBV negative at baseline and all received prophylactic acyclovir. For the 5 patients in the tacrolimus granules group, 2 donors were EBV positive, 1 donor was EBV negative and information on EBV status was unavailable for 2 donors. No information was available on the EBV status of the donor for the patient in the CsA-ME group. Two patients with suspected PTLD and 2 patients with established PTLD had an AE of EBV infection. Three of the 5 PTLD patients in the tacrolimus granules group were switched to other immunosuppressive regimens by month 12. None of the patients died. Overall, of the 6 PTLD patients Table 35) in the study, 3 patients discontinued due to an AE (2 tacrolimus granules [1 event each of lymphoma like reaction and EBV infection], 1 CsA-ME [graft rejection]), 1 patient (tacrolimus granules) discontinued due to suspension of study drug and 2 patients (tacrolimus granules) completed the study.

Clinical Reviewer's Comment

PTLD is more commonly observed in pediatric transplant patients compared to adult transplant patients due to the higher rates of EBV seronegativity in pediatric patients among whom a higher proportion have not encountered EBV yet hence have not developed antibodies against the EBV virus. EBV virus infection is incriminated in most cases of PTLD such as that acquired by transplantation of an organ from an EBV (+) donor to a EBV (-) recipient.

A numerically higher rate of PTLD was observed among tacrolimus patients compared to CsA patients. As discussed in Section 5.1.2 of this review, the proportions of EBV-negative patients with an EBV-positive donor or with a donor with unknown EBV status were higher in the tacrolimus granules group compared to the CsA-ME group which was more pronounced among patients < 1 year of age. These imbalances may have disadvantaged the tacrolimus granules group in terms of the PTLD risk since EBV seronegativity especially when combined with a EBV (+) donor is a risk factor for PTLD.

Study FG-506-01-08

Infections

AEs classified as infections were reported in a total of 25 (89.3%) patients. SAEs classified as infection were reported in 5 (17.9%) patients overall. CMV and EBV infections reported in 1 (3.6%) patient each were SAEs.

Table 38 Common (≥ 2 Patients Overall) AEs Identified as Infections (Study FG-506-01-08)

System Organ Class Preferred Term	Tacrolimus, n (%)			
	Total n = 28	≥ 5 Years n = 10	< 5 Years n = 18	< 1 Year n = 7
Any AE classified as infection	**25 (89.3)**	**9 (90.0)**	**16 (88.9)**	**7 (100.0)**
Body as a Whole	**24 (85.7)**	**9 (90.0)**	**15 (83.3)**	**7 (100.0)**
Fever	16 (57.1)	3 (30.0)	13 (72.2)	5 (71.4)
Infection	16 (57.1)	6 (60.0)	10 (55.6)	6 (85.7)
CMV infection	6 (21.4)	3 (30.0)	3 (16.7)	1 (14.3)
EBV infection	6 (21.4)	3 (30.0)	3 (16.7)	1 (14.3)
Sepsis	4 (14.3)	3 (30.0)	1 (5.6)	1 (14.3)
Cardiovascular System	**2 (7.1)**	**0**	**2 (11.1)**	**0**
Digestive System	**20 (71.4)**	**6 (60.0)**	**14 (77.8)**	**6 (85.7)**
Diarrhea	11 (39.3)	2 (20.0)	9 (50.0)	2 (28.6)
Gastroenteritis	4 (14.3)	0	4 (22.2)	2 (28.6)
Oral moniliasis	4 (14,3)	3 (30.0)	1 (5.6)	1 (14.3)
Esophagitis	3 (10.7)	0	3 (16.7)	2 (28.6)
Cholangitis	2 (7.1)	2 (20.0)	0	0
GI moniliasis	2 (7.1)	0	2 (11.1)	2 (28.6)
Respiratory System	**16 (57.1)**	**4 (40.0)**	**12 (66.7)**	**5 (71.4)**

Pharyngitis	8 (28.6)	1 (10.0)	7 (38.9)	3 (42.9)
Bronchitis	7 (25.0)	2 (20.0)	5 (27.8)	3 (42.9)
Pleural effusion	2 (7.1)	1 (10.0)	1 (5.6)	0
Pneumonia	2 (7.1)	0	2 (11.1)	0
Skin and Appendages	**4 (14.3)**	**3 (30.0)**	**1 (5.6)**	**0**
Herpes simplex	3 (10.7)	2 (20.0)	1 (5.6)	0
Special Senses	**4 (14.3)**	**0**	**4 (22.2)**	**1 (14.3)**
Otitis media	3 (10.7)	0	3 (16.7)	1 (14.3)
Urogenital System	**3 (10.7)**	**0**	**3 (16.7)**	**2 (28.6)**
Urinary tract infection	2 (7.1)	0	2 (11.1)	1 (14.3)

Nephrological Disorders
AEs classified as nephrological disorders were reported in a total of 15 (53.6%) patients. SAEs classified as nephrological disorders were reported in 2 patients, with kidney function abnormal and toxic nephropathy reported in 1 (3.6%) patient each.

Glucose Metabolism Disorders
Glucose metabolism disorders were reported in 2 (7.1%) patients. A single (3.6%) patient (≥ 5 years of age) was diagnosed with hyperglycemia and 1 (3.6%) patient (< 1 year of age) was diagnosed with hypoglycemia and there were no reports of diabetes mellitus. Antidiabetic concomitant medications were administered to 2 patients during the study.

Neurological Disorders
Neurological disorders were reported in 10 (35.7%) patients. Agitation, headache and insomnia were the most common AEs, reported in 5 (17.9%), 3 (10.7%) and 2 (7.1%) patients, respectively.

Cardiovascular Events
Seventeen (60.7%) patients experienced a cardiovascular AE. Hypertension reported in 13 (46.4%) patients was the most common AE, followed by cardiomegaly reported in 4 (14.3%) patients. SAEs classified as cardiovascular events were reported in 9 (32.1%) patients and included hemorrhage reported in 3 (10.7%) patients and thrombosis in 2 (7.1%) patients overall.

Malignancies
One (3.6%) patient experienced an SAE of lymphoma like reaction that was classified as a malignant event on study day 52 following treatment with tacrolimus and immunosuppressive medications. This patient (< 5 years of age) had several diagnoses and AEs with unresolved outcomes during the study. The patient discontinued study drug on day 68 and subsequently died of a suspected intestinal volvulus on study day 243.

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In Study FG-506-01-08, the adverse events and the rates of these adverse events summarized above are as expected in this patient population although any possible contribution of the study drug (tacrolimus) cannot be ruled out with certainty similar to other clinical transplantation studies. Most of these adverse events are the result of suppressed immune state or may be directly contributed by the study drug as in the case of diabetes or neurological disorders which are all acceptable trade-offs to maintain a viable transplant.

Study F506-CL-0404A

No AE of special interest were defined per study protocol.

7.4.5. Laboratory Findings

Study FG-506-01-13
Hematology
Mean hemoglobin was slightly reduced after surgery but increased throughout the study to normal values in both treatment groups. Similarly, mean platelet counts were below normal after transplantation but increased to normal levels within the first study week. Platelet counts remained at normal levels after week 1, though being lower in the tacrolimus granules group than in the CsA-ME group throughout the study. Mean white blood cell counts were at the upper margin of the normal ranges and remained comparable and stable throughout the study. Hematocrit values remained at about 0.3 throughout the study in both treatment groups.

Biochemistry
After transplantation, LDL and total cholesterol values were higher in the CsA-ME group than in the tacrolimus granules group. HDL values remained similar between the treatment groups over the course of the study. Possibly due to parenteral nutrition immediately posttransplantation, the mean blood glucose levels were elevated after surgery but normalized within the first month of the study in both treatment groups. No treatment differences were observed in potassium or magnesium values. Also, no treatment differences were observed with respect to any of the other measured biochemical laboratory parameters sodium, LDH, serum albumin or total protein.

Biochemistry-related AEs that were reported by ≥ 10% of patients in either the tacrolimus granules group or the CsA-ME group included hypomagnesemia (36 [39.6%] and 26 [28.9%] patients, respectively) and hyperkalemia (11 [12.1%] and 9 [10.0%] patients respectively). Most of these events were assessed by the investigator as related to study drug (hypomagnesemia: 33 [36.3%] and 23 [25.6%] patients, respectively; hyperkalemia: 10 [11.0%] and 7 [7.8%] patients, respectively)

Liver Function Tests
Most mean values for hepatic laboratory parameters (including ALT, AST and alkaline

phosphatase) were similar for both treatment groups at screening and throughout the study . Apart from day 1, mean total bilirubin values were lower in the tacrolimus granules group than in the CsA-ME group immediately after transplantation (up to day 21). At later time points, mean total bilirubin values were comparable between the treatment groups. No pronounced differences were observed for any of the other liver function parameters.

Renal Function
No pronounced treatment differences were detected for the renal parameters. In both treatment groups, similar slight decreases in serum eGFR were noted in comparison to baseline, with those decreases starting 1 month later in the tacrolimus granules group than in the CsA-ME group (Table 40). In both treatment groups, the serum creatinine level increased slightly after transplantation in comparison to baseline and then remained approximately constant until the end of the study.

Table 39 eGFR (mL/min/1.73 m2) (Study FG-506-01-13)

Visit	Tacrolimus Granules n = 91				Cyclosporine-ME n = 90			
	Actual Value		Change from Baseline		Actual Value		Change from Baseline	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	89	154.2 (83.6)	89	NA	83	133.9 (57.6)	83	NA
Day 1	89	147.4 (108.0)	89	-6.8 (111.4)	83	112.5 (51.9)	82	-20.6 (43.6)
Month 1	78	119.2 (52.0)	78	-35.4 (83.9)	62	102.3 (41.6)	61	-27.5 (43.8)
Month 3	76	106.0 (42.1)	76	-45.0 (80.9)	52	109.4 (42.4)	51	-30.1 (52.1)
Month 6	69	118.6 (36.5)	69	-32.1 (85.4)	48	114.2 (46.7)	47	-18.7 (56.8)
Month 12	76	128.5 (50.9)	76	-28.7 (88.7)	66	117.5 (49.9)	65	-13.4 (62.6)

Study FG-506-01-08

Hematology
Many patients had hemoglobin and hematocrit values below the normal range at baseline, and these values tended not to change over time. Anemia was reported in 1 (3.6%) patient as a hematological AE assessed by the investigator as related to study drug.

Biochemistry
Total cholesterol levels were within the normal range at baseline and throughout the duration of the study. Blood glucose levels returned to baseline by day 28 and remained stable throughout the 12-month study period. The most common (≥ 2 patients overall) biochemistry-related AE assessed by the investigator as related to study drug was hyperuricemia reported in 6 (21.4%) patients.

Renal Function
Mean serum creatinine concentrations and eGFR did not change appreciably from the

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baseline over time and no clinically significant changes were noted during the 12-month study period (Table 41).

Table 40 Renal Function (Study FG-506-01-08)

Visit	Tacrolimus n = 28					
	Actual Value			Change from Baseline		
	n	Mean	SD	n	Mean	SD
eGFR (mL/min/1.73 m^2)						
Baseline	28	130.4	37.3	NA	NA	NA
Day 28	26	125.1	51.4	26	-11.2	48.6
Day 91 (Month 3)	22	128.3	43.3	22	-6.6	44.3
Day 183 (Month 6)	23	127.3	31.9	23	-8.6	33.9
Day 365 (Month 12)	22	115.2	24.5	22	-20.5	28.2

Hepatic Function
For parameters indicative of hepatic function (bilirubin, GGT, alkaline phosphatase, ALT and AST), mean values indicated a recovery of function by day 28 with continued decreases until month 3 and stable values thereafter. Most patients experienced a decrease of liver function values to within normal range.

Study F506-CL-0404A

Hematology
One 0.8-year-old female patient with liver transplant experienced a drug-related AE of platelet count decreased. No other clinically significant hematologic AEs were reported.

Biochemistry
One 10.9-year-old male patient with kidney transplant experienced serious drug-related AE of blood creatinine increased (2 episodes) and drug-related AEs of ALT and gamma-glutamyl-transferase (GGT) increased. One 11.1-year-old female patient with kidney transplant also experienced a drug-related AE of blood creatinine increased. One 2.0-year-old male with liver transplant experienced a serious drug-related AE of hepatic enzyme increased. One 3.8-year-old male with kidney transplant experienced a serious drug-related AE of transaminases increased.

Clinical Reviewer's Comment
Both in Study FG-506-01-13 and Study FG-506-01-08 no unexpected laboratory abnormalities have been identified for the studied patient populations.

7.4.6. Vital Signs and Growth Measurements

Mean values were obtained for the various characteristics at screening; days 1, 5, 9, 14 and 21; weeks 6 and 10; and months 1, 2, 3, 6, 9 and 12. The mean temperature remained approximately constant throughout the study and was similar at each time period for both treatment groups.

Mean weights and mean heights were similar for the 2 treatment groups at each time period during the study. The mean (SD) increase in weight from screening to month 12 was 3.359 (3.043) kg in the tacrolimus granules group and 3.136 (1.965) kg in the CsA-ME group. The mean (SD) increase in height from screening to month 12 was 10.32 (5.62) cm in the tacrolimus granules group, and 10.12 (6.13) cm in the CsA-ME group. No unexpected clinically relevant treatment differences were noted in an analysis of weight by age groups.

An analysis of height by age group observed treatment differences for the age category ≥ 5 years but not for the age categories < 5 years or < 1 year: among patients ≥ 5 years, the mean (SD) increase in height from screening to month 12 was smaller in the tacrolimus granules group than in the CsA-ME group (3.86 [2.62] cm and 6.22 [4.68] cm, respectively. The mean (SD) increase in height from screening to month 12 was comparable between the tacrolimus granules and CsA-ME groups among patients < 5 years (12.53 [4.56] cm and 11.79 [5.99] cm, respectively) and among patients < 1 year (14.90 [4.20] cm and 14.50 [3.67] cm, respectively).

Clinical Reviewer's Comment
Among patients ≥ 5 years of age, a slower growth rate in terms of height in Tacrolimus patients compared to CsA patients was observed in this study. In this subgroup, the mean (SD) increase in height from screening to month 12 was (3.9 [2.6] cm in the tacrolimus granules group compared to 6.2 [4.7] cm in the CsA-ME group. Since a similar observation has not been made in the younger (≤ 5 years) age group the validity of this observation is not clear and may need to be reassessed in future randomized controlled trials. This difference may be due to baseline differences in this small study.

Study FG-506-01-08
No clinically relevant changes in blood pressure were noted during this study. The common (≥ 2 patients overall) cardiovascular AEs assessed by the investigator as related to study drug were hypertension in 12 (42.9%) patients and cardiomegaly in 4 (14.3%) patients.

Growth measurements showed slight increases in height of patients at day 28 and 3 months from study initiation with no change in weight. Increases in mean values of height and weight were noted at months 6 and 12.

Study F506-CL-0404A
Drug-related AEs of hypertension were reported by 7 [14.9%] patients; 2 [11.8%] patients (10.9 and 0.6-year-old males) with heart transplant, 3 [16.7%] patients (11.9 and 2.0-year-old

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males and 0.8-year-old female) with liver transplant and 2 [16.7%] patients (4.3-year-old male and 7.0-year-old female) with kidney transplant. One 7.2-year-old female patient with kidney transplant experienced serious drug-related AE of body temperature increased.

7.4.7. Electrocardiograms (ECGs)

Study FG-506-01-13: Not systematically performed in this pediatric study.
Study FG-506-01-08: No clinically relevant changes were observed in ECG during this study. Echocardiography results were normal at baseline for a majority of patients with no clinically relevant changes at the end of the 12-month study duration.
Study F506-CL-0404A: Not systematically performed in this pediatric study.

7.4.8. QT

See Section 7.4.7., Electrocardiograms (ECGs) above.

7.4.9. Immunogenicity

Not applicable

7.5. Analysis of Submission-Specific Safety Issues

Not applicable

7.6.Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroups including by gender and different age groups are discussed in other sections of the safety review where relevant.

7.7. Specific Safety Studies/Clinical Trials

Not applicable

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

Prograf granules is a new dosage form of an approved product (tacrolimus) which has been on the US market since 1994.

7.8.2. Human Reproduction and Pregnancy

Prograf granules is a new dosage form of an approved product (tacrolimus) which has been on

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the US market since 1994. PLLR conversion is part of this NDA submission. Please see the Pharmacology/Toxicology review and the relevant sections of this review for the PLLR conversion.

7.8.3. Pediatrics and Assessment of Effects on Growth

See Section 7.4.6

7.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

7.9. Safety in the Postmarket Setting

7.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable

7.9.2. Expectations on Safety in the Postmarket Setting

Not applicable

7.9.3. Additional Safety Issues From Other Disciplines

Not applicable

7.10. Integrated Assessment of Safety

Safety assessments of the individual studies submitted in support of the NDA 210,115 are provided above. Based on the safety reviews of the studies FG-506-01-13, FG-506-01-08 and F506-CL-0404 tacrolimus for oral suspension has acceptable safety for the indications studied in pediatric transplant recipients. Prograf for oral suspension is a new dosage form of an approved product (tacrolimus) which has been on the US market since 1994. No new safety issues have been identified during the review of NDA 210,115 other than those already covered in the approved US package insert.

8. Advisory Committee Meeting and Other External Consultations

Not applicable

9. Labeling Recommendations

9.1.Prescription Drug Labeling

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9.1.1. General Information about Labeling

Clinical Reviewer's note: At the time when this clinical review was finalized, the Division's work on the product package insert (PI) was still ongoing. Therefore, although no major changes are anticipated, there may be further minor changes to the PI not covered in this review. Sections 1- 8 and 14 of the Prograf Labeling as negotiated with the applicant and likely to be final are included in the Appendix at the end of this review.

Since NDA 210,115 is for a new dosage form (granules) of a lawfully marketed product in US as Prograf® (tacrolimus) capsules and injection, new information related to the granule dosage form will be added to the existing Prograf package insert (PI). Per the Pregnancy and Lactation Labeling Rule (PLLR) legislation, the Prograf labeling is required to be updated in Section 8 Use in Special Populations to comply with PLLR. Currently proposed labeling by the applicant is compliant with PLLR. The PLLR portion of the labeling is reviewed by the Pharmacology/Toxicology discipline, and discussed with the Clinical discipline. The findings, conclusions and recommended labeling revisions will be summarized in the Pharmacology/Toxicology discipline review.

However, Section 8 also includes human data which will be discussed in this NDA review (9.1.2. PLLR Conversion below). The latest labeling proposal by the applicant was submitted on January 24, 2018 which includes the applicant's revisions in Section 2, Dosage and Administration per the Division's December 21, 2017 letter.

9.1.2. Applicant's Proposed Starting Dose and Conversion from Granules to Capsules

Other main issues communicated to the applicant in the FDA December 21, 2017 letter:

- The applicant's rationale for the proposed lower starting dose of Prograf Granules than the dose that was evaluated in Study FG- 506- 01-13.
- The applicant proposed to include the following language in the PI: (b) (4) (b) (4)

  Clinical Pharmacology Team requested the rationale for the proposed language above, since it may seem more probable that there would be switch from the granules to Prograf capsules. Additionally, the available PK data from Study F506-CL-0404B that was aimed to generate data about dose changes and tacrolimus whole blood trough levels after eventual conversion from tacrolimus granules to Prograf capsules were requested from the applicant.

Applicant's January 24, 208 response to the December 21, 2017 FDA letter:

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- ***FDA Question: Rationale for the proposed lower starting dose of Prograf Granules than the dose that was evaluated in Study FG- 506- 01-13***:

  Reviewer's Note: In Study FG-506-01-13, the protocol specified starting dose of tacrolimus granules for de novo pediatric liver transplant recipients was 0.3 mg/kg per day administered in 2 divided doses. However, in the proposed PI, the recommended starting dose of tacrolimus granules for de novo pediatric liver transplant recipients is 0.15-0.20 mg/kg/day.

  Applicant's response:
  In Study FG-506-01-13, the protocol-recommended initial dose of tacrolimus granules was 0.3 mg/kg per day administered in 2 divided doses; subsequently, the doses were adjusted based on target whole blood trough levels (10 to 20 ng/mL in the first 2 weeks; 10 to 15 ng/mL during weeks 3 and 4; 5 to 15 ng/mL during months 2 and 3; 5 to 10 ng/mL thereafter). The median initial dose of 0.29 mg/kg per day resulted in median trough levels that were on the high end of the target range for at least 50% of patients (P50 ≥ 18.2 ng/mL) and above the range for at least 40% of patient (P60 ≥ 20.8 ng/mL) during the first 2 days posttransplant (days 0 and 1). By days 2 and 3 posttransplant, the median dose was adjusted down to 0.17 and 0.14 mg/kg per day, respectively, resulting in median trough levels of 16.8 ng/mL and 14.4 ng/mL on days 3 and 4. For the rest of the trial, trough values were maintained within the target ranges for most patients via therapeutic drug monitoring (TDM).

  Astellas' decision to include a recommended starting dose of tacrolimus granules of 0.3 mg/kg per day in the protocol took into consideration the following points:
  - Tacrolimus therapy would be administered as a dual immunosuppressive regimen without antibody induction and without azathioprine.
  - Clearance of tacrolimus in pediatric liver transplant patients is approximately 2-fold higher than in adults

  Astellas now proposes a starting dose of tacrolimus granules that is lower than the dose administered in study FG-506-01-13 for the following reasons. Consistent with the data described above, the initial protocol-recommended dose resulted in higher tacrolimus exposure than recommended for at least 40% of patients, which resulted in investigators lowering the dose to ≤ 0.2 mg/kg per day for a transient period. Being a dual therapy regimen in this study, the concern in the early posttransplant period was to avoid underdosing. In addition, treatment paradigms have evolved in management of solid organ transplantation since the time the trial was conducted. Current clinical practice utilizes tacrolimus combined with mycophenolate mofetil (MMF) with/without corticosteroids, as dual or triple drug regimen, allowing a lower initial dose of tacrolimus to be administered without compromising efficacy. Additionally, in the US, the use of antibody induction in conjunction with a tacrolimus-based regimen is more prevalent. The use of antibody induction provides immunosuppressive coverage in the immediate posttransplant period, thus, permitting use of lower initial dose therapy for the first 4 to 5 days of treatment.

- ***FDA Question: Rationale for the PI recommendation*** (b) (4) (b) (4) (b) (4) ***and the available PK data from Study F506-CL-0404B to support***

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1 to 1 conversion from granules to capsules:

Applicant's response:
Astellas acknowledges the Agency's recommendation (b) (4) of the text in subsection 2.5 of the draft product labeling (b) (4). In addition, Astellas has included the line listings from study F506-CL-0404B, which is a 1-month extension from F506-CL-0404A (n = 47), where 6 patients (3 kidney, 2 liver and 1 heart) entered into study F506-CL-0404B. The protocol for study F506-CL-0404 did not include collection of pharmacokinetic data; however, dosing and trough data were collected pre- and post conversion from granules to Prograf capsules [Study F506-CL-0404B, Listings 13.2.5.1 and 13.2.5.3]. Patients were converted from granules to Prograf capsules on a 1:1, mg:mg dose basis. In case conversion on a 1:1, mg:mg basis was not possible due to the available dosage strengths, the Prograf capsule dose was adjusted upwards to the nearest 0.5 or 1.0 mg. Following conversion, the Prograf dose remained unchanged for 7 days post conversion. These data suggest that following conversion, trough levels remained in the recommended target range. The observed safety profile throughout the study was consistent with the known characteristics of tacrolimus and no new safety issues were identified.

Clinical Reviewer's Comment
From a clinical perspective, the applicant's rationale for the lower starting dose recommended in the PI (0.15-0.20 mg/kg/day) compared to the higher starting dose (0.30 mg/kg/day) that was administered in the comparative Study FG-506-01-13 in pediatric *de novo* liver transplant recipients and the rationale for the 1 to 1 (mg per mg) conversion from the granule formulation to the capsule formulation (when needed) based on data from 6 patients (3 kidney, 2 liver and 1 heart) in study F506-CL-0404B are acceptable.

I agree with the applicant that "*the initial protocol-recommended dose resulted in higher tacrolimus exposure than recommended for at least 40% of patients, which resulted in investigators lowering the dose to ≤ 0.2 mg/kg per day for a transient period*." However, it is important to keep in mind that in the starting dose recommendation in the PI is made without any mention of concomitant induction treatment or any supplemental immunosuppressives (such as MPA products or azathioprine). Therefore, starting dose recommendations cannot be based on the assumption that Prograf, in clinical practice, will be administered concomitantly with an induction agent and supplemental immunosuppressants.

Clinical Pharmacology Team recommends 0.20 mg/kg/day as the starting dose instead of the applicant's proposed range of 0.15-0.20 mg/kg/day and I agree with this recommendation.

9.1.3. Applicant's Proposed New Information for the Prograf PI Pertaining to the Clinical Discipline

(Applicant's proposed new wording is in red fonts and proposed deletions are ~~stricken out~~.)

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(b) (4)

(b) (4)

Patient Population	(b) (4)	(b) (4) Whole Blood Trough Concentrations
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	Month 1-12: 5-20 ng/mL

(b) (4)

The required dose for PROGRAF granules is calculated based on the weight of the patient. Use the minimum number of packets that corresponds to the dose. Do not use tubing, syringes and other equipment (cups) containing PVC to prepare or administer tacrolimus products.

- To prepare the dose, empty the entire contents of each PROGRAF granules packet into a (b) (4) (glass) cup. Check for any remaining granules in the packet(s) and empty these into the cup.
- Add 1 to 2 tablespoons (15 to 30 milliliters) of room temperature drinking water to the cup containing the PROGRAF granules.
- Mix and administer the entire contents of the cup. The granules will not completely dissolve. The suspension should be given immediately after preparation.

- For younger patients, the suspension can be drawn up via a non-PVC oral syringe.
- The cup or syringe should be rinsed with the same quantity of water (15 to 30 milliliters) and given to the patient to ensure all of the medication is taken.

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

6.1 Clinical Studies Experience

Table 8. Pediatric Liver Transplantation: Adverse Reactions Occurring in > 10% of Patients Treated with PROGRAF Granules (STUDY 01-13)

	PROGRAF granules (N = 91)	Cyclosporine (N = 90)
Body as a Whole		
Fever	46%	51%
Infection	25%	29%
Sepsis	22%	20%
CMV Infection	15%	24%
EBV Infection	26%	11%
Ascites	17%	20%
Peritonitis	12%	7%
Cardiovascular System		
Hypertension	39%	47%
Digestive System		
Liver Function Tests Abnormal	37%	28%
Diarrhea	26%	26%
Vomiting	15%	13%
Gastrointestinal Hemorrhage	11%	12%
Bile Duct Disorder	12%	8%
Gastroenteritis	12%	4%
Hemic and Lymphatic System		
Anemia	29%	19%
Metabolic and Nutritional Disorders		
Hypomagnesemia	40%	29%
Acidosis	26%	17%
Hyperkalemia	12%	10%
Respiratory System		
Pleural Effusion	22%	19%
Bronchitis	11%	8%

Urogenital System		
Kidney Function Abnormal	13%	14%

14.2 Liver Transplantation

(b) (4)

Clinical Reviewer's Comment

From a clinical perspective, I concur with the applicant's proposed wording and the new information for Section 6.1, including Table 8 which reflects the safety data from the comparative efficacy Study FG-506-01-13.

(b) (4)

In Section 14.2, the applicant provides (b) (4)

(b) (4)

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(b) (4) Therefore, I recommend that the efficacy analysis results as conducted by the FDA Biostatistics reviewer Hongling Zhou be included in the Section 14.2 of the Prograf PI.

9.1.4. PLLR Conversion

The applicant's proposed wording for Section 8 for the PLLR conversion is below. As part of NDA 210-115, the applicant submitted a report titled "*Cumulative Analysis of Pregnancy During Use of Systemic Tacrolimus*" in Module V. Pregnancy data is also summarized in Module II under Summary of Clinical safety. A summary of the applicant's analysis report is included following the applicant's proposed wording for Section 8 of the PI. Only the Human Data under 8.1 and the new information under 8.4 Pediatric Use will be commented on in this clinical review.

Applicant's Proposed Wording:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

The Transplantation Pregnancy Registry International (TPRI) is a voluntary pregnancy exposure registry that monitors outcomes of pregnancy in female transplant recipients and those fathered by male transplant recipients exposed to immunosuppressants including tacrolimus. Healthcare providers are encouraged to advise their patients to register by contacting the Transplantation Pregnancy Registry International at 1-877-955-6877 or https://www.transplantpregnancyregistry.org/.

Risk Summary

Tacrolimus can cause fetal harm when administered to a pregnant woman. Data from postmarketing surveillance and TPRI suggest that infants exposed to tacrolimus *in utero* are at a risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress *[see Human Data]*. Advise pregnant women of the potential risk to the fetus.

(b) (4)

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

(b) (4)

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(b) (4)

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Risks during pregnancy are increased in organ transplant recipients.

The risk of premature delivery following transplantation is increased. Pre-existing hypertension and diabetes confer additional risk to the pregnancy of an organ transplant recipient. Pre-gestational and gestational diabetes are associated with birth defects/congenital anomalies, hypertension, low birth weight and fetal death.

Cholestasis of pregnancy (COP) was reported in 7% of liver or liver-kidney (LK) transplant recipients, compared with approximately 1% of pregnancies in the general population. However, COP symptoms resolved postpartum and no long-term effects on the offspring were reported.

Maternal Adverse Reactions

PROGRAF may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly.

PROGRAF may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure.

Fetal/Neonatal Adverse Reactions

Renal dysfunction and transient neonatal hyperkalemia have been reported at the time of delivery in infants of mothers taking PROGRAF.

Labor or Delivery

There is an increased risk for premature delivery (< 37 weeks) following transplantation and maternal exposure to PROGRAF.

Data

Human Data

There are no adequate and well controlled studies on the effects of tacrolimus in human pregnancy.

Safety data from the TPRI and postmarketing surveillance suggest infants exposed to tacrolimus in utero have an increased risk for miscarriage, pre-term delivery (< 37 weeks), low birth weight (< 2500 g), birth defects/congenital anomalies and fetal distress.

TPRI reported 450 and 241 total pregnancies in kidney and liver transplant recipients exposed to tacrolimus, respectively. The TPRI pregnancy outcomes are summarized in Table 15. The number of recipients exposed to mycophenolate mofetil (MMF) during the preconception and first trimester periods is high (27% and 29% for renal and liver

recipients, respectively) (b) (4) (b) (4).

Table 15. TPRI Reported Pregnancy Outcomes in Transplant Recipients with Exposure to Tacrolimus

	Kidney	Liver
Pregnancy Outcomes*	**462**	**253**
Miscarriage	24.5%	25%
Live births	**331**	**180**
Pre-term delivery (< 37 weeks)	49%	42%
Low birth weight (< 2500 g)	42%	30%
Birth defects	8%†	5%

* Includes multiple births and terminations.
† Birth defect rate confounded by concomitant (b) (4) in over half of offspring with birth defects.

Additional information reported by TPRI in pregnant transplant patients receiving tacrolimus included diabetes during pregnancy in 9% of kidney recipients and 13% of liver recipients and hypertension during pregnancy in 53% of kidney recipients and 16.2% of liver recipients.

Animal Data

(b) (4)

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8.2 (b) (4) Lactation

Risk Summary

Controlled lactation studies have not been conducted in humans, however tacrolimus has been reported to be present in human milk. The effects of tacrolimus on the breastfed infant, or on milk production have not been assessed. Tacrolimus is excreted in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PROGRAF and any potential adverse effects on the breastfed child from PROGRAF or from the underlying maternal condition.

(b) (4)

8.3 Females and Males of Reproductive Potential

Contraception

PROGRAF can cause fetal harm when administered to pregnant women. Advise female and male patients of reproductive potential to speak to their healthcare provider on family planning options including appropriate contraception prior to starting treatment with PROGRAF *[see Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)]*.

Infertility

Based on findings in animals, male and female fertility may be compromised by treatment with PROGRAF *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

(b) (4)

Safety and efficacy using PROGRAF granules in a pediatric *de novo* liver transplant patients less than 16 years of age (b) (4)

(b) (4)

(b) (4)

9.1.5. Clinical Reviewer's Summary of the Information Provided in the NDA Submission to support the newly added 'Human Data' under 8.1, Pregnancy Section of the Prograf PI

Clinical Reviewer's Comment
Terminology:

Miscarriage:
A miscarriage is the spontaneous loss of a fetus before the 20th week of pregnancy (pregnancy losses after the 20th week are called stillbirths). Miscarriage is a naturally occurring event, unlike medical or surgical abortions. A miscarriage may also be called a "spontaneous abortion." (https://medlineplus.gov/ency/article/001488.htm**)**

Abortion:
An abortion is a procedure to end a pregnancy by medical or surgical intervention to remove the embryo or fetus and placenta from the uterus.

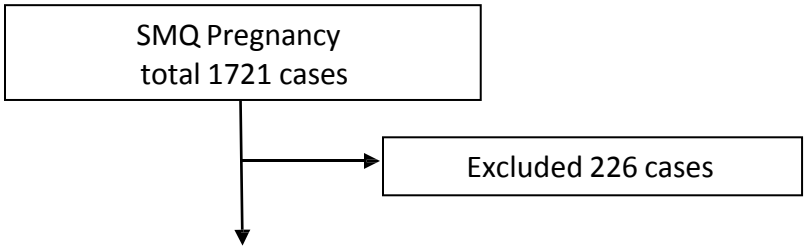
The applicant utilized three different resources to collect and analyze pregnancy data in connection with tacrolimus exposure:

1. Astellas Argus safety database
2. Scientific medical literature
3. Registry data

1. Astellas Argus safety database:

The search yielded 1721 cases with exposure to systemic tacrolimus during pregnancy. 226 cases were excluded due to various reasons such as unconfirmed exposure and duplicate cases (Figure 5).

Figure 5 Flowchart of Pregnancy Cases



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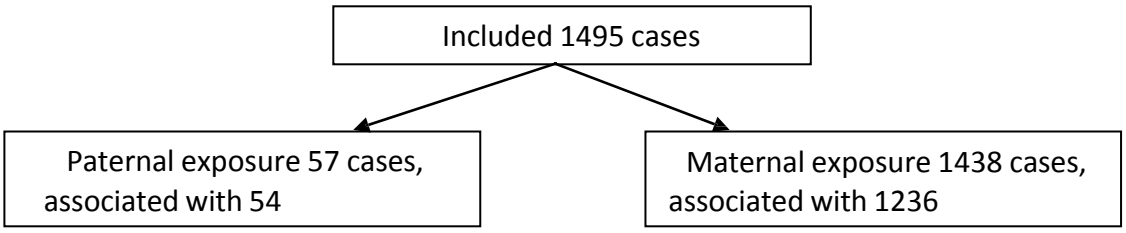

Maternal Exposure

Of the 1438 maternal exposure cases, 259 were child cases, of which 202 were linked to a maternal case that was also included in the case series. This yields a total of 1236 unique pregnancies (i.e. 1438 minus 202 to account for reports regarding the same pregnancy), including twin pregnancies and other multipara (Table 41). The majority of the cases were related to exposure as a result of kidney or liver transplantation.

Table 41 Pregnancy Cases with Maternal Tacrolimus Exposure by Indication (Applicant's Database)

Indication	Disease or Organ	Pregnancy (n)	Total (n)
SOT	Kidney	367	
	Liver	228	
	Kidney and liver	1	
	Pancreas	5	
	Kidney and pancreas	32	
	Liver, intestine, and pancreas	1	
	Intestine	3	
	Heart	28	
	Lung	20	
	Heart and lung	6	
Other transplant	Stem cell	2	**691**
	GVHD	1	
Unknown transplant	Unspecified transplant		**3**
			75
Non-transplant	Myasthenia Gravis	6	
	Rheumatoid arthritis	8	
	Polymyositis dermatomyositis	1	
	Collagen disorder / connective tissue disease	3	
	Ulcerative colitis	13	
	SLE and Lupus Nephritis	93	
	Glomerulonephritis / glomerulosclerosis	3	
	Nephropathy / Nephrotic syndrome	5	
	Still's disease	4	

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	Uveitis	1	
	TMA	1	
	Habitual abortion	21	
	Infertility	1	
			160
Not reported	-		**307**
All			**1236**

A birth defect was reported in 89/1042 (8.5%) of the live birth cases in the Astellas global safety database (Table 42). The birth defects/congenital anomalies included 12 reports of cardiac malformations, 9 reports of craniofacial malformations, 25 cases of multiple malformations,
20 renal/urogenital disorders, 3 skeletal abnormalities, 6 neurological abnormalities, 11 other types of birth defects, and 3 unknown/unspecified defects.

Most cases had one or more risk factors such as concomitant medication or familial disorders. However, this information was not available for all cases.

Table 42 Pregnancy Outcomes of 1236 Cases of Maternal Tacrolimus Exposure (Applicant's Database)

Outcome		N
Progressed to delivery (n=1066; 86%)		
Live birth		(n=1042)
	No adverse event reported	576
	Birth defects	89
	Other events	377
Stillbirth	Fetal death	24
Ectopic pregnancy (n=4; 0,3%)		4
Abortions	**(n=166; 13%)**	
	Spontaneous abortion	129
	Induced abortion	24
	Missed abortion / incomplete / NOS	13
Total		**1236**

Of all transplant patients, birth defects were reported in 87/882 (9.8%), compared with only 2/160 (1.2%) of non-transplant patients. Of the two non-transplant cases, one case was a genetic disorder (Alagille syndrome); the other had no information.

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Other events
In pregnant women, 17 cases of gestational diabetes and 9 cases of gestational hypertension were reported.

Prematurity
In total, 154/1042 (15%) of live birth cases in the Astellas safety database reported prematurity (PTs Premature baby, Premature labor, Premature delivery, Premature rupture of membranes, Premature separation of placenta). Most the 154 preterm cases did not report other adverse events, or only reported events typical of prematurity including low birth weight, fetal distress, or bradycardia.

Neonatal Renal Adverse Events
Neonatal renal adverse events were reported in 9/1042 (0.8%) of the live birth cases and included renal hypoplasia, renal failure, hyperkalemia and hydronephrosis among others.

Abortions
There were 24/1236 (2%) cases of induced abortion. Of these, 10 reported termination of pregnancy for medical reasons due to birth defects revealed during prenatal investigations.

Ectopic pregnancy
The 4 ectopic pregnancies occurred, all in solid organ transplant patients.

Fatal cases (including maternal deaths)
Stillbirth/fetal death was reported in 24 cases, with details provided for only some of the Cases. Of the maternal cases, 2 mothers died shortly after premature delivery. One with 2 liver transplants experienced intra-renal aortic graft clotting during labor and died 2 days after delivery. The second mother experienced acute and chronic liver graft rejection during pregnancy 3 years after transplant, and died 4 weeks after Cesarean-section due to cerebral aspergillus infection.

Paternal Exposure
There were 57 reported cases of paternal exposure, i.e. the father of the child was being treated with systemic tacrolimus before or during the conception date, with a total of 54 associated pregnancies. The 3 additional cases reported involved 3 sets of twins.

Most cases (43/54, 79.6% pregnancies) were reported without adverse events (Table 43). Of the 54 paternal exposure pregnancies, 51/54 (94%) progressed to delivery (all were live births) and 3/54 (6%) terminated spontaneously. Three paternal exposure cases reported a fatal outcome in the child.

Table 43 Pregnancy Outcomes of 54 Cases of Paternal Tacrolimus Exposure

(Applicant's Database)

Outcome		N
Progressed to delivery (n=51; 94%)		
Live birth	No events reported	43
	Birth defects	5
	Other events reported	3
Abortions (n=3; 6%)		
	Spontaneous abortion	3
Total		**54**

2. Scientific medical literature

A review of the scientific medical literature was conducted by the applicant for the period up to 31 March 2016, using the wide criteria for the key words "tacrolimus" and "pregnancy." This resulted in 221 literature references for data analysis. The worldwide medical literature on tacrolimus identified 1607 prospectively exposed pregnancies. The rates of pregnancy complications such as hypertension, pre-eclampsia, diabetes vary widely in numbers and - particularly for hypertension and pre-eclampsia - show a clear increase in rate in the transplant patient versus the normal population. Tacrolimus did not appear to increase the rate of congenital abnormalities. A moderate increase in pregnancy complications such as hypertension, pre-eclampsia, and premature delivery was observed and in the applicant's opinion, this can be explained by the underlying disease or malfunctioning of allografts.

Epidemiological review of the literature

The applicant also performed an epidemiological review of the literature in PUBMED. Limits: Meta- Analysis, Review, English, and Publication Date from 1999. In total, 61 publications were identified up to 29 September 2016. Most authors reported favorable pregnancy outcomes, and the use of tacrolimus at appropriate clinical doses was not associated with additional risk of congenital malformations. Generally, the results mimic the Transplant Pregnancy Registry International (TPRI) outcomes (see Registry data below) for women with renal and hepatic transplants with a live birth rate of 72-80%, a miscarriage of 14- 15.6%, and a mean gestational age of 35-36 weeks. Similar to the TPRI data, the published literature suggests increased risk of low birth weight and premature birth which may also be related to baseline condition of these patients and concomitant medications in addition to the tacrolimus exposure.

Pregnancy outcomes in non-transplant patients in the Literature

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Only a small number of pregnancies (n=40) concerned non-transplant patients. Fifteen patients received tacrolimus respectively for lupus nephritis (N = 10), SLE (N = 3), ulcerative colitis or adult-onset Still's disease (N = 1 each). No pregnancy complications were reported for these non-transplant patients. All deliveries took place after 37 weeks gestation, with adequate birth weight, suggesting that many of the reported pregnancy complications after transplant may be a consequence of the transplant procedure and/or underlying disease, rather than from tacrolimus. The information in the Astellas global safety database for patients receiving tacrolimus for non-transplant reasons appears to support this.

3. Registry data

The National Transplant Pregnancy Registry was established in 1991 to study the outcomes of pregnancies in transplant recipients in North America, but its name was changed to Transplant Pregnancy Registry International (TPRI) in 2016 and its remit was extended to be an international data repository.

Pregnancy Outcomes in All Transplant Recipients

As of December 2015, the TPRI reported that a total of 2,609 pregnancies in 1,461 recipients and 1,359 pregnancies fathered by 879 recipients were entered into the TPRI. Most pregnancies registered are in the kidney transplant group. Transplant recipients receiving immunosuppressants show the estimated risk of major birth defects was 4.3% in kidney and 4.2% in liver recipients. The risk for miscarriage was 18% in kidney and 21% in liver recipients.

Pregnancy Outcomes in Transplant Recipients with Tacrolimus Exposure

New participants to the registry are predominantly on tacrolimus-based treatment regimen and these are reported by TPRI separately for kidney and liver transplant recipients. Female kidney and liver transplant recipients taking tacrolimus have reported successful pregnancies although, as shown in Table 44, there continues to be a high incidence of prematurity (425-49%) and low birthweight (30%-42%) among the infants. The number of recipients exposed to MMF during the preconception and first trimester period is high in this group (27% and 29% for renal and liver recipients, respectively) and should be taken into consideration when reviewing the data for birth defects. Cholestasis of pregnancy (COP) occurred in 7% of liver or liver-kidney recipient pregnancies in the TPRI, compared with approximately 1% of the general population.

Table 44 Pregnancy Outcomes in Transplant Recipients with Exposure to Tacrolimus (TPRI)

Details	Renal Recipients	Liver Recipients
Recipients	263	133
Pregnancies	450	241

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Age at first transplant	25 ± 6.2 (2.9-44.3)	22±8.6 (0.5-42.3)
Conception age (yrs)	31.1±4.9	28.7±6.0
Mean transplant to conception interval (yrs)	5±3.5	6.8±5.4
MPA exposure (6 wks preconception – trimester 1)	27%	29%
Hypertension during pregnancy	53%	16.2%
Diabetes during pregnancy	9%	13%
Preeclampsia	34%	21%
Rejection episode during pregnancy	2%	3%
Graft loss within 2 yrs of delivery	5%	5%
Pregnancy outcomes*	462	253
Terminations	2.2%	1.6%
Miscarriages	24.5%	25.0%
Ectopic	0.4%	0.8%
Stillborn	1.3%	1.2%
Live births	331	180
Premature (<37 weeks)	49%	42%
Low birth weight (<2500 g)	42%	30%
Cesarian Section	57%	45%
Birth defects	8% [1]	5%
Neonatal deaths (within 30 days of birth)	1.5%	1.1%

*includes multiple births.

Paternal Exposure

No detailed analysis of cases with paternal exposure was reported by the TPRI. A 2013 TPRI study revealed no increase in the number of adverse pregnancy outcomes when a transplant recipient fathered a pregnancy while taking MPA, but similar information about the outcome of pregnancies fathered by transplant recipients taking tacrolimus is unavailable.

Clinical Reviewer's Comment

From a clinical perspective, I concur with the applicant's proposed wording for Section 8 of the PI including the PI Table 15 which is mainly based on TPRI data. All cases of tacrolimus exposure including paternal exposure prior to or during pregnancy is highly confounded due to the baseline condition of the patients and concomitantly administered drugs including MPA products which is a known teratogen. I agree with the applicant that data from postmarketing surveillance and TPRI suggest that infants exposed to tacrolimus in utero are at a risk of

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prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress. The contribution of tacrolimus exposure to these risks cannot be ruled out which is also supported by the available non-clinical data.

I also concur with the applicant's proposed wording in 8.4 Pediatric Use which accurately reflects the clinical study outcomes reviewed as part of the NDA 210-115.

Clinical Reviewer's Published Literature Search for Maternal and Embroyofetal Toxicity of Tacrolimus

In addition to the information provided by the applicant as part of the NDA submission, the clinical reviewer performed a search of published literature for clinical experience with tacrolimus administered during pregnancy. Following is a summary of the most relevant publications that the reviewer could find:

1. **Reyes et.al. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. Transplantation. 2003 Sep 15;76(5):827-32:**

In this single center experience, all pregnancies after liver transplantation with tacrolimus immunosuppression were followed prospectively. All patients received tacrolimus during the entire pregnancy period. Average trough levels were 7.0 ng/mL before pregnancy and in the beging of the first trimester; 4.5 ng/mL at the end of first trimester and during the second trimester; 5.7 ng/mL during the third trimester. In addition to tacrolimus, three patients received azathioprine. In one mother, azathioprine was discontinued during the first trimester; the other two mothers continued to take azathioprine during the pregnancy (75 and 50 mg/day), respectively. Twelve mothers (27%) received prednisone (5–10 mg/day) before and at the time of conception. In two of them, the prednisone was discontinued during the pregnancy.

Thirty-seven (37) mothers delivered 49 babies. Three mothers delivered three times, and six mothers delivered two times. Thirty-six (36) mothers (97%) survived the pregnancy, and 36 allografts (97%) survived. The one patient death, subsequent to liver graft loss was in a patient who demonstrated infra-aortic arterial liver graft, which clotted by the gravid uterus during labor. The patient developed a gangrenous liver and died before she could undergo retransplantation.

The mean gestational period was 36.4±3.2 weeks[10], excluding two premature deliveries at 23 and 24 weeks of gestation (premature deliveries were not in patients who received azathioprine). The authors state that these two premature babies were conceived soon after liver transplantation when the immunosuppression is relatively high. Per the authors, the general recommendation for women wanting to conceive post-liver transplantation is to wait 1 to 2 years until overall immunosuppression is lower and graft function is stable. Twenty-two

[10] Generally a normal human pregnancy can range from 37 to 42 weeks.

babies (46.9%) were delivered by cesarean section, and the other babies were delivered vaginally. The mean birth weight was 2,797±775 g, with 38 babies (78%) weighing more than 2,000 g. The mean birth weight percentile to gestational period was 54±23. Four babies (8.5%) had a birth weight percentile of less than 25, and 28 babies (59.6%) had a birth weight percentile greater than 50.

Of the 49 babies, there (3) babies died: The two premature babies died soon after delivery and another baby, born to a mother with Alagille syndrome[11], died from congenital birth defects. The mother subsequently remarried and had two viable babies from the second marriage. Other than this baby, there was only one case of congenital anomaly which consisted of a nonfunctional unilateral cystic kidney and an accessory nipple on one side in the same baby. The mother had a history of a similar abnormality in two sons with one extra nipple and one son with two extra nipples born before the liver transplantation. The remaining 46 babies (25 boys and 21 girls) were alive and well at the last follow-up

Twelve mothers demonstrated an increase in hepatic enzymes without jaundice during the pregnancy. All of them responded to augmentation of immunosuppression. Four mothers were hypertensive before pregnancy, which required treatment. They remained stable during the pregnancy, except in one case in whom emergency cesarean section was required. Nine of the 37 mothers (25%) received fludrocortisone (0.1 mg/day) to control hyperkalemia. Three mothers were receiving insulin before and during the viable pregnancy.

Per the authors, this report reconfirms the safety of tacrolimus during pregnancy after liver transplantation and preterm delivery and low birth weight seem to be a persistent problem in all solid-organ transplantation under any form of immunosuppression.

2. Westbrook et.al. Outcomes of pregnancy following liver transplantation: The King's College Hospital experience. Liver Transpl. 2015;21(9):1153-9.

In this retrospective analysis of pregnancy cases following liver transplantation from a single center in UK, 117 conceptions in 79 patients between 1988 and 2011 are reported. Patients were identified from a prospectively collated liver database using the search terms pregnancy, Liver transplantation (LT), miscarriage, termination, and live birth. Mothers were questioned by the hepatologist regarding the development and any health problems relating to their child over the follow-up period, but no formal pediatric assessment of the child's health was made unless otherwise indicated.

[11] Alagille syndrome is an autosomal dominant, complex multisystem disorder characterized by the presence of three out of five major clinical criteria: cholestasis with bile duct paucity on liver biopsy, congenital cardiac defects (with particular involvement of the pulmonary arteries), posterior embryotoxon in the eye, characteristic facial features, and butterfly vertebrae.

The majority of conceptions occurred in patients maintained on either cyclosporine (n=34) or tacrolimus (n=81) as their primary IS. In addition, 1 patient was taking sirolimus, and 1 was maintained on azathioprine and prednisolone. Two conceptions occurred in women on mycophenolate mofetil and tacrolimus; 1 of these women had an elective termination, and the second delivered at 28 weeks following hepatic decompensation on a background of chronic rejection. The neonate required admission to the SCBU for 7 weeks but has no congenital abnormalities and normal developmental milestones on follow-up.

The median age at conception was 29 years (range, 19-47 years) and the median interval between LT and conception was 48 months (range, 1-240 months). Overall, 49 women had 1 conception, 19 women had 2 conceptions, 7 women had 3 conceptions, 1 woman had 4 conceptions, and 1 woman had 5 conceptions.

Maternal Outcomes:
No patient died as a direct result of pregnancy. Four women (5%) had a complication associated with pregnancy that necessitated admission to the liver intensive care unit (LITU):

- *One patient developed hepatic artery thrombosis (HAT) in association with a spontaneous miscarriage at 12-weeks gestation. It was unclear if the HAT was a trigger for the miscarriage or arose as a secondary event. She was later relisted for LT.*
- *One patient had septicemia secondary to a liver abscess in her auxiliary graft 5 days following pregnancy termination due to patient choice,*
- *One patient had infected ascites and streptococcal sepsis at 20-weeks gestation on a background of chronic ductopenic rejection which was diagnosed before conception. (She delivered at 28 weeks following spontaneous rupture of membranes, and the neonate required a prolonged stay in the special care baby unit (SCBU).)*
- *One patient had gram-negative sepsis following intravenous methylprednisolone for treatment of ACR following a cesarean delivery at 36-weeks gestation.*

Additional maternal complications encountered during pregnancy included hypertension (n=22), preeclampsia (n=16), eclampsia (n=3), and gestational diabetes (n=8). Seventeen patients with ACR were identified on clinical and biochemical parameters during pregnancy or in the immediate postpartum period (within 8 weeks of delivery). Sixteen were confirmed histologically. No episode of rejection resulted in graft loss. Rejection was significantly more common in those women who conceived within 12 months of LT (P=0.001) and was associated nonsignificantly with cyclosporine-based IS (P=0.08). The authors provide a comparison of CsA vs tacrolimus based immunosuppression in terms of maternal complications. It is important to note that since these two groups are not randomized it may be misleading to make comparisons across the two treatments. These two different treatments are also likely to represent two different eras since CsA was available prior to tacrolimus. Nevertheless, the same maternal complications were observed with both treatments but possibly at different rates. The

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contribution of baseline conditions of these patients vs. the immunosuppressants (tacrolimus or CsA) to the observed outcomes is not known.

Maternal Complications Related to Pregnancy in Relation to Primary IS

Maternal Complication	All, n = 115 (%)	Cyclosporine, n = 34 (%)	Tacrolimus, n = 81 (%)	*P* Value
Pregnancy-induced hypertension	22 (19)	4 (12)	18 (22)	0.29
Pre-eclampsia	16 (14)	5 (15)	11 (14)	0.35
Eclampsia	3 (3)	1 (3)	2 (2)	0.99
Gestational diabetes	8 (7)	1 (3)	7 (9)	0.43
Bacterial sepsis	6 (5)	1 (3)	5 (6)	0.67
Viral infections	5 (4)	2 (6)	3 (4)	0.63
ACR	17 (15)	8 (24)	9 (11)	0.08

In the long term, over a median follow-up of 52 months after delivery, there were 3 maternal deaths. The first death was related to posttransplant lymphoproliferative disease, 18 months after the delivery of a healthy neonate. The second died of graft failure following a redo LT for chronic rejection, 7 years following a molar pregnancy. The final patient who died had autoimmune hepatitis and had been transplanted 4 times for chronic rejection. Her pregnancy miscarried at 10 weeks. No death was considered to be pregnancy related.

Eight patients underwent retransplantation at median time of 60 months after LT (range, 18-120 months). Indications for retransplantation included chronic rejection (n54), recurrent disease (n53), and late HAT (n51). In all patients, graft loss was thought to be unrelated to pregnancy. Interestingly, women who had an episode of ACR during pregnancy were more likely to undergo retransplantation over long term follow-up than those women who did not (5/18 versus 3/99; P=0.001).

Fetal Outcomes
The live birth rate was 73% (85/117) including 2 twin births. Of the remaining conceptions, 20 (17%) miscarried (spontaneous loss of pregnancy before 24 weeks), and 12 (10%) underwent an elective terminations of pregnancy (TOP). The indications for patients having a TOP were medical advice secondary to deterioration in graft function/ persistent severe chronic rejection (n=3), warfarin therapy in the first trimester (n=2), uncontrolled psychiatric illness (n=1), and patient choice (n=6). Overall median gestation for the 85 live births was 38 weeks, with 26/85 (31%) of neonates born before 37-weeks gestation and 5/85 (6%) born at >30-weeks gestation. Of the 26 neonates born before 37-weeks gestation, 9 were secondary to medically induced prematurity for maternal pre-eclampsia/eclampsia (n=6), maternal hepatic decompensation (n=1), and intrauterine growth retardation (n=2). Median birth weight was 2745 g (range, 554-4256 g); 71% of newborns were of normal birth weight (>2500 g); 19% were of low birth weight (1500-2500 g); and 10% were of very low birth weight (<1500 g). This finding is likely linked to the high incidence of prematurity (31%) in this cohort. There were no congenital anomalies.

The authors also provide a comparison of CsA vs tacrolimus based immunosuppression in terms of fetal outcomes. Same comments made above for the maternal outcomes also apply to the fetal outcomes comparison of the two different immunosuppressants. Premature delivery and low birth weight rates are higher than the general population with both treatments which are also likely to be related to the baseline condition of these patients.

Fetal Outcomes in Relation to Pregnancy and Maternal IS

	All, n (%)	Cyclosporine, n (%)	Tacrolimus, n (%)	*P* Value
Fetal outcome/complication	n = 115	n = 34	n = 81	
Miscarriage	20 (17)	5 (15)	15 (19)	0.62
TOP	12 (10)	1 (3)	11 (14)	0.10
Live birth rate	83 (72)	28 (82)	55 (68)	0.17
Fetal outcomes for live births	n = 83	n = 28	n = 55	
Cesarean delivery	34 (41)	10 (36)	24 (44)	0.45
Normal birth weight	59 (71)	18 (64)	41 (75)	0.30
Low/very low birth weight	24 (29)	10 (36)	14 (25)	0.30
Gestation <37 weeks	26 (31)	10 (36)	16 (29)	0.50
SCBU admission	7 (8)	3 (11)	4 (7)	0.68

In the authors' summary, the incidence of pre-eclampsia was 14% compared to an incidence of between 2% and 6% reported for the general population. Furthermore, the development of pre-eclampsia was found to be significantly associated with prematurity (P=0.001) and low birth weight (P=0.001), likely in part due to iatrogenic premature delivery in order to maintain maternal safety. The fetal outcomes demonstrated a live birth rate of 73%, no congenital abnormalities and only 1 child born at 24 weeks with delayed developmental milestones. However, the prevalence of low (19%) and very low birth weight (10%) is considerably higher than that of the general population. The cause for the high incidence of prematurity and low birth weight in babies born to LT recipients remains unclear and is likely to be multifactorial, contributed to by IS, the high incidence of pre-eclampsia/ eclampsia and iatrogenic delivery, ACR, and maternal comorbidity.

3. Webster et.al. Tacrolimus is an effective treatment for lupus nephritis in pregnancy. Lupus. 2014;23(11):1192-6.

Systemic lupus erythematosus (SLE) frequently affects women of childbearing age without affecting fertility, therefore pregnancy is not uncommon, but both maternal and neonatal complications are higher than background, particularly for women with lupus nephritis. In this publication, the authors present nine (9) patients in whom tacrolimus was successfully used to maintain stable disease or treat disease flare during pregnancy. All pregnant women with LN in the authors' clinic database between 1997–2012 with at least one tacrolimus concentration measured between their last menstrual period and date of delivery were included. Tacrolimus dose was titrated to achieve trough levels of 5–8 ng/ml and increases in doses were frequently required. Of the 9 cases, cases 1–3 took tacrolimus before conception and had stable disease throughout their pregnancies. Cases 4–9 all experienced disease flare; for 5 out of 6 women this

occurred in the first trimester. In cases 5, 8 and 9 tacrolimus replaced azathioprine in their treatment regimens. Tacrolimus was added to a regimen including azathioprine in cases 4, 6 and 7. Cases 4 and 7 also received single doses of IV methylprednisolone at the time of flare. Case 4 received escalated oral prednisolone at the time of flare. There were nine live births with weights appropriate for gestational age and no congenital abnormalities.

Pregnancy Case No.	Gestation Tac started (wks/40)	Concurrent Treatment	Gestation at Delivery (wks)	Birth weight (g)/Sex
1	Pre-conception	Aza	39	3460/F
2	Pre-conception	Aza	36	2512/F
3	Pre-conception	Pred	39	2786/F
4	18	Aza, Pred, MPred	37	2476/F
5	30	Pred	37	2988/M
6	8	Aza, HCQ, MPred	30	1130/F
7	10	Aza, HCQ, Pred	38	3320/F
8	20	Pred	35	2912/M
9	21	Pred, HCQ	33	1400/M

Aza: azathioprine, HCQ: hydroxychloroquine; MPred: methylprednisolone; Pred: prednisolone;

The authors state that both tacrolimus and cyclosporine are associated with preterm delivery and low birth weight,16 complications that are also more common in women with LN. In the authosr' view, in this series, tacrolimus was well tolerated, and the authors propose its use as either an adjuvant or alternative therapy to steroids in treating stable LN and disease flares during pregnancy, particularly due to the risk of harm to the fetus from conventional therapies.

Clinical Reviewer's Overall Assessment of Tacrolimus Related Fetomaternal Risk

Based on the applicant provided information in the NDA 210,115 and the clinical reviewer's own search of the published literature the following conclusions are reached:

- In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
- Based on the TPRI registry data, the same risks in transplant patients with tacrolimus exposure is 5-8% and 24-25% respectively and there does not seem to be a specific pattern in the reported congenital anomalies following tacrolimus exposure.
- Although the risk of the above mentioned adverse pregnancy outcomes seem to be increased in transplant patients with tacrolimus exposure, it is not clear what share tacrolimus has in causing these adverse outcomes since transplant patients have other baseline conditions and confounders such as diabetes, hypertension, chronic end-stage organ failure prior to transplantation, concomitant drug exposures such as MPA products and corticosteroids.

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- In the applicant's own database search there were 160 cases of tacrolimus exposure during pregnancies in nontransplant patients with no reported congenital anomalies. Based on the applicant's published literature search of pregnancy outcomes in non-transplant patients with tacrolimus exposure, consisting of 40 patients, no pregnancy complications or congenital anomalies were reported. All deliveries took place after 37 weeks gestation, with adequate birth weight. These data from nontransplant patients suggest that many of the reported pregnancy complications and congenital anomalies after transplant may be a consequence of the underlying disease and other confounders, rather than from tacrolimus.
- The Clinical reviewer's own published literature search, summarized above suggest the same conclusions reached by the applicant. In all three publications, there were no congenital anomalies reported both in transplant and nontransplant patients exposed to tacrolimus during pregnancy except for one mother with Allagille Syndrome in the Reye et.al. publication. The possible contribution of tacrolimus to the observed adverse pregnancy outcomes cannot be ruled out with certainty. However, in today's clinical practice transplant patients on tacrolimus based immunosuppressive therapy are not recommended against conception and a substantial majority of these mothers give birth to healthy babies without any major unacceptable maternal or fetal toxicities.
- As explained in the summary of the clinical reviewer's own literature search above, the general practice seems to advise patients not to conceive during the first year following transplantation during which the tacrolimus exposure is generally higher. Also based on the reported trough levels during pregnancy in the published literature it looks like the tacrolimus exposure (target trough levels) may be intentionally lowered during pregnancies which concomitantly increases the risk of rejection.
- Among the major recognized fetomaternal risks potentially associated with tacrolimus exposure during pregnancy are gestational diabetes, perinatal jaundice, maternal hypertension, preeclampsia/eclampsia, premature birth, low birth weight, possible renal insufficiency in the newborn and electrolyte abnormalities in the newborn which are generally mitigated/treated successfully in clinical practice.
- The potential long term adverse outcomes on babies born to mothers with tacrolimus exposure during pregnancy may not be fully realized based on currently available data. These potential hypothetical risks include late occurring renal insufficiency during adulthood.
- In my opinion the applicant proposed language in the Prograf PI adequately conveys the potential fetomaternal risks associated with tacrolimus exposure during pregnancy.

9.2.Nonprescription Drug Labeling

N/A

10. Risk Evaluation and Mitigation Strategies (REMS)

Reference ID: 4267221

N/A

11. Postmarketing Requirements and Commitments

None

12. Appendices

12.1. References

Not applicable

12.2. Financial Disclosure

Reference ID: 4267221

Provided in the relevant sections of the review.

APPEARS THIS WAY ON ORIGINAL

APPENDIX

(Sections 1- 8 and 14 of the Prograf Labeling as negotiated with the applicant and likely to be final)

FULL PRESCRIBING INFORMATION

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS

Reference ID: 4267221

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS

- **Increased risk for developing serious infections and malignancies with PROGRAF or other immunosuppressants that may lead to hospitalization or death (5.1, 5.2)**

1 INDICATIONS AND USAGE

• 1.1 Prophylaxis of Organ Rejection in Kidney, Liver, and Heart Transplant

PROGRAF® is indicated for the prophylaxis of organ rejection, in patients receiving allogeneic kidney transplant *[see Clinical Studies (14.1)],* liver transplants *[see Clinical Studies (14.2)]* and heart transplant *[see Clinical Studies (14.3)],* in combination with other immunosuppressants.

2 DOSAGE AND ADMINISTRATION

• 2.1 General Instructions

PROGRAF capsules and PROGRAF Granules are not interchangeable or substitutable with other tacrolimus extended-release products. This is because rate of absorption following the administration of an extended-release tacrolimus product is not equivalent to that of an immediate-release tacrolimus drug product. Under- or overexposure to tacrolimus may result in graft rejection or other serious adverse reactions *[see Warnings and Precautions (5.3)]*.

PROGRAF should not be used without supervision of a physician with experience in immunosuppressive therapy.

Intravenous Formulation

Intravenous use is recommended for patients who cannot tolerate oral formulations, and conversion from intravenous to oral PROGRAF is recommended as soon as oral therapy can be tolerated to minimize the risk of anaphylactic reactions that occurred with injectables containing castor oil derivatives *[see Warnings and Precautions (5.9)]*.

Patients receiving PROGRAF injection should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If signs or symptoms of anaphylaxis occur, the infusion should be stopped. An aqueous solution of epinephrine should be available at the bedside as well as a source of oxygen.

Oral Formulations (Capsules and Oral Suspension)

If patients are able to initiate therapy, the recommended starting doses should be initiated. Advise patients not to eat grapefruit or drink grapefruit juice while under treatment with PROGRAF *[see Drug Interactions (7.2)]*.

Therapeutic drug monitoring is recommended for all patients receiving PROGRAF *[see Dosage and Administration (2.7)]*.

• 2.2 Administration

PROGRAF may be taken with or without food. However, since the presence of food affects the bioavailability of PROGRAF, if taken with food, it should be taken consistently the same way each time *[see Clinical Pharmacology (12.3)]*.

Patients should not eat grapefruit or drink grapefruit juice in combination with PROGRAF *[see Drug Interactions (7.2)]*.

PROGRAF should not be used simultaneously with cyclosporine. PROGRAF or cyclosporine should be discontinued at least 24 hours before initiating the other. In the presence of elevated PROGRAF or cyclosporine concentrations, dosing with the other drug usually should be further delayed.

- **2.3 Dosing for Adult Kidney, Liver, or Heart Transplant Patients - Capsules and Injection**

Capsules

The initial dose of PROGRAF capsules should be administered no sooner than 6 hours after transplantation in the liver and heart transplant patients. In kidney transplant patients, the initial dose of PROGRAF capsules may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered.

The initial oral PROGRAF capsule dosage recommendations for adult patients with kidney, liver, or heart transplants and whole blood trough concentration range are shown in Table 1. Perform therapeutic drug monitoring (TDM) to ensure that patients are within the ranges listed in Table 1.

Table 1. Summary of Initial Oral PROGRAF Capsules Dosing Recommendations and Whole Blood Trough Concentration Range in Adults

Patient Population	PROGRAF Capsules* Initial Oral Dosing	Whole Blood Trough Concentration Range
Kidney Transplant		
With Azathioprine	0.2 mg/kg/day, divided in two doses, administered every 12 hours	Month 1-3: 7-20 ng/mL Month 4-12: 5-15 ng/mL
With MMF/IL-2 receptor antagonist†	0.1 mg/kg/day, divided in two doses, administered every 12 hours	Month 1-12: 4-11 ng/mL
Liver Transplant		
With corticosteroids	0.10-0.15 mg/kg/day, divided in two doses, administered every 12 hours	Month 1-12: 5-20 ng/mL
Heart Transplant		
With azathioprine or MMF	0.075 mg/kg/day, divided in two doses, administered every 12 hours	Month 1-3: 10-20 ng/mL Month ≥ 4: 5-15 ng/mL

* African-American patients may require higher doses compared to Caucasians *(see Table 2)*

† In a second smaller trial, the initial dose of tacrolimus was 0.15-0.2 mg/kg/day and observed tacrolimus concentrations were 6-16 ng/mL during month 1-3 and 5-12 ng/mL during month 4-12 *[see Clinical Studies (14.1)]*.

Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower PROGRAF dosages than the recommended initial dosage may be sufficient as maintenance therapy. Adjunct therapy with adrenal corticosteroids is recommended early post-transplant.

The data in kidney transplant patients indicate that the African-American patients required a higher dose to attain comparable trough concentrations compared to Caucasian patients (Table 2) *[see Clinical Pharmacology (12.3)]*.

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Table 2. Comparative Dose and Trough Concentrations Based on Race

Time After Transplant	Caucasian n = 114		African-American n = 56	
	Dose (mg/kg)	Trough Concentrations (ng/mL)	Dose (mg/kg)	Trough Concentrations (ng/mL)
Day 7	0.18	12.0	0.23	10.9
Month 1	0.17	12.8	0.26	12.9
Month 6	0.14	11.8	0.24	11.5
Month 12	0.13	10.1	0.19	11.0

Intravenous Injection

PROGRAF injection should be used only as a continuous intravenous infusion and should be discontinued as soon as the patient can tolerate oral administration. The first dose of PROGRAF capsules should be given 8-12 hours after discontinuing the intravenous infusion.

The recommended starting dose of PROGRAF injection is 0.03-0.05 mg/kg/day in kidney and liver transplant and
0.01 mg/kg/day in heart transplant given as a continuous intravenous infusion. Adult patients should receive doses at the lower end of the dosing range. Concomitant adrenal corticosteroid therapy is recommended early post-transplantation.

The whole blood trough concentration range described in Table 1 pertain to oral administration of PROGRAF only; while monitoring PROGRAF concentrations in patients receiving PROGRAF injection as a continuous intravenous infusion may have some utility, the observed concentrations will not represent comparable exposures to those estimated by the trough concentrations observed in patients on oral therapy.

Anaphylactic reactions have occurred with injectables containing castor oil derivatives, such as PROGRAF injection. Therefore, monitoring for signs and symptoms of anaphylaxis is recommended *[see Warnings and Precautions (5.9)]*.

- **2.4 Dosing for Pediatric Kidney, Liver, and Heart Transplant Patients**

Oral formulations (capsules or oral suspension)

Pediatric patients in general need higher tacrolimus doses compared to adults: the higher dose requirements may decrease as the child grows older. Recommendations for the initial oral dosing for pediatric transplant patients and whole blood trough concentration range are shown in Table 3. Perform TDM to ensure that patients are within the ranges listed in Table 3.

Table 3. Summary of Initial PROGRAF Capsule and PROGRAF Granules Dosing Recommendations and Whole Blood Trough Concentration Range in Children

Patient Population	Initial PROGRAF Capsule and PROGRAF Granules Dosing	Whole Blood Trough Concentration Range
Pediatric kidney transplant patients	0.3 mg/kg/day capsules or oral suspension, divided in two doses, administered every 12 hours	Month 1-12: 5-20 ng/mL

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Pediatric liver transplant patients	0.15-0.2 mg/kg/day capsules or 0.2 mg/kg/day oral suspension, divided in two doses, administered every 12 hours	Month 1-12: 5-20 ng/mL
Pediatric heart transplant patients	0.3 mg/kg/day* capsules or oral suspension, divided in two doses, administered every 12 hours	Month 1-12: 5-20 ng/mL

*0.1 mg/kg/day if cell depleting induction treatment is administered.

For conversion of pediatric patients from PROGRAF Granules to PROGRAF capsules or from PROGRAF capsules to PROGRAF Granules, the total daily dose should remain the same. Following conversion from one formulation to another formulation to another formulation of tacrolimus, therapeutic drug monitoring is recommended *[see Dosage and Administration (2.7)]*. If a patient is unable to receive an oral formulation, the patient may be started on PROGRAF injection. For pediatric liver transplant patients, the intravenous dose is 0.03-0.05 mg/kg/day.

- **2.5 Dosage Adjustment in Patients with Renal Impairment**

Due to its potential for nephrotoxicity, consideration should be given to dosing PROGRAF at the lower end of the therapeutic dosing range in patients who have received a liver or heart transplant and have pre-existing renal impairment. Further reductions in dose below the targeted range may be required.

In kidney transplant patients with post-operative oliguria, the initial dose of PROGRAF should be administered no sooner than 6 hours and within 24 hours of transplantation, but may be delayed until renal function shows evidence of recovery *[see Dosage and Administration (2.3), Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

- **2.6 Dosage Adjustments in Patients with Hepatic Impairment**

Due to the reduced clearance and prolonged half-life, patients with severe hepatic impairment (Child Pugh ≥ 10) may require lower doses of PROGRAF. Close monitoring of blood concentrations is warranted.

The use of PROGRAF in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole blood concentrations of tacrolimus. These patients should be monitored closely and dosage adjustments should be considered. Some evidence suggests that lower doses should be used in these patients *[see Dosage and Administration (2.3), Warnings and Precautions (5.5), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

- **2.7 Therapeutic Drug Monitoring**

Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments, and compliance. Whole blood trough concentration range can be found in Table 1.

Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting drugs and the post-transplant time. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies. Data from clinical trials show that tacrolimus whole blood concentrations were most variable during the first week post-transplantation.

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The relative risks of toxicity and efficacy failure are related to tacrolimus whole blood trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity and efficacy failure.

Methods commonly used for the assay of tacrolimus include high-performance liquid chromatography with tandem mass spectrometric detection (HPLC/MS/MS) and immunoassays. Immunoassays may react with metabolites as well as parent compound. Therefore, assay results obtained with immunoassays may have a positive bias relative to results of HPLC/MS. The bias may depend upon the specific assay and laboratory. Comparison of the concentrations in published literature to patient concentrations using the current assays must be made with detailed knowledge of the assay methods and biological matrices employed. Whole blood is the matrix of choice and specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-coagulant. Heparin anti-coagulation is not recommended because of the tendency to form clots on storage. Samples which are not analyzed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; see assay instructions for specifics. If samples are to be kept longer they should be deep frozen at -20° C. One study showed drug recovery > 90% for samples stored at -20° C for 6 months, with reduced recovery observed after 6 months.

- **2.8 Preparation and Administration Instructions of PROGRAF Injection for Pharmacists**

Tacrolimus can cause fetal harm. Follow applicable special handling and disposal procedures[1] *[see How Supplied/ Storage and Handling (16.4)]*.

PROGRAF injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a concentration between 0.004 mg/mL and 0.02 mg/mL prior to use. Diluted infusion solution should be stored in glass or polyethylene containers and should be discarded after 24 hours. The diluted infusion solution should not be stored in a polyvinyl chloride (PVC) container due to decreased stability and the potential for extraction of phthalates. In situations where more dilute solutions are utilized (e.g., pediatric dosing, etc.), PVC-free tubing should likewise be used to minimize the potential for significant drug adsorption onto the tubing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Due to the chemical instability of tacrolimus in alkaline media, PROGRAF injection should not be mixed or co-infused with solutions of pH 9 or greater (e.g., ganciclovir or acyclovir).

- **2.9 Preparation and Administration Instructions of PROGRAF Granules**

Tacrolimus can cause fetal harm. Follow applicable special handling and disposal procedures[1] *[see How Supplied/ Storage and Handling (16.4)]*.

The required dose for PROGRAF Granules is calculated based on the weight of the patient. Use the minimum whole number of packets that corresponds to the required morning or evening dose. If the morning or evening dose is not covered by the whole number of packets, use one additional 0.2 mg packet to round up the dose. Do not use tubing, syringes and other equipment (cups) containing PVC to prepare or administer tacrolimus products. Do not sprinkle PROGRAF Granules on food.

- To prepare the dose, empty the entire contents of each PROGRAF Granules packet into a glass cup. Check for any remaining granules in the packet(s) and empty these into the cup.
- Add 1 to 2 tablespoons (15 to 30 milliliters) of room temperature drinking water to the cup containing the PROGRAF Granules.

- Mix and administer the entire contents of the cup. The granules will not completely dissolve. The suspension should be given immediately after preparation.
- For younger patients, the suspension can be drawn up via a non-PVC oral syringe that will be dispensed with the prescription.
- The cup or syringe should be rinsed with the same quantity of water (15 to 30 milliliters) and given to the patient to ensure all of the medication is taken.
- The pharmacy must dispense with the Instructions for Use. Alert the patient to read the Instructions for Use.

3 DOSAGE FORMS AND STRENGTHS

PROGRAF is available in the following dosage forms and strengths:

Capsules	Oblong, hard capsule for oral administration contains anhydrous tacrolimus USP as follows: • 0.5 mg, light-yellow color, imprinted in red "0.5 mg" on the capsule cap and "f 607" on capsule body • 1 mg, white color, imprinted in red "1 mg" on the capsule cap and "f 617" on capsule body • 5 mg, grayish-red color, imprinted with white "5 mg" on the capsule cap and "f 657" on capsule body
Injection	1 mL ampule for intravenous infusion contains anhydrous tacrolimus USP 5 mg/mL
For Oral Suspension	Unit-dose packets with white granules for oral suspension contains anhydrous tacrolimus USP: • 0.2 mg • 1 mg

4 CONTRAINDICATIONS

PROGRAF is contraindicated in patients with a hypersensitivity to tacrolimus. PROGRAF injection is contraindicated in patients with a hypersensitivity to HCO-60 (polyoxyl 60 hydrogenated castor oil). Hypersensitivity symptoms reported include dyspnea, rash, pruritus, and acute respiratory distress syndrome *[see Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

• 5.1 Lymphoma and Other Malignancies

Patients receiving immunosuppressants, including PROGRAF, are at increased risk of developing lymphomas and other malignancies, particularly of the skin *[see Boxed Warning]*. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Post-transplant lymphoproliferative disorder (PTLD) has been reported in immunosuppressed organ transplant recipients. The majority of PTLD events appear related to Epstein Barr Virus (EBV) infection. The risk of PTLD appears greatest in those individuals who are EBV seronegative, a population which includes many young children.

- **5.2 Serious Infections**

Patients receiving immunosuppressants, including PROGRAF, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Serious viral infections reported include:

- Polyoma virus-associated nephropathy (PVAN), mostly due to BK virus infection
- JC virus-associated progressive multifocal leukoencephalopathy (PML)
- Cytomegalovirus infections: CMV seronegative transplant patients who receive an organ from a CMV seropositive donor disease are at higher risk of developing CMV viremia and CMV disease.

Monitor for the development of infection and adjust the immunosuppressive regimen to balance the risk of rejection with the risk of infection *[see Adverse Reactions (6.1, 6.2)]*.

- **5.3 Not Interchangeable With Extended-Release Tacrolimus Products - Medication Errors**

Medication errors, including substitution and dispensing errors, between tacrolimus immediate-release products and tacrolimus extended-release products were reported outside the U.S. This led to serious adverse reactions, including graft rejection, or other adverse reactions due to under-or over-exposure to tacrolimus. PROGRAF is not interchangeable or substitutable with tacrolimus extended-release products. Instruct patients and caregivers to recognize the appearance of PROGRAF dosage forms *[see Dosage Forms and Strengths (3)]*.

- **5.4 New Onset Diabetes After Transplant**

PROGRAF was shown to cause new onset diabetes mellitus in clinical trials of kidney, liver, and heart transplantation. New onset diabetes after transplantation may be reversible in some patients. African-American and Hispanic kidney transplant patients are at an increased risk. Blood glucose concentrations should be monitored closely in patients using PROGRAF *[see Adverse Reactions (6.1)]*.

- **5.5 Nephrotoxicity**

PROGRAF, like other calcineurin inhibitors, can cause acute or chronic nephrotoxicity. Nephrotoxicity was reported in clinical trials *[see Adverse Reactions (6.1)]*. Consider dosage reduction in patients with elevated serum creatinine and tacrolimus whole blood trough concentrations greater than the recommended range. The risk for nephrotoxicity may increase when PROGRAF is concomitantly administered with CYP3A inhibitors (by increasing tacrolimus whole blood concentrations) or drugs associated with nephrotoxicity (e.g., aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors, protease inhibitors) *[see Drug Interactions (7.2)]*. Monitor renal function and consider dosage reduction if nephrotoxicity occurs.

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- **5.6 Neurotoxicity**

PROGRAF may cause a spectrum of neurotoxicities. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, seizure and coma; others include tremors, paresthesias, headache, mental status changes, and changes in motor and sensory functions *[see Adverse Reactions (6.1, 6.2)]*. As symptoms may be associated with tacrolimus whole blood trough concentrations at or above the recommended range, monitor for neurologic symptoms and consider dosage reduction or discontinuation of PROGRAF if neurotoxicity occurs.

- **5.7 Hyperkalemia**

Hyperkalemia has been reported with PROGRAF use. Serum potassium levels should be monitored. Careful consideration should be given prior to use of other agents also associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) during PROGRAF therapy *[see Adverse Reactions (6.1)]*.

- **5.8 Hypertension**

Hypertension is a common adverse effect of PROGRAF therapy and may require antihypertensive therapy *[see Adverse Reactions (6.1)]*. The control of blood pressure can be accomplished with any of the common antihypertensive agents, though careful consideration should be given prior to use of antihypertensive agents associated with hyperkalemia
(e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) *[see Warnings and Precautions (5.7)]*. Calcium-channel blocking agents may increase tacrolimus blood concentrations and therefore require dosage reduction of PROGRAF *[see Drug Interactions (7.2)]*.

- **5.9 Anaphylactic Reactions with PROGRAF Injection**

Anaphylactic reactions have occurred with injectables containing castor oil derivatives, including PROGRAF, in a small percentage of patients (0.6%). The exact cause of these reactions is not known. PROGRAF injection should be reserved for patients who are unable to take PROGRAF orally. Monitor patients for anaphylaxis when using the intravenous route of administration *[see Dosage and Administration (2.1)]*.

- **5.10 Not Recommended for Use with Sirolimus**

PROGRAF is not recommended for use with sirolimus:

- The use of sirolimus with PROGRAF in studies of *de novo* liver transplant patients was associated with an excess mortality, graft loss, and hepatic artery thrombosis (HAT) and is not recommended.
- The use of sirolimus (2 mg per day) with PROGRAF in heart transplant patients in a U.S. trial was associated with increased risk of renal function impairment, wound healing complications, and insulin-dependent post-transplant diabetes mellitus, and is not recommended *[see Clinical Studies (14.3)]*.

- **5.11 Interactions with CYP3A4 Inhibitors and Inducers**

When co-administering PROGRAF with strong CYP3A4 inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong inducers (e.g., rifampin, rifabutin), adjustments in the dosing regimen of PROGRAF and subsequent frequent monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions are recommended *[see Drug Interactions (7)]*.

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- **5.12 QT Prolongation**

PROGRAF may prolong the QT/QTc interval and may cause *Torsade de Pointes*. Avoid PROGRAF in patients with congenital long QT syndrome. In patients with congestive heart failure, bradyarrhythmias, those taking certain antiarrhythmic medications or other medicinal products that lead to QT prolongation, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia, consider obtaining electrocardiograms and monitoring electrolytes (magnesium, potassium, calcium) periodically during treatment.

When co-administering PROGRAF with other substrates and/or inhibitors of CYP3A4 that also have the potential to prolong the QT interval, a reduction in PROGRAF dose, frequent monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended. Use of PROGRAF with amiodarone has been reported to result in increased tacrolimus whole blood concentrations with or without concurrent QT prolongation *[see Drug Interactions (7)]*.

- **5.13 Myocardial Hypertrophy**

Myocardial hypertrophy has been reported in infants, children, and adults, particularly those with high tacrolimus trough concentrations, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving PROGRAF therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of PROGRAF should be considered *[see Adverse Reactions (6.2)]*.

- **5.14 Immunizations**

The use of live vaccines should be avoided during treatment with tacrolimus; examples include (not limited to) the following: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

- **5.15 Pure Red Cell Aplasia**

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. A mechanism for tacrolimus-induced PRCA has not been elucidated. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. If PRCA is diagnosed, discontinuation of PROGRAF should be considered *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:

- Lymphoma and Other Malignancies *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Serious Infections *[see Boxed Warning, Warnings and Precautions (5.2)]*
- New Onset Diabetes After Transplant *[see Warnings and Precautions (5.4)]*
- Nephrotoxicity *[see Warnings and Precautions (5.5)]*
- Neurotoxicity *[see Warnings and Precautions (5.6)]*
- Hyperkalemia *[see Warnings and Precautions (5.7)]*
- Hypertension *[see Warnings and Precautions (5.8)]*

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- Anaphylactic Reactions with PROGRAF Injection *[see Warnings and Precautions (5.9)]*
- Myocardial Hypertrophy *[see Warnings and Precautions (5.13)]*
- Pure Red Cell Aplasia *[see Warnings and Precautions (5.15)]*

• 6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In addition, the clinical trials were not designed to establish comparative differences across study arms with regards to the adverse reactions discussed below.

Kidney Transplantation
The incidence of adverse reactions was determined in three randomized kidney transplant trials. One of the trials used azathioprine (AZA) and corticosteroids and two of the trials used mycophenolate mofetil (MMF) and corticosteroids concomitantly for maintenance immunosuppression.

PROGRAF-based immunosuppression in conjunction with azathioprine and corticosteroids following kidney transplantation was assessed in a trial where 205 patients received PROGRAF-based immunosuppression and 207 patients received cyclosporine-based immunosuppression. The trial population had a mean age of 43 years (mean ± SD was 43 ± 13 years on PROGRAF and 44 ± 12 years on cyclosporine arm), the distribution was 61% male, and the composition was White (58%), African-American (25%), Hispanic (12%), and Other (5%). The 12-month post-transplant information from this trial is presented below.

The most common adverse reactions (≥ 30%) observed in PROGRAF-treated kidney transplant patients are: infection, tremor, hypertension, abnormal renal function, constipation, diarrhea, headache, abdominal pain, insomnia, nausea, hypomagnesemia, urinary tract infection, hypophosphatemia, peripheral edema, asthenia, pain, hyperlipidemia, hyperkalemia, and anemia. Based on reported adverse reactions terms related to decreased renal function, nephrotoxicity was reported in approximately 52% of kidney transplantation patients.

Adverse reactions that occurred in ≥ 15% of kidney transplant patients treated with PROGRAF in conjunction with azathioprine are presented below:

Table 4. Kidney Transplantation: Adverse Reactions Occurring in ≥ 15% of Patients Treated with PROGRAF in Conjunction with Azathioprine (AZA)

	PROGRAF/AZA (N = 205)	Cyclosporine/AZA (N = 207)
Nervous System		
Tremor	54%	34%
Headache	44%	38%
Insomnia	32%	30%
Paresthesia	23%	16%
Dizziness	19%	16%
Gastrointestinal		
Diarrhea	44%	41%
Nausea	38%	36%
Constipation	35%	43%
Vomiting	29%	23%
Dyspepsia	28%	20%

	PROGRAF/AZA (N = 205)	Cyclosporine/AZA (N = 207)
Cardiovascular		
Hypertension	50%	52%
Chest Pain	19%	13%
Urogenital		
Creatinine Increased	45%	42%
Urinary Tract Infection	34%	35%
Metabolic and Nutritional		
Hypophosphatemia	49%	53%
Hypomagnesemia	34%	17%
Hyperlipemia	31%	38%
Hyperkalemia	31%	32%
Diabetes Mellitus	24%	9%
Hypokalemia	22%	25%
Hyperglycemia	22%	16%
Edema	18%	19%
Hemic and Lymphatic		
Anemia	30%	24%
Leukopenia	15%	17%
Miscellaneous		
Infection	45%	49%
Peripheral Edema	36%	48%
Asthenia	34%	30%
Abdominal Pain	33%	31%
Pain	32%	30%
Fever	29%	29%
Back Pain	24%	20%
Respiratory System		
Dyspnea	22%	18%
Cough Increased	18%	15%
Musculoskeletal		
Arthralgia	25%	24%
Skin		
Rash	17%	12%
Pruritus	15%	7%

Two trials were conducted for PROGRAF-based immunosuppression in conjunction with MMF and corticosteroids. In
the non-US trial (Study 1), the incidence of adverse reactions was based on 1195 kidney transplant patients that received PROGRAF (Group C, n = 403), or one of two cyclosporine (CsA) regimens (Group A, n = 384 and Group B, n = 408) in combination with MMF and corticosteroids; all patients, except those in one of the two cyclosporine groups, also received induction with daclizumab. The trial population had a mean age of 46 years (range 17 to 76), the distribution was 65% male, and the composition was 93% Caucasian. The 12-month post-transplant information from this trial is presented below.

Adverse reactions that occurred in ≥ 10% of kidney transplant patients treated with PROGRAF in conjunction with MMF in Study 1 [Note: This trial was conducted entirely outside of the United States.

Such trials often report a lower incidence of adverse reactions in comparison to U.S. trials] are presented below:

Table 5. Kidney Transplantation: Adverse Reactions Occurring in ≥ 10% of Patients Treated with PROGRAF in Conjunction with MMF (Study 1)

	PROGRAF (Group C)	Cyclosporine (Group A)	Cyclosporine (Group B)
	(N = 403)	(N = 384)	(N = 408)
Diarrhea	25%	16%	13%
Urinary Tract Infection	24%	28%	24%
Anemia	17%	19%	17%
Hypertension	13%	14%	12%
Leukopenia	13%	10%	10%
Edema Peripheral	11%	12%	13%
Hyperlipidemia	10%	15%	13%
Key: Group A = CsA/MMF/CS, B = CsA/MMF/CS/Daclizumab, C = Tac/MMF/CS/Daclizumab CsA = Cyclosporine, CS = Corticosteroids, Tac = Tacrolimus, MMF = mycophenolate mofetil			

In the U.S. trial (Study 2) with PROGRAF-based immunosuppression in conjunction with MMF and corticosteroids, 424 kidney transplant patients received PROGRAF (n = 212) or cyclosporine (n = 212) in combination with MMF 1 gram twice daily, basiliximab induction, and corticosteroids. The trial population had a mean age of 48 years (range 17 to 77), the distribution was 63% male, and the composition was White (74%), African-American (20%), Asian (3%), and Other (3%). The 12-month post-transplant information from this trial is presented below.

Adverse reactions that occurred in ≥ 15% of kidney transplant patients treated with PROGRAF in conjunction with MMF in Study 2 are presented below:

Table 6. Kidney Transplantation: Adverse Reactions Occurring in ≥ 15% of Patients Treated with PROGRAF in Conjunction with MMF (Study 2)

	PROGRAF/MMF (N = 212)	Cyclosporine/MMF (N = 212)
Gastrointestinal Disorders		
Diarrhea	44%	26%
Nausea	39%	47%
Constipation	36%	41%
Vomiting	26%	25%
Dyspepsia	18%	15%
Injury, Poisoning, and Procedural Complications		
Post-Procedural Pain	29%	27%
Incision Site Complication	28%	23%
Graft Dysfunction	24%	18%
Metabolism and Nutrition Disorders		
Hypomagnesemia	28%	22%
Hypophosphatemia	28%	21%
Hyperkalemia	26%	19%
Hyperglycemia	21%	15%
Hyperlipidemia	18%	25%

Hypokalemia	16%	18%
Nervous System Disorders		
Tremor	34%	20%
Headache	24%	25%
Blood and Lymphatic System Disorders		
Anemia	30%	28%
Leukopenia	16%	12%
Miscellaneous		
Edema Peripheral	35%	46%
Hypertension	32%	35%
Insomnia	30%	21%
Urinary Tract Infection	26%	22%
Blood Creatinine Increased	23%	23%

Less frequently observed adverse reactions in kidney transplantation patients are described under the subsection "Less Frequently Reported Adverse Reactions (> 3% and < 15%) in Liver, Kidney, and Heart Transplant Studies."

Liver Transplantation

There were two randomized comparative liver transplant trials. In the U.S. trial, 263 adult and pediatric patients received tacrolimus and steroids and 266 patients received cyclosporine-based immunosuppressive regimen (CsA/AZA). The trial population had a mean age of 44 years (range 0.4 to 70), the distribution was 52% male, and the composition was White (78%), African-American (5%), Asian (2%), Hispanic (13%), and Other (2%). In the European trial, 270 patients received tacrolimus and steroids and 275 patients received CsA/AZA. The trial population had a mean age of 46 years (range 15 to 68), the distribution was 59% male, and the composition was White (95.4%), Black (1%), Asian (2%), and Other (2%).

The proportion of patients reporting more than one adverse event was > 99% in both the tacrolimus group and the CsA/AZA group. Precautions must be taken when comparing the incidence of adverse reactions in the U.S. trial to that in the European trial. The 12-month post-transplant information from the U.S. trial and from the European trial is presented below. The two trials also included different patient populations and patients were treated with immunosuppressive regimens of differing intensities. Adverse reactions reported in ≥ 15% in tacrolimus patients (combined trial results) are presented below for the two controlled trials in liver transplantation.

The most common adverse reactions (≥ 40%) observed in PROGRAF-treated liver transplant patients are: tremor, headache, diarrhea, hypertension, nausea, abnormal renal function, abdominal pain, insomnia, paresthesia, anemia, pain, fever, asthenia, hyperkalemia, hypomagnesemia, and hyperglycemia. These all occur with oral and IV administration of PROGRAF and some may respond to a reduction in dosing (e.g., tremor, headache, paresthesia, hypertension). Diarrhea was sometimes associated with other gastrointestinal complaints such as nausea and vomiting. Based on reported adverse reactions terms related to decreased renal function, nephrotoxicity was reported in approximately 40% and 36% of liver transplantation patients receiving PROGRAF in the U.S. and European randomized trials.

Table 7. Liver Transplantation: Adverse Reactions Occurring in ≥ 15% of Patients Treated with PROGRAF

	U.S. TRIAL		EUROPEAN TRIAL	
	PROGRAF (N = 250)	Cyclosporine/ AZA (N = 250)	PROGRAF (N = 264)	Cyclosporine/ AZA (N = 265)
Nervous System				
Headache	64%	60%	37%	26%
Insomnia	64%	68%	32%	23%
Tremor	56%	46%	48%	32%
Paresthesia	40%	30%	17%	17%
Gastrointestinal				
Diarrhea	72%	47%	37%	27%
Nausea	46%	37%	32%	27%
LFT Abnormal	36%	30%	6%	5%
Anorexia	34%	24%	7%	5%
Vomiting	27%	15%	14%	11%
Constipation	24%	27%	23%	21%
Cardiovascular				
Hypertension	47%	56%	38%	43%
Urogenital				
Kidney Function Abnormal	40%	27%	36%	23%
Creatinine Increased	39%	25%	24%	19%
BUN Increased	30%	22%	12%	9%
Oliguria	18%	15%	19%	12%
Urinary Tract Infection	16%	18%	21%	19%
Metabolic and Nutritional				
Hypomagnesemia	48%	45%	16%	9%
Hyperglycemia	47%	38%	33%	22%
Hyperkalemia	45%	26%	13%	9%
Hypokalemia	29%	34%	13%	16%
Hemic and Lymphatic				
Anemia	47%	38%	5%	1%
Leukocytosis	32%	26%	8%	8%
Thrombocytopenia	24%	20%	14%	19%
Miscellaneous				
Pain	63%	57%	24%	22%
Abdominal Pain	59%	54%	29%	22%
Asthenia	52%	48%	11%	7%
Fever	48%	56%	19%	22%
Back Pain	30%	29%	17%	17%
Ascites	27%	22%	7%	8%
Peripheral Edema	26%	26%	12%	14%
Respiratory System				
Pleural Effusion	30%	32%	36%	35%
Dyspnea	29%	23%	5%	4%
Atelectasis	28%	30%	5%	4%
Skin and Appendages				
Pruritus	36%	20%	15%	7%
Rash	24%	19%	10%	4%

Table 8. Pediatric Liver Transplantation: Adverse Reactions Occurring in > 10% of Patients Treated with PROGRAF Granules (STUDY 01-13)

	PROGRAF Granules (N = 91)	Cyclosporine (N = 90)
Body as a Whole		
Fever	46%	51%
Infection	25%	29%
Sepsis	22%	20%
CMV Infection	15%	24%
EBV Infection	26%	11%
Ascites	17%	20%
Peritonitis	12%	7%
Cardiovascular System		
Hypertension	39%	47%
Digestive System		
Liver Function Tests Abnormal	37%	28%
Diarrhea	26%	26%
Vomiting	15%	13%
Gastrointestinal Hemorrhage	11%	12%
Bile Duct Disorder	12%	8%
Gastroenteritis	12%	4%
Hemic and Lymphatic System		
Anemia	29%	19%
Metabolic and Nutritional Disorders		
Hypomagnesemia	40%	29%
Acidosis	26%	17%
Hyperkalemia	12%	10%
Respiratory System		
Pleural Effusion	22%	19%
Bronchitis	11%	8%
Urogenital System		
Kidney Function Abnormal	13%	14%

Less frequently observed adverse reactions in liver transplantation patients are described under the subsection "Less Frequently Reported Adverse Reactions (> 3% and < 15%) in Liver, Kidney, and Heart Transplant Studies."

Heart Transplantation

The incidence of adverse reactions was determined based on two trials in primary orthotopic heart transplantation. In a trial conducted in Europe, 314 patients received a regimen of antibody induction, corticosteroids, and azathioprine (AZA) in combination with PROGRAF (n = 157) or cyclosporine (n = 157) for 18 months. The trial population had a mean age of 51 years (range 18 to 65), the distribution was 82% male, and the composition was White (96%), Black (3%), and other (1%).

The most common adverse reactions (≥ 15%) observed in PROGRAF-treated heart transplant patients are: abnormal renal function, hypertension, diabetes mellitus, CMV infection, tremor, hyperglycemia, leukopenia, infection, anemia, bronchitis, pericardial effusion, urinary tract infection, and hyperlipemia. Based on reported adverse reactions terms related to decreased renal function, nephrotoxicity was reported in approximately 59% of heart transplantation patients in the European trial.

Adverse reactions in heart transplant patients in the European trial are presented below:

Table 9. Heart Transplantation: Adverse Reactions Occurring in ≥ 15% of Patients Treated with PROGRAF in Conjunction with Azathioprine (AZA)

	PROGRAF/AZA (n = 157)	Cyclosporine/AZA (n = 157)
Cardiovascular System		
Hypertension	62%	69%
Pericardial Effusion	15%	14%
Body as a Whole		
CMV Infection	32%	30%
Infection	24%	21%
Metabolic and Nutritional Disorders		
Diabetes Mellitus	26%	16%
Hyperglycemia	23%	17%
Hyperlipemia	18%	27%
Hemic and Lymphatic System		
Anemia	50%	36%
Leukopenia	48%	39%
Urogenital System		
Kidney Function Abnormal	56%	57%
Urinary Tract Infection	16%	12%
Respiratory System		
Bronchitis	17%	18%
Nervous System		
Tremor	15%	6%

In the European trial, the cyclosporine trough concentrations were above the pre-defined target range (i.e., 100 to 200 ng/mL) at Day 122 and beyond in 32% to 68% of the patients in the cyclosporine treatment arm, whereas the tacrolimus trough concentrations were within the pre-defined target range (i.e., 5 to 15 ng/mL) in 74% to 86% of the patients in the tacrolimus treatment arm.

In a U.S. trial, the incidence of adverse reactions was based on 331 heart transplant patients that received corticosteroids and PROGRAF in combination with sirolimus (n=109), PROGRAF in combination with MMF (n=107) or cyclosporine modified in combination with MMF (n=115) for 1 year. The trial population had a mean age of 53 years (range 18 to 75), the distribution was 78% male, and the composition was White (83%), African-American (13%) and other (4%).

Only selected targeted treatment-emergent adverse reactions were collected in the U.S. heart transplantation trial. Those reactions that were reported at a rate of 15% or greater in patients treated with PROGRAF and MMF include the following: any target adverse reactions (99%), hypertension (89%), hyperglycemia requiring antihyperglycemic therapy (70%), hypertriglyceridemia (65%), anemia (hemoglobin < 10.0 g/dL) (65%), fasting blood glucose > 140 mg/dL (on two separate occasions) (61%), hypercholesterolemia (57%), hyperlipidemia (34%), WBCs < 3000 cells/mcL (34%), serious bacterial infections (30%), magnesium < 1.2 mEq/L (24%), platelet count < 75,000 cells/mcL (19%), and other opportunistic infections (15%).

Other targeted treatment-emergent adverse reactions in PROGRAF-treated patients occurred at a rate of less than 15%, and include the following: Cushingoid features, impaired wound healing, hyperkalemia,

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Candida infection, and CMV infection/syndrome. Other less frequently observed adverse reactions in heart transplantation patients are described under the subsection "Less Frequently Reported Adverse Reactions (> 3% and < 15%) in Liver, Kidney and Heart Transplant Studies."

New Onset Diabetes After Transplant

Kidney Transplantation

New Onset Diabetes After Transplant (NODAT) is defined as a composite of fasting plasma glucose ≥ 126 mg/dL,
HbA_{1C} ≥ 6%, insulin use ≥ 30 days, or oral hypoglycemic use. In a trial in kidney transplant patients (Study 2), NODAT was observed in 75% in the PROGRAF-treated and 61% in the NEORAL-treated patients without pre-transplant history of diabetes mellitus (Table 10) *[see Clinical Studies (14.1)]*.

Table 10. Incidence of New Onset Diabetes After Transplant at 1 year in Kidney Transplant Recipients in a Phase 3 Trial (Study 2)

Parameter	Treatment Group	
	PROGRAF/MMF (n = 212)	NEORAL/MMF (n = 212)
NODAT	112/150 (75%)	93/152 (61%)
Fasting Plasma Glucose ≥ 126 mg/dL	96/150 (64%)	80/152 (53%)
HbA_{1C} ≥ 6%	59/150 (39%)	28/152 (18%)
Insulin Use ≥ 30 days	9/150 (6%)	4/152 (3%)
Oral Hypoglycemic Use	15/150 (10%)	5/152 (3%)

In early trials of PROGRAF, Post-Transplant Diabetes Mellitus (PTDM) was evaluated with a more limited criterion of "use of insulin for 30 or more consecutive days with < 5-day gap" in patients without a prior history of insulin-dependent diabetes mellitus or non-insulin dependent diabetes mellitus. Data are presented in Tables 11 to 14. PTDM was reported in 20% of PROGRAF/Azathioprine (AZA)-treated kidney transplant patients without pre-transplant history of diabetes mellitus in a Phase 3 trial (Table 11). The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these PTDM patients at one year and in 50% at 2 years post-transplant. African-American and Hispanic kidney transplant patients were at an increased risk of development of PTDM (Table 12).

Table 11. Incidence of Post-Transplant Diabetes Mellitus and Insulin Use at 2 Years in Kidney Transplant Recipients in a Phase 3 Trial using Azathioprine (AZA)

Status of PTDM*	PROGRAF/AZA	CsA/AZA
Patients without pre-transplant history of diabetes mellitus	151	151
New onset PTDM*, 1st Year	30/151 (20%)	6/151 (4%)
Still insulin-dependent at one year in those without prior history of diabetes	25/151 (17%)	5/151 (3%)
New onset PTDM* post 1 year	1	0
Patients with PTDM* at 2 years	16/151 (11%)	5/151 (3%)

*Use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin-dependent diabetes mellitus or non-insulin dependent diabetes mellitus.

Table 12. Development of Post-Transplant Diabetes Mellitus by Race or Ethnicity and by Treatment Group During First Year Post Kidney Transplantation in a Phase 3 Trial

Patient Race	Patients Who Developed PTDM*	
	PROGRAF	Cyclosporine

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African-American	15/41 (37%)	3 (8%)
Hispanic	5/17 (29%)	1 (6%)
Caucasian	10/82 (12%)	1 (1%)
Other	0/11 (0%)	1 (10%)
Total	30/151 (20%)	6 (4%)

*Use of insulin for 30 or more consecutive days, with < 5-day gap, without a prior history of insulin-dependent diabetes mellitus or non-insulin dependent diabetes mellitus.

Liver Transplantation

Insulin-dependent PTDM was reported in 18% and 11% of PROGRAF-treated liver transplant patients and was reversible in 45% and 31% of these patients at 1 year post-transplant, in the U.S. and European randomized trials, respectively (Table 13). Hyperglycemia was associated with the use of PROGRAF in 47% and 33% of liver transplant recipients in the U.S. and European randomized trials, respectively, and may require treatment *[see Adverse Reactions (6.1)]*.

Table 13. Incidence of Post-Transplant Diabetes Mellitus and Insulin Use at 1 Year in Liver Transplant Recipients

Status of PTDM*	US Trial		European Trial	
	PROGRAF	Cyclosporine	PROGRAF	Cyclosporine
Patients at risk†	239	236	239	249
New Onset PTDM*	42 (18%)	30 (13%)	26 (11%)	12 (5%)
Patients still on insulin at 1 year	23 (10%)	19 (8%)	18 (8%)	6 (2%)

*Use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin-dependent diabetes mellitus or non-insulin dependent diabetes mellitus.
†Patients without pre-transplant history of diabetes mellitus.

Heart Transplantation

Insulin-dependent PTDM was reported in 13% and 22% of PROGRAF-treated heart transplant patients receiving mycophenolate mofetil (MMF) or azathioprine (AZA) and was reversible in 30% and 17% of these patients at one year post-transplant, in the U.S. and European randomized trials, respectively (Table 14). Hyperglycemia defined as two fasting plasma glucose levels ≥126 mg/dL was reported with the use of PROGRAF plus MMF or AZA in 32% and 35% of heart transplant recipients in the U.S. and European randomized trials, respectively, and may require treatment
[see Adverse Reactions (6.1)].

Table 14. Incidence of Post-Transplant Diabetes Mellitus and Insulin Use at 1 Year in Heart Transplant Recipients

Status of PTDM*	US Trial		European Trial	
	PROGRAF/MMF	Cyclosporine/MMF	PROGRAF/AZA	Cyclosporine/AZA
Patients at risk†	75	83	132	138
New Onset PTDM*	10 (13%)	6 (7%)	29 (22%)	5 (4%)
Patients still on insulin at 1 year‡	7 (9%)	1 (1%)	24 (18%)	4 (3%)

*Use of insulin for 30 or more consecutive days without a prior history of insulin-dependent diabetes mellitus or non-insulin dependent diabetes mellitus.
†Patients without pre-transplant history of diabetes mellitus.
‡7-12 months for the U.S. trial.

Less Frequently Reported Adverse Reactions (> 3% and < 15%) in Liver, Kidney, and Heart Transplant Studies

The following adverse reactions were reported in either liver, kidney, and/or heart transplant recipients who were treated with tacrolimus in clinical trials.

- Nervous System *[see Warnings and Precautions (5.6)]:* Abnormal dreams, agitation, amnesia, anxiety, confusion, convulsion, crying, depression, elevated mood, emotional lability, encephalopathy, hemorrhagic stroke, hallucinations, hypertonia, incoordination, monoparesis, myoclonus, nerve compression, nervousness, neuralgia, neuropathy, paralysis flaccid, psychomotor skills impaired, psychosis, quadriparesis, somnolence, thinking abnormal, vertigo, writing impaired
- Special Senses: Abnormal vision, amblyopia, ear pain, otitis media, tinnitus
- Gastrointestinal: Cholangitis, cholestatic jaundice, duodenitis, dysphagia, esophagitis, flatulence, gastritis, gastroesophagitis, gastrointestinal hemorrhage, GGT increase, GI disorder, GI perforation, hepatitis, hepatitis granulomatous, ileus, increased appetite, jaundice, liver damage, esophagitis ulcerative, oral moniliasis, pancreatic pseudocyst, stomatitis
- Cardiovascular: Abnormal ECG, angina pectoris, arrhythmia, atrial fibrillation, atrial flutter, bradycardia, cardiac fibrillation, cardiopulmonary failure, congestive heart failure, deep thrombophlebitis, echocardiogram abnormal, electrocardiogram QRS complex abnormal, electrocardiogram ST segment abnormal, heart failure, heart rate decreased, hemorrhage, hypotension, phlebitis, postural hypotension, syncope, tachycardia, thrombosis, vasodilatation
- Urogenital: Acute kidney failure *[see Warnings and Precautions (5.5)],* albuminuria, BK nephropathy, bladder spasm, cystitis, dysuria, hematuria, hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, pyuria, toxic nephropathy, urge incontinence, urinary frequency, urinary incontinence, urinary retention, vaginitis
- Metabolic/Nutritional: Acidosis, alkaline phosphatase increased, alkalosis, ALT (SGPT) increased, AST (SGOT) increased, bicarbonate decreased, bilirubinemia, dehydration, GGT increased, gout, healing abnormal, hypercalcemia, hypercholesterolemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hyponatremia, hypoproteinemia, lactic dehydrogenase increase, weight gain
- Endocrine: Cushing's syndrome
- Hemic/Lymphatic: Coagulation disorder, ecchymosis, hematocrit increased, hypochromic anemia, leukocytosis, polycythemia, prothrombin decreased, serum iron decreased
- Miscellaneous: Abdomen enlarged, abscess, accidental injury, allergic reaction, cellulitis, chills, fall, flu syndrome, generalized edema, hernia, mobility decreased, peritonitis, photosensitivity reaction, sepsis, temperature intolerance, ulcer
- Musculoskeletal: Arthralgia, cramps, generalized spasm, leg cramps, myalgia, myasthenia, osteoporosis

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- Respiratory: Asthma, emphysema, hiccups, lung function decreased, pharyngitis, pneumonia, pneumothorax, pulmonary edema, rhinitis, sinusitis, voice alteration
- Skin: Acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, herpes zoster, hirsutism, neoplasm skin benign, skin discoloration, skin ulcer, sweating

- **6.2 Postmarketing Adverse Reactions**

The following adverse reactions have been reported from worldwide marketing experience with tacrolimus. Because these reactions are reported voluntarily from a population of uncertain size it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to the drug.

Other reactions include:

- Cardiovascular: Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest, electrocardiogram T wave abnormal, flushing, myocardial infarction, myocardial ischemia, pericardial effusion, QT prolongation, *Torsade de Pointes*, venous thrombosis deep limb, ventricular extrasystoles, ventricular fibrillation, myocardial hypertrophy *[see Warnings and Precautions (5.13)]*
- Gastrointestinal: Bile duct stenosis, colitis, enterocolitis, gastroenteritis, gastroesophageal reflux disease, hepatic cytolysis, hepatic necrosis, hepatotoxicity, impaired gastric emptying, liver fatty, mouth ulceration, pancreatitis hemorrhagic, pancreatitis necrotizing, stomach ulcer, veno-occlusive liver disease
- Hemic/Lymphatic: Agranulocytosis, disseminated intravascular coagulation, hemolytic anemia, neutropenia, pancytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pure red cell aplasia *[see Warnings and Precautions (5.15)]*
- Infections: Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal; polyoma virus-associated nephropathy, (PVAN) including graft loss *[see Warnings and Precautions (5.2)]*
- Metabolic/Nutritional: Glycosuria, increased amylase including pancreatitis, weight decreased
- Miscellaneous: Feeling hot and cold, feeling jittery, hot flushes, multi-organ failure, primary graft dysfunction
- Nervous System: Carpal tunnel syndrome, cerebral infarction, hemiparesis, leukoencephalopathy, mental disorder, mutism, posterior reversible encephalopathy syndrome (PRES) *[see Warnings and Precautions (5.6)]*, progressive multifocal leukoencephalopathy (PML) *[see Warnings and Precautions (5.2)]*, quadriplegia, speech disorder, syncope
- Respiratory: Acute respiratory distress syndrome, interstitial lung disease, lung infiltration, respiratory distress, respiratory failure
- Skin: Stevens-Johnson syndrome, toxic epidermal necrolysis
- Special Senses: Blindness, blindness cortical, hearing loss including deafness, photophobia
- Urogenital: Acute renal failure, cystitis hemorrhagic, hemolytic-uremic syndrome

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8 USE IN SPECIFIC POPULATIONS

• 8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to PROGRAF during pregnancy.
The Transplantation Pregnancy Registry International (TPRI) is a voluntary pregnancy exposure registry that monitors outcomes of pregnancy in female transplant recipients and those fathered by male transplant recipients exposed to immunosuppressants including tacrolimus. Healthcare providers are encouraged to advise their patients to register by contacting the Transplantation Pregnancy Registry International at 1-877-955-6877 or https://www.transplantpregnancyregistry.org/.

Risk Summary

Tacrolimus can cause fetal harm when administered to a pregnant woman. Data from postmarketing surveillance and TPRI suggest that infants exposed to tacrolimus *in utero* are at a risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress *[see Human Data]*. Advise pregnant women of the potential risk to the fetus.
Administration of oral tacrolimus to pregnant rabbits and rats throughout the period of organogenesis was associated with maternal toxicity/lethality, and an increased incidence of abortion, malformation and embryofetal death at clinically relevant doses (0.5 to 6.9 times the recommended clinical dose range [0.2 to 0.075 mg/kg/day], on a mg/m^2 basis). Administration of oral tacrolimus to pregnant rats after organogenesis and throughout lactation produced maternal toxicity, effects on parturition, reduced pup viability and reduced pup weight at clinically relevant doses (0.8 to 6.9 times the recommended clinical dose range, on a mg/m^2 basis). Administration of oral tacrolimus to rats prior to mating, and throughout gestation and lactation produced maternal toxicity/lethality, marked effects on parturition, embryofetal loss, malformations, and reduced pup viability at clinically relevant doses (0.8 to 6.9 times the recommended clinical dose range, on a mg/m^2 basis). Interventricular septal defects, hydronephrosis, craniofacial malformations and skeletal effects were observed in offspring that died *[see Animal Data]*.

The background risk of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Risks during pregnancy are increased in organ transplant recipients.

The risk of premature delivery following transplantation is increased. Pre-existing hypertension and diabetes confer additional risk to the pregnancy of an organ transplant recipient. Pre-gestational and gestational diabetes are associated with birth defects/congenital anomalies, hypertension, low birth weight and fetal death.

Cholestasis of pregnancy (COP) was reported in 7% of liver or liver-kidney (LK) transplant recipients, compared with approximately 1% of pregnancies in the general population. However, COP symptoms resolved postpartum and no long-term effects on the offspring were reported.

Maternal Adverse Reactions

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PROGRAF may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly *[see Warnings and Precautions (5.4)]*.

PROGRAF may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure *[see Warnings and Precautions (5.7, 5.8)]*.

Fetal/Neonatal Adverse Reactions

Renal dysfunction, transient neonatal hyperkalemia and low birth weight have been reported at the time of delivery in infants of mothers taking PROGRAF.

Labor or Delivery

There is an increased risk for premature delivery (< 37 weeks) following transplantation and maternal exposure to PROGRAF.

Data

Human Data

There are no adequate and well controlled studies on the effects of tacrolimus in human pregnancy.

Safety data from the TPRI and postmarketing surveillance suggest infants exposed to tacrolimus in utero have an increased risk for miscarriage, pre-term delivery (< 37 weeks), low birth weight (< 2500 g), birth defects/congenital anomalies and fetal distress.

TPRI reported 450 and 241 total pregnancies in kidney and liver transplant recipients exposed to tacrolimus,
respectively. The TPRI pregnancy outcomes are summarized in Table 15. In the table below, the number of recipients exposed to tacrolimus concomitantly with mycophenolic acid (MPA) products during the preconception and first trimester periods is high (27% and 29% for renal and liver transplant recipients, respectively). Because MPA products may also cause birth defects, the birth defect rate may be confounded and this should be taken into consideration when reviewing the data, particularly for birth defects. Birth defects observed include cardiac malformations, craniofacial malformations, renal/urogenital disorders, skeletal abnormalities, neurological abnormalities and multiple malformations.

Table 16. TPRI Reported Pregnancy Outcomes in Transplant Recipients with Exposure to Tacrolimus

	Kidney	Liver
Pregnancy Outcomes*	**462**	**253**
Miscarriage	24.5%	25%
Live births	**331**	**180**
Pre-term delivery (< 37 weeks)	49%	42%
Low birth weight (< 2500 g)	42%	30%
Birth defects	8%†	5%

*Includes multiple births and terminations.
†Birth defect rate confounded by concomitant MPA products exposure in over half of offspring with birth defects.

Additional information reported by TPRI in pregnant transplant patients receiving tacrolimus included diabetes during pregnancy in 9% of kidney recipients and 13% of liver recipients and hypertension during pregnancy in 53% of kidney recipients and 16.2% of liver recipients.

Animal Data

Administration of oral tacrolimus to pregnant rabbits throughout organogenesis produced maternal toxicity and abortion at 0.32 mg/kg (0.5 to 1.4 times the recommended clinical dose range [0.2 to 0.075

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mg/kg/day], on a mg/m^2 basis). At 1 mg/kg (1.6 to 4.3 times the recommended clinical dose range), embryofetal lethality and fetal malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosus, omphalocele, gallbladder agenesis, skeletal anomalies) were observed. Administration of 3.2 mg/kg oral tacrolimus (2.6 to 6.9 times the recommended clinical dose range) to pregnant rats throughout organogenesis produced maternal toxicity/lethality, embryofetal lethality and decreased fetal body weight in the offspring of C-sectioned dams; and decreased pup viability and interventricular septal defect in offspring of dams that delivered.

In a peri-/postnatal development study, oral administration of tacrolimus to pregnant rats during late gestation (after organogenesis) and throughout lactation produced maternal toxicity, effects on parturition, and reduced pup viability at 3.2 mg/kg (2.6 to 6.9 times the recommended clinical dose range); among these pups that died early, an increased incidence of kidney hydronephrosis was observed. Reduced pup weight was observed at 1.0 mg/kg (0.8 to 2.2 times the recommended clinical dose range).

Administration of oral tacrolimus to rats prior to mating, and throughout gestation and lactation produced maternal toxicity/lethality, embryofetal loss and reduced pup viability at 3.2 mg/kg (2.6 to 6.9 times the recommended clinical dose range). Interventricular septal defects, hydronephrosis, craniofacial malformations and skeletal effects were observed in offspring that died. Effects on parturition (incomplete delivery of nonviable pups) were observed at 1 mg/kg (0.8 to 2.2 times the recommended clinical dose range) *[see Nonclinical Toxicology (13.1)]*.

- **8.2 Lactation**

Risk Summary

Controlled lactation studies have not been conducted in humans; however tacrolimus has been reported to be present in human milk. The effects of tacrolimus on the breastfed infant, or on milk production have not been assessed. Tacrolimus is excreted in rat milk and in peri-/postnatal rat studies, exposure to tacrolimus during the postnatal period was associated with developmental toxicity in the offspring at clinically relevant doses *[see Pregnancy (8.1), Nonclinical Toxicology (13.1)]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PROGRAF and any potential adverse effects on the breastfed child from PROGRAF or from the underlying maternal condition.

- **8.3 Females and Males of Reproductive Potential**

Contraception

PROGRAF can cause fetal harm when administered to pregnant women. Advise female and male patients of reproductive potential to speak to their healthcare provider on family planning options including appropriate contraception prior to starting treatment with PROGRAF *[see Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)]*.

Infertility

Based on findings in animals, male and female fertility may be compromised by treatment with PROGRAF *[see Nonclinical Toxicology (13.1)]*.

- **8.4 Pediatric Use**

Safety and effectiveness have been established in pediatric liver, kidney, and heart transplant patients.

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Liver transplant:
Safety and efficacy using PROGRAF Granules in pediatric *de novo* liver transplant patients less than 16 years of age are based on evidence from active controlled studies that included 56 pediatric patients, 31 of which received PROGRAF and supported by two pharmacokinetic and safety studies in 151 children who received PROGRAF. Additionally, 122 pediatric patients were studied in an uncontrolled trial of tacrolimus in living related donor liver transplantation. Dose adjustments were made in the PK studies based on clinical status and whole blood concentrations. Pediatric patients generally required higher doses of PROGRAF to maintain blood trough concentrations of tacrolimus similar to adult patients *[see Dosage and Administration (2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

Kidney and heart transplant:
Use of PROGRAF capsules and PROGRAF Granules in pediatric kidney and heart transplant patients is supported by adequate and well-controlled studies and pharmacokinetic data in adult kidney and heart transplant patients with additional pharmacokinetic data in pediatric kidney and heart transplant patients and safety data in pediatric liver transplant patients *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].*

- **8.5 Geriatric Use**

Clinical trials of PROGRAF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

- **8.6 Use in Renal Impairment**

The pharmacokinetics of PROGRAF in patients with renal impairment was similar to that in healthy volunteers with normal renal function. However, consideration should be given to dosing PROGRAF at the lower end of the therapeutic dosing range in patients who have received a liver or heart transplant and have pre-existing renal impairment. Further reductions in dose below the targeted range may be required *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

- **8.7 Use in Hepatic Impairment**

The mean clearance of tacrolimus was substantially lower in patients with severe hepatic impairment (mean Child-Pugh score: > 10) compared to healthy volunteers with normal hepatic function. Close monitoring of tacrolimus trough concentrations is warranted in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

The use of PROGRAF in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole blood trough concentrations of tacrolimus. These patients should be monitored closely and dosage adjustments should be considered. Some evidence suggests that lower doses should be used in these patients *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)]*.

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14 CLINICAL STUDIES

• 14.1 Kidney Transplantation

PROGRAF/Azathioprine (AZA)

PROGRAF-based immunosuppression in conjunction with azathioprine and corticosteroids following kidney transplantation was assessed in a randomized, multicenter, non-blinded, prospective trial. There were 412 kidney transplant patients enrolled at 19 clinical sites in the United States. Study therapy was initiated when renal function was stable as indicated by a serum creatinine ≤ 4 mg/dL (median of 4 days after transplantation, range 1 to 14 days). Patients less than 6 years of age were excluded.

There were 205 patients randomized to PROGRAF-based immunosuppression and 207 patients were randomized to cyclosporine-based immunosuppression. All patients received prophylactic induction therapy consisting of an antilymphocyte antibody preparation, corticosteroids, and azathioprine. Overall 1-year patient and graft survival was 96.1% and 89.6%, respectively.

Data from this trial of PROGRAF in conjunction with azathioprine indicate that during the first 3 months of that trial, 80% of the patients maintained trough concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through 1 year.

PROGRAF/Mycophenolate Mofetil (MMF)

PROGRAF-based immunosuppression in conjunction with MMF, corticosteroids, and induction has been studied. In a randomized, open-label, multicenter trial (Study 1), 1589 kidney transplant patients received PROGRAF (Group C, n = 401), sirolimus (Group D, n = 399), or one of two cyclosporine (CsA) regimens (Group A, n = 390 and Group B, n = 399) in combination with MMF and corticosteroids; all patients, except those in one of the two cyclosporine groups, also received induction with daclizumab. The trial was conducted outside the United States; the trial population was 93% Caucasian. In this trial, mortality at 12 months in patients receiving PROGRAF/MMF was similar (3%) compared to patients receiving cyclosporine/MMF (3% and 2%) or sirolimus/MMF (3%). Patients in the PROGRAF group exhibited higher estimated creatinine clearance rates (eCL_{cr}) using the Cockcroft-Gault formula (Table 20) and experienced fewer efficacy failures, defined as biopsy-proven acute rejection (BPAR), graft loss, death, and/or lost to follow-up (Table 21) in comparison to each of the other three groups. Patients randomized to PROGRAF/MMF were more likely to develop diarrhea and diabetes after the transplantation and experienced similar rates of infections compared to patients randomized to either cyclosporine/MMF regimen *[see Adverse Reactions (6.1)]*.

Table 20. Estimated Creatinine Clearance at 12 Months (Study 1)

Group	eCL_{cr} [mL/min] at Month 12*				
	N	MEAN	SD	MEDIAN	Treatment Difference with Group C (99.2% CI†)
(A) CsA/MMF/CS	390	56.5	25.8	56.9	-8.6 (-13.7, -3.7)
(B) CsA/MMF/CS/Daclizumab	399	58.9	25.6	60.9	-6.2 (-11.2, -1.2)
(C) Tac/MMF/CS/Daclizumab	401	65.1	27.4	66.2	-
(D) Siro/MMF/CS/Daclizumab	399	56.2	27.4	57.3	-8.9 (-14.1, -3.9)

Total	1589	59.2	26.8	60.5	

Key: CsA = Cyclosporine, CS = Corticosteroids, Tac = Tacrolimus, Siro = Sirolimus

*All death/graft loss (n = 41, 27, 23, and 42 in Groups A, B, C, and D) and patients whose last recorded creatinine values were prior to month 3 visit (n = 10, 9, 7, and 9 in Groups A, B, C, and D, respectively) were imputed with Glomerular Filtration Rate (GFR) of 10 mL/min; a subject's last observed creatinine value from month 3 on was used for the remainder of subjects with missing creatinine at month 12 (n = 11, 12, 15, and 19 for Groups A, B, C, and D, respectively). Weight was also imputed in the calculation of estimated GFR, if missing.
†Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

Table 21. Incidence of BPAR, Graft Loss, Death, or Loss to Follow-up at 12 Months (Study 1)

	Group A N = 390	**Group B N = 399**	**Group C N = 401**	**Group D N = 399**
Overall Failure	141 (36.2%)	126 (31.6%)	82 (20.4%)	185 (46.4%)
Components of efficacy failure				
BPAR	113 (29.0%)	106 (26.6%)	60 (15.0%)	152 (38.1%)
Graft loss excluding death	28 (7.2%)	20 (5.0%)	12 (3.0%)	30 (7.5%)
Mortality	13 (3.3%)	7 (1.8%)	11 (2.7%)	12 (3.0%)
Lost to follow-up	5 (1.3%)	7 (1.8%)	5 (1.3%)	6 (1.5%)
Treatment Difference of efficacy failure compared to Group C (99.2% CI*)	15.8% (7.1%, 24.3%)	11.2% (2.7%, 19.5%)	-	26.0% (17.2%, 34.7%)

Key: Group A = CsA/MMF/CS, B = CsA/MMF/CS/Daclizumab, C = Tac/MMF/CS/Daclizumab, and D = Siro/MMF/CS/Daclizumab

*Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

The protocol-specified target tacrolimus trough concentrations ($C_{trough,Tac}$) were 3-7 ng/mL; however, the observed median $C_{troughs,Tac}$ approximated 7 ng/mL throughout the 12-month trial (Table 22). Approximately 80% of patients maintained tacrolimus whole blood concentrations between 4-11 ng/mL through 1 year post-transplant.

Table 22. Tacrolimus Whole Blood Trough Concentration Range (Study 1)

Time	**Median (P10-P90*) tacrolimus whole blood trough concentration range (ng/mL)**
Day 30 (N = 366)	6.9 (4.4 – 11.3)
Day 90 (N = 351)	6.8 (4.1 – 10.7)
Day 180 (N = 355)	6.5 (4.0 – 9.6)
Day 365 (N = 346)	6.5 (3.8 – 10.0)

*10 to 90th Percentile: range of $C_{trough,Tac}$ that excludes lowest 10% and highest 10% of $C_{trough,Tac}$

The protocol-specified target cyclosporine trough concentrations ($C_{trough,CsA}$) for Group B were 50-100 ng/mL; however, the observed median $C_{troughs,CsA}$ approximated 100 ng/mL throughout the 12-month trial. The protocol-specified target $C_{troughs,CsA}$ for Group A were 150-300 ng/mL for the first 3 months and 100-200 ng/mL from month 4 to month 12; the observed median $C_{troughs,CsA}$ approximated 225 ng/mL for the first 3 months and 140 ng/mL from month 4 to month 12.

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While patients in all groups started MMF at 1 gram twice daily, the MMF dose was reduced to less than 2 g per day in 63% of patients in the tacrolimus treatment arm by month 12 (Table 23); approximately 50% of these MMF dose reductions were due to adverse reactions. By comparison, the MMF dose was reduced to less than 2 g per day in 49% and 45% of patients in the two cyclosporine arms (Group A and Group B, respectively), by month 12 and approximately 40% of MMF dose reductions were due to adverse reactions.

Table 23. MMF Dose Over Time in PROGRAF/MMF (Group C) (Study 1)

Time period (Days)	Time-averaged MMF dose (grams per day)*		
	Less than 2.0	2.0	Greater than 2.0
0-30 (N = 364)	37%	60%	2%
0-90 (N = 373)	47%	51%	2%
0-180 (N = 377)	56%	42%	2%
0-365 (N = 380)	63%	36%	1%
Key: Time-averaged MMF dose = (total MMF dose)/(duration of treatment)			

*Percentage of patients for each time-averaged MMF dose range during various treatment periods. Administration of 2 g
per day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

In a second randomized, open-label, multicenter trial (Study 2), 424 kidney transplant patients received PROGRAF (N = 212) or cyclosporine (N = 212) in combination with MMF 1 gram twice daily, basiliximab induction, and corticosteroids. In this trial, the rate for the combined endpoint of BPAR, graft failure, death, and/or lost to follow-up at 12 months in the PROGRAF/MMF group was similar to the rate in the cyclosporine/MMF group. There was, however,
an imbalance in mortality at 12 months in those patients receiving PROGRAF/MMF (4%) compared to those receiving cyclosporine/MMF (2%), including cases attributed to over-immunosuppression (Table 24).

Table 24. Incidence of BPAR, Graft Loss, Death, or Loss to Follow-up at 12 Months (Study 2)

	PROGRAF/MMF (N = 212)	Cyclosporine/MMF (N = 212)
Overall Failure	32 (15.1%)	36 (17.0%)
Components of efficacy failure		
BPAR	16 (7.5%)	29 (13.7%)
Graft loss excluding death	6 (2.8%)	4 (1.9%)
Mortality	9 (4.2%)	5 (2.4%)
Lost to follow-up	4 (1.9%)	1 (0.5%)
Treatment Difference of efficacy failure compared to PROGRAF/MMF group (95% CI*)		1.9% (-5.2%, 9.0%)

*95% confidence interval calculated using Fisher's Exact Test

The protocol-specified target tacrolimus whole blood trough concentrations ($C_{trough,Tac}$) in Study 2 were 7-16 ng/mL for the first three months and 5-15 ng/mL thereafter. The observed median $C_{troughs,Tac}$ approximated 10 ng/mL during the first three months and 8 ng/mL from month 4 to month 12 (Table 25). Approximately 80% of patients maintained tacrolimus whole blood trough concentrations between 6 to 16 ng/mL during months 1 through 3 and, then, between 5 to 12 ng/mL from month 4 through 1 year.

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Table 25. Tacrolimus Whole Blood Trough Concentration Range (Study 2)

Time	Median (P10-P90*) tacrolimus whole blood trough concentration range (ng/mL)
Day 30 (N = 174)	10.5 (6.3 – 16.8)
Day 60 (N = 179)	9.2 (5.9 – 15.3)
Day 120 (N = 176)	8.3 (4.6 – 13.3)
Day 180 (N = 171)	7.8 (5.5 – 13.2)
Day 365 (N = 178)	7.1 (4.2 – 12.4)

*10 to 90th Percentile: range of $C_{trough,Tac}$ that excludes lowest 10% and highest 10% of $C_{trough,Tac}$

The protocol-specified target cyclosporine whole blood concentrations ($C_{trough,CsA}$) were 125 to 400 ng/mL for the first three months, and 100 to 300 ng/mL thereafter. The observed median $C_{troughs,CsA}$ approximated 280 ng/mL during the first three months and 190 ng/mL from month 4 to month 12.

Patients in both groups started MMF at 1 gram twice daily. The MMF dose was reduced to less than 2 grams per day by month 12 in 62% of patients in the PROGRAF/MMF group (Table 26) and in 47% of patients in the cyclosporine/MMF group. Approximately 63% and 55% of these MMF dose reductions were because of adverse reactions in the PROGRAF/MMF group and the cyclosporine/MMF group, respectively *[see Adverse Reactions (6.1)]*.

Table 26. MMF Dose Over Time in the PROGRAF/MMF Group (Study 2)

Time period (Days)	Time-averaged MMF dose (g/day)*		
	Less than 2.0	2.0	Greater than 2.0
0-30 (N = 212)	25%	69%	6%
0-90 (N = 212)	41%	53%	6%
0-180 (N = 212)	52%	41%	7%
0-365 (N = 212)	62%	34%	4%
Key: Time-averaged MMF dose=(total MMF dose)/(duration of treatment)			

*Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two grams per day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

- **14.2 Liver Transplantation**

The safety and efficacy of PROGRAF-based immunosuppression following orthotopic liver transplantation were assessed in two prospective, randomized, non-blinded multicenter trials. The active control groups were treated with a cyclosporine-based immunosuppressive regimen (CsA/AZA). Both trials used concomitant adrenal corticosteroids as part of the immunosuppressive regimens. These trials compared patient and graft survival rates at 12 months following transplantation.

In one trial, 529 patients were enrolled at 12 clinical sites in the United States; prior to surgery, 263 were randomized to the PROGRAF-based immunosuppressive regimen and 266 to the CsA/AZA. In 10 of the 12 sites, the same CsA/AZA protocol was used, while 2 sites used different control protocols. This trial excluded patients with renal dysfunction, fulminant hepatic failure with Stage IV encephalopathy, and cancers; pediatric patients (≤ 12 years old) were allowed.

In the second trial, 545 patients were enrolled at 8 clinical sites in Europe; prior to surgery, 270 were randomized to the PROGRAF-based immunosuppressive regimen and 275 to CsA/AZA. In this trial, each center used its local standard CsA/AZA protocol in the active-control arm. This trial excluded pediatric

patients, but did allow enrollment of subjects with renal dysfunction, fulminant hepatic failure in Stage IV encephalopathy, and cancers other than primary hepatic with metastases.

One-year patient survival and graft survival in the PROGRAF-based treatment groups were similar to those in the CsA/AZA treatment groups in both trials. The overall 1-year patient survival (CsA/AZA and PROGRAF-based treatment groups combined) was 88% in the U.S. trial and 78% in the European trial. The overall 1-year graft survival (CsA/AZA and PROGRAF-based treatment groups combined) was 81% in the U.S. trial and 73% in the European trial. In both trials, the median time to convert from IV to oral PROGRAF dosing was 2 days.

Although there is a lack of direct correlation between tacrolimus concentrations and drug efficacy, data from clinical trials of liver transplant patients have shown an increasing incidence of adverse reactions with increasing trough blood concentrations. Most patients are stable when trough whole blood concentrations are maintained between 5 to 20 ng/mL. Long-term post-transplant patients often are maintained at the low end of this target range.

Data from the U.S. clinical trial show that the median trough blood concentrations, measured at intervals from the second week to one year post-transplantation, ranged from 9.8 ng/mL to 19.4 ng/mL.

Pediatric Liver Transplantation Using PROGRAF Granules

The efficacy and safety of PROGRAF Granules plus corticosteroids were compared with a triple regimen of cyclosporine/corticosteroids/azathioprine in a randomized, open-label study, in *de novo* pediatric liver transplant patients. The study was conducted outside the United States and enrolled patients aged 16 years or younger. The distribution of pediatric patients by age was similar in both treatment groups, with a majority < 5 years. Patients were randomized to either tacrolimus for oral suspension 0.3 mg/kg/day (N = 91) or cyclosporine 10 mg/kg/day orally (N = 90) initiated 6 hours after completion of transplant surgery. Doses throughout the 1-year study period were adjusted to maintain whole blood trough levels within 5-20 ng/mL *[see Dosage and Administration (2.4)]*. Based on trough levels, doses of tacrolimus were adjusted to 0.17 mg/kg/day and 0.14 mg/kg/day by days 2 and 3, respectively. At 12 months, the incidence rate of BPAR, graft loss, death, or lost to follow-up was 52.7% in the tacrolimus group and 61.1% in the cyclosporine group (Table 27).

Table 27. Key Efficacy Results at 12 Months in Pediatric Liver Transplant Recipients Receiving PROGRAF Granules or Cyclosporine

	PROGRAF Granules (N = 91)	**Cyclosporine (N = 90)**
Overall Failure	48 (52.7%)	55 (61.1%)
Components of efficacy failure		
BPAR	40 (44.0%)	49 (54.4%)
Graft loss	7 (7.7%)	13 (14.4%)
Graft loss excluding death	1 (1.1%)	6 (6.7%)
Mortality	6 (6.6%)	7 (7.8%)
Lost to follow-up	2 (2.2%)	0
Treatment Difference of efficacy failure compared to Cyclosporine (95% CI*)	-8.4% (-22.7%, 6.0%)	

*95% confidence interval calculated using normal approximation.

- **14.3 Heart Transplantation**

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

In the European trial, patient/graft survival at 18 months post-transplant was similar between treatment arms, 92% in the tacrolimus group and 90% in the cyclosporine group. In the U.S. trial, patient and graft survival at 12 months was similar with 93% survival in the PROGRAF plus MMF group and 86% survival in the cyclosporine modified plus MMF group. In the European trial, the cyclosporine trough concentrations were above the pre-defined target range (i.e., 100 to 200 ng/mL) at Day 122 and beyond in 32% to 68% of the patients in the cyclosporine treatment arm, whereas the tacrolimus trough concentrations were within the pre-defined target range (i.e., 5 to 15 ng/mL) in 74% to 86% of the patients in the tacrolimus treatment arm. Data from this European trial indicate that from 1 week to 3 months post-transplant, approximately 80% of patients maintained trough concentrations between 8 to 20 ng/mL and, from 3 months through 18 months post-transplant, approximately 80% of patients maintained trough concentrations between 6 to 18 ng/mL.

The U.S. trial contained a third arm of a combination regimen of sirolimus, 2 mg per day, and full-dose PROGRAF; however, this regimen was associated with increased risk of wound-healing complications, renal function impairment, and insulin-dependent post-transplant diabetes mellitus, and is not recommended *[see Warnings and Precautions (5.10)]*.

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Clinical Review of NDA 210115 Prograf Granules (Tacrolimus for Oral Suspension)

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