CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

50708s053, 50709s045, 210115s005

Trade Name:	Prograf capsules, injection, oral suspension
Generic or Proper Name:	tacrolimus
Sponsor:	Astellas Pharma US, Inc.
Approval Date:	July 16, 2021
Indication:	For the prevention of rejection in lung transplantation

CENTER FOR DRUG EVALUATION AND RESEARCH

50708s053, 50709s045, 210115s005

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50708s053, 50709s045, 210115s005

APPROVAL LETTER

NDA 50708/S-053
NDA 50709/S-045
NDA 210115/S-005

SUPPLEMENT APPROVAL

Astellas Pharma US, Inc.
1 Astellas Way
Northbrook, IL 60062

Attention: Mary Jo Pritza, MPH, PharmD
Senior Director, Regulatory Affairs

Dear Dr. Pritza:

Please refer to your supplemental new drug applications (sNDA) dated December 15, 2020, received December 15, 2020, and your amendments, submitted under section 505(b)of the Federal Food, Drug, and Cosmetic Act (FDCA) for:

NDA 50708/S-053: Prograf (tacrolimus) capsules
NDA 50709/S-045: Prograf (tacrolimus) injection
NDA 210115/S-005: Prograf Granules (tacrolimus) oral suspension

These Prior Approval supplemental new drug applications provide updates to the USPI for Prograf (tacrolimus) use for the prevention of rejection in lung transplantation.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Prescribing Information, Patient Package Insert, and Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for these NDAs, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for these indications have orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Rhee, Regulatory Project Manager, at 301-796-2402.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Deputy Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

OZLEM A BELEN
07/16/2021 03:43:11 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50708s053, 50709s045, 210115s005

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROGRAF® safely and effectively. See full prescribing information for PROGRAF.

PROGRAF (tacrolimus) capsules, for oral use
PROGRAF (tacrolimus) injection, for intravenous use
PROGRAF Granules (tacrolimus for oral suspension)
Initial U.S. Approval: 1994

WARNING: MALIGNANCIES and SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.

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

RECENT MAJOR CHANGES

Indications and Usage (1.1)	7/2021
Dosage and Administration (2.2, 2.3)	7/2021
Warnings and Precautions (5.11)	12/2020

INDICATIONS AND USAGE

PROGRAF is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic liver, kidney, heart, or lung transplants, in combination with other immunosuppressants. (1.1)

DOSAGE AND ADMINISTRATION

ADULT		
Patient Population	Initial Oral Dosage (formulation)	Whole Blood Trough Concentration Range
Kidney Transplant		
With azathioprine	0.2 mg/kg/day capsules, divided in two doses, 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 capsules, divided in two doses, every 12 hours	Month 1-12: 4-11 ng/mL
Liver Transplant		
With corticosteroids only	0.1-0.15 mg/kg/day capsules, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL
Heart Transplant		
With azathioprine or MMF	0.075 mg/kg/day capsules, divided in two doses, every 12 hours	Month 1-3: 10-20 ng/mL Month ≥ 4: 5-15 ng/mL
Lung Transplant		
With azathioprine or MMF	0.075 mg/kg/day[1] capsules, divided in two doses, every 12 hours	Month 1-3: 10-15 ng/mL Month 4-12: 8-12 ng/mL

PEDIATRIC		
Patient Population	Initial Oral Dosage (formulation)	Whole Blood Trough Concentration Range
Kidney Transplant		
	0.3 mg/kg/day capsules or oral suspension, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL
Liver Transplant		
	0.15-0.2 mg/kg/day capsules or 0.2 mg/kg/day oral suspension, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL
Heart Transplant		
	0.3 mg/kg/day[2] capsules or oral suspension, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL
Lung Transplant		
	0.3 mg/kg/day[1, 2] capsules or oral suspension, divided in two doses, every 12 hours	Weeks 1-2: 10-20 ng/mL Week 2 to Month 12: 10-15 ng/mL

MMF= Mycophenolate mofetil

1. Patients with cystic fibrosis may require higher doses due to lower bioavailability.

2. Dose at 0.1 mg/kg/day if antibody induction treatment is administered.

- Intravenous (IV) use recommended for patients who cannot tolerate oral formulations (capsules or suspension). (2.1, 2.2)
- Administer capsules or suspension consistently with or without food. (2.1)
- Therapeutic drug monitoring is recommended. (2.1, 2.6)
- Avoid eating grapefruit or drinking grapefruit juice. (2.1)
- See dosage adjustments for African-American patients (2.2), hepatic and renal impaired. (2.4, 2.5)
- For complete dosing information, see the full prescribing information.

DOSAGE FORMS AND STRENGTHS

- Capsules: 0.5 mg, 1 mg and 5 mg (3)
- Injection: 5 mg/mL (3)
- For oral suspension: 0.2 mg, 1 mg unit-dose packets containing granules (3)

CONTRAINDICATIONS

- Hypersensitivity to tacrolimus or HCO-60 (polyoxyl 60 hydrogenated castor oil). (4)

WARNINGS AND PRECAUTIONS

- Not Interchangeable with Extended-Release Tacrolimus Products - Medication Errors: Instruct patients or caregivers to recognize the appearance of PROGRAF capsules. (5.3)
- New Onset Diabetes After Transplant: Monitor blood glucose. (5.4)
- Nephrotoxicity (acute and/or chronic): Reduce the dose; use caution with other nephrotoxic drugs. (5.5)
- Neurotoxicity: Including risk of Posterior Reversible Encephalopathy Syndrome (PRES); monitor for neurologic abnormalities; reduce or discontinue PROGRAF. (5.6)
- Hyperkalemia: Monitor serum potassium levels. Consider carefully before using with other agents also associated with hyperkalemia. (5.7)
- Hypertension: May require antihypertensive therapy. Monitor relevant drug-drug interactions. (5.8)
- Anaphylactic Reactions with IV formulation: Observe patients receiving PROGRAF injection for signs and symptoms of anaphylaxis. (5.9)
- Not recommended for use with sirolimus: Not recommended in liver and heart transplant due to increased risk of serious adverse reactions. (5.10)
- Myocardial Hypertrophy: Consider dose reduction/discontinuation. (5.13)
- Immunizations: Avoid live vaccines. (5.14)

- Pure Red Cell Aplasia: Consider discontinuation of PROGRAF. (5.15)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥ 15%) were abnormal renal function, hypertension, diabetes mellitus, fever, CMV infection, tremor, hyperglycemia, leukopenia, infection, anemia, bronchitis, pericardial effusion, urinary tract infection, constipation, diarrhea, headache, abdominal pain, insomnia, paresthesia, peripheral edema, nausea, hyperkalemia, hypomagnesemia, and hyperlipemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Mycophenolic Acid Products: Can increase MPA exposure after crossover from cyclosporine to PROGRAF; monitor for MPA-related adverse reactions and adjust MMF or MPA dose as needed. (7.1)
- Nelfinavir and Grapefruit Juice: Increased tacrolimus concentrations via CYP3A inhibition; avoid concomitant use. (7.2)
- CYP3A Inhibitors: Increased tacrolimus concentrations; monitor concentrations and adjust tacrolimus dose as needed. (5.11, 7.2)
- CYP3A4 Inducers: Decreased tacrolimus concentrations; monitor concentrations and adjust tacrolimus dose as needed. (5.11, 7.2)

---------- USE IN SPECIFIC POPULATIONS ----------

Pregnancy: Can cause fetal harm. Advise pregnant women of the potential risk to the fetus. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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, Heart, or Lung Transplant

PROGRAF® is indicated for the prophylaxis of organ rejection, in adult and pediatric patients receiving allogeneic kidney transplant *[see Clinical Studies (14.1)]*, liver transplant *[see Clinical Studies (14.2)]*, heart transplant *[see Clinical Studies (14.3)]*, or lung transplant *[see Clinical Studies (14.4)]* in combination with other immunosuppressants.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

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

PROGRAF capsules and PROGRAF Granules are not interchangeable or substitutable for 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. Changes between tacrolimus immediate-release and extended-release dosage forms must occur under physician supervision *[see Warnings and Precautions (5.3)]*.

Intravenous Formulation - Administration Precautions due to Risk of Anaphylaxis

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 oral therapy, the recommended starting doses should be initiated. PROGRAF Granules for oral suspension or PROGRAF capsules 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)]*.

General Administration Instructions

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.

Therapeutic drug monitoring (TDM) is recommended for all patients receiving PROGRAF *[see Dosage and Administration (2.6)]*.

2.2 Dosage Recommendations for Adult Kidney, Liver, Heart, or Lung Transplant Patients - Capsules and Injection

Capsules

If patients are able to tolerate oral therapy, the recommended oral starting doses should be initiated. The initial dose of PROGRAF capsules should be administered no sooner than 6 hours after transplantation in the liver, heart, or lung 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, heart, or lung 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 Dosage Recommendations and Whole Blood Trough Concentration Range in Adults

Patient Population	PROGRAF Capsules[1] Initial Oral Dosage	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[2]	0.1 mg/kg/day, divided in two doses, administered every 12 hours	Month 1-12: 4-11 ng/mL
Liver Transplant		
With corticosteroids only	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
Lung Transplant		
With azathioprine or MMF	0.075 mg/kg/day[3], divided in two doses, administered every 12 hours	Month 1-3: 10-15 ng/mL Month 4-12: 8-12 ng/mL

1. African-American patients may require higher doses compared to Caucasians *(see Table 2)*.
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)]*.
3. Patients with cystic fibrosis may require higher doses due to lower bioavailability *[see Clinical Pharmacology (12.3)]*.

Dosage should be titrated based on clinical assessments of rejection and tolerability. PROGRAF dosages lower 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 Use in Specific Populations (8.8) and Clinical Pharmacology (12.3)]*.

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

In lung transplantation, cystic fibrosis patients may have a reduced bioavailability of orally administered tacrolimus resulting in the need for higher doses to achieve target tacrolimus trough concentrations. Monitor tacrolimus trough concentrations and adjust the dose accordingly.

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 or liver transplant, 0.01 mg/kg/day in heart transplant, and 0.01-0.03 mg/kg/day in lung 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 pertains 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)]*.

2.3 Dosage Recommendations for Pediatric Kidney, Liver, Heart, or Lung 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 dosage 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 Dosage 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[1]	0.3 mg/kg/day capsules or oral suspension, divided in two doses, administered every 12 hours	Month 1-12: 5-20 ng/mL
Pediatric liver transplant patients[2]	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[1]	0.3 mg/kg/day[3] capsules or oral suspension, divided in two doses, administered every 12 hours	Month 1-12: 5-20 ng/mL
Pediatric lung transplant patients	0.3 mg/kg/day[3,4] capsules or oral suspension, divided in two doses, administered every 12 hours	Week 1-2: 10-20 ng/mL Week 2 to Month 12: 10-15 ng/mL

1. See *Clinical Pharmacology (12.3)*, PROGRAF Granules Pharmacokinetics in Pediatric Patients.
2. See *Clinical Studies (14.2)*, Liver Transplantation.
3. Dose at 0.1 mg/kg/day if antibody induction treatment is administered.
4. Patients with cystic fibrosis may require higher doses due to lower bioavailability *[see Clinical Pharmacology (12.3)]*.

In lung transplantation, cystic fibrosis patients may have a reduced bioavailability of orally administered tacrolimus resulting in the need for higher doses to achieve target tacrolimus trough concentrations. Monitor tacrolimus trough concentrations and adjust the dose accordingly.

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 of tacrolimus, therapeutic drug monitoring is recommended *[see Dosage and Administration (2.6)]*.

Intravenous Injection

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.

2.4 Dosage Adjustment in Patients with Renal Impairment

Due to its potential for nephrotoxicity, consider dosing PROGRAF at the lower end of the therapeutic dosing range in patients who have received a liver, heart, or lung 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 (2.2), Warnings and Precautions (5.5), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

2.5 Dosage Adjustment 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 (2.2), Warnings and Precautions (5.5), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

2.6 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.

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) anticoagulant. Heparin anticoagulation 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.

2.7 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).

2.8 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. Prepare and administer PROGRAF Granules as follows:

- 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 “f607” on

	capsule body • 1 mg, white color, imprinted in red “1 mg” on the capsule cap and “f617” on capsule body • 5 mg, grayish-red color, imprinted with white “5 mg” on the capsule cap and “f657” 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. 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, examine patients for skin changes; exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum 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. Monitor EBV serology during treatment.

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:

- Polyomavirus-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 overexposure to tacrolimus. PROGRAF is not interchangeable or

substitutable for tacrolimus extended-release products. Changes between tacrolimus immediate-release and extended-release dosage forms must occur under physician supervision. Instruct patients and caregivers to recognize the appearance of PROGRAF dosage forms *[see Dosage Forms and Strengths (3)]* and to confirm with the healthcare provider if a different product is dispensed.

5.4 New Onset Diabetes After Transplant

PROGRAF was shown to cause new onset diabetes mellitus in clinical trials of kidney, liver, heart, or lung 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.

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)]*. Monitor serum potassium levels periodically during treatment.

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. A rapid, sharp rise in tacrolimus levels has been reported after co-administration with a strong CYP3A4 inhibitor, clarithromycin, despite an initial reduction of tacrolimus dose. Early and frequent monitoring of tacrolimus whole blood trough levels is recommended *[see Drug Interactions (7.2)]*.

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 (7.2)]*.

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

Whenever possible, administer the complete complement of vaccines before transplantation and treatment with PROGRAF.

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.

Inactivated vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic during treatment with PROGRAF.

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 Warnings and Precautions (5.1)]*
- Serious Infections *[see 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)]*
- 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 reaction 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%
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%

	PROGRAF/AZA (N = 205)	Cyclosporine/AZA (N = 207)
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) (N = 403)	Cyclosporine (Group A) (N = 384)	Cyclosporine (Group B) (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 reaction 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 reaction 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, *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)

	Treatment Group	
Parameter	**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[1]	**PROGRAF/AZA**	**CsA/AZA**
Patients without pre-transplant history of diabetes mellitus	151	151
New onset PTDM[1], 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[1] post 1 year	1	0

Patients with PTDM[1] at 2 years	16/151 (11%)	5/151 (3%)

1. 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[1]	
	PROGRAF	Cyclosporine
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%)

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

1. 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.
2. 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[1]	US Trial		European Trial	
	PROGRAF/MMF	Cyclosporine/MMF	PROGRAF/AZA	Cyclosporine/AZA
Patients at risk[2]	75	83	132	138
New Onset PTDM[1]	10 (13%)	6 (7%)	29 (22%)	5 (4%)
Patients still on insulin at 1 year[3]	7 (9%)	1 (1%)	24 (18%)	4 (3%)

1. Use of insulin for 30 or more consecutive days without a prior history of insulin-dependent diabetes mellitus or non-insulin dependent diabetes mellitus.

2. Patients without pre-transplant history of diabetes mellitus.
3. 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: 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, 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 increased, 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
- 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

Lung Transplantation

Adverse reactions in lung transplant patients were similar to those in kidney, liver, or heart transplant patients treated with PROGRAF *[see Adverse Reactions (6.2)]*.

6.2 Postmarketing Experience

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
- 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, febrile neutropenia, pancytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pure red cell aplasia
- Infections: Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal; polyoma virus-associated nephropathy (PVAN) including graft loss
- Metabolic/Nutritional: Glycosuria, increased amylase including pancreatitis, weight decreased
- Miscellaneous: Feeling hot and cold, feeling jittery, hot flushes, multi-organ failure, primary graft dysfunction
- Musculoskeletal and Connective Tissue Disorders: Pain in extremity including Calcineurin-Inhibitor Induced Pain Syndrome (CIPS)
- Nervous System: Carpal tunnel syndrome, cerebral infarction, hemiparesis, leukoencephalopathy, mental disorder, mutism, posterior reversible encephalopathy syndrome (PRES), progressive multifocal leukoencephalopathy (PML), 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, optic neuropathy, blindness cortical, hearing loss including deafness, photophobia
- Urogenital: Acute renal failure, cystitis hemorrhagic, hemolytic-uremic syndrome

Postmarketing Adverse Reactions in Lung Transplantation

Based on U.S. Scientific Registry of Transplant Recipients (SRTR) data, published clinical trials, and postmarketing reports, the safety profile for lung transplant patients treated with PROGRAF is consistent with the safety profile in kidney, liver, and heart transplant patients treated with PROGRAF. The primary adverse reactions described include renal dysfunction, infection, diabetes, gastrointestinal disturbances (e.g., diarrhea), hypertension, and neurological events (e.g., tremor). As expected, lung transplant patients have a higher incidence of pulmonary complications (e.g., pneumonia, bronchiolitis obliterans syndrome) than other solid organ transplant patients, which is in part due to the underlying disease and to the nature of the transplanted organ.

7 DRUG INTERACTIONS

7.1 Mycophenolic Acid

When PROGRAF is prescribed with a given dose of a mycophenolic acid (MPA) product, exposure to MPA is higher with PROGRAF co-administration than with cyclosporine co-administration with MPA, because cyclosporine interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Monitor for MPA-associated adverse reactions and reduce the dose of concomitantly administered mycophenolic acid products as needed.

7.2 Effects of Other Drugs on PROGRAF

Table 15 displays the effects of other drugs on PROGRAF.

Table 15: Effects of Other Drugs/Substances on PROGRAF[1]

Drug/Substance Class or Name	Drug Interaction Effect	Recommendations
Grapefruit or grapefruit juice[2]	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.11, 5.12)]*.	Avoid grapefruit or grapefruit juice.
Strong CYP3A Inducers[3]: Antimycobacterials (e.g., rifampin, rifabutin), anticonvulsants (e.g., phenytoin, carbamazepine and phenobarbital), St John's Wort	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see Warnings and Precautions (5.11)]*.	Increase PROGRAF dose and monitor tacrolimus whole blood trough concentrations *[see Dosage and Administration (2.2, 2.6) and Clinical Pharmacology (12.3)]*.
Strong CYP3A Inhibitors[3]: Protease inhibitors (e.g, nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone, letermovir, *Schisandra sphenanthera* extracts	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation). A rapid, sharp rise in tacrolimus levels may occur early, despite an immediate reduction of tacrolimus dose *[see Warnings and Precautions (5.6, 5.11, 5.12)]*.	Reduce PROGRAF dose (for voriconazole and posaconazole, give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations *[see Dosage and Administration (2.2, 2.6) and Clinical Pharmacology (12.3)]*. Early and frequent monitoring of tacrolimus whole blood trough levels should start within 1-3 days and continue monitoring as necessary *[see Warnings and Precautions (5.11)]*.
Mild or Moderate CYP3A Inhibitors: Clotrimazole, antibiotics (e.g., erythromycin, fluconazole), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl estradiol, cimetidine, lansoprazole and omeprazole	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.11, 5.12)]*.	Monitor tacrolimus whole blood trough concentrations and reduce PROGRAF dose if needed *[see Dosage and Administration (2.2, 2.6) and Clinical Pharmacology (12.3)]*.
Other drugs, such as: Magnesium and aluminum hydroxide antacids Metoclopramide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.11, 5.12)]*.	Monitor tacrolimus whole blood trough concentrations and reduce PROGRAF dose if needed *[see Dosage and Administration (2.2, 2.6) and Clinical Pharmacology (12.3)]*.
Mild or Moderate CYP3A Inducers Methylprednisolone, prednisone	May decrease tacrolimus concentrations.	Monitor tacrolimus whole blood trough concentrations and adjust PROGRAF dose if needed *[see Dosage and Administration (2.2, 2.6)]*.

1. PROGRAF dosage adjustment recommendation based on observed effect of coadministered drug on tacrolimus exposures *[see Clinical Pharmacology (12.3)]*, literature reports of altered tacrolimus exposures, or the other drug's known CYP3A inhibitor/inducer status.
2. High dose or double strength grapefruit juice is a *strong* CYP3A inhibitor; low dose or single strength grapefruit juice is a *moderate* CYP3A inhibitor.

3. Strong CYP3A inhibitor/inducer, based on reported effect on exposures to tacrolimus along with supporting *in vitro* CYP3A inhibitor/inducer data, or based on drug-drug interaction studies with midazolam (sensitive CYP3A probe substrate).

Direct Acting Antiviral (DAA) Therapy

The pharmacokinetics of tacrolimus may be impacted by changes in liver function during DAA therapy, related to clearance of HCV virus. Close monitoring and potential dose adjustment of PROGRAF is warranted to ensure continued efficacy and safety *[see Dosage and Administration (2.2, 2.6)]*.

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

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 16. 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[1]	**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%[2]	5%

1. Includes multiple births and terminations.
2. 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 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 Use in Specific Populations (8.1) and 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) and 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, heart, and lung transplant patients.

Liver Transplantation

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 (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

Kidney and Heart Transplantation

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 (2.3) and Clinical Pharmacology (12.3)]*.

Lung Transplantation

The use of PROGRAF capsules and PROGRAF Granules in pediatric lung transplantation is supported by the experience in the U.S. Scientific Registry of Transplant Recipients (SRTR) including 450 pediatric patients receiving tacrolimus immediate-release products in combination with mycophenolate mofetil and 72 pediatric patients receiving tacrolimus immediate-release products in combination with azathioprine between 1999-2017.

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 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 (2.4) and Clinical Pharmacology (12.3)]*.

8.7 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 (2.5) and Clinical Pharmacology (12.3)]*.

8.8 Race or Ethnicity

African-American patients may need to be titrated to higher dosages to attain comparable trough concentrations compared to Caucasian patients *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

African-American and Hispanic patients are at increased risk for new onset diabetes after transplant. Monitor blood glucose concentrations and treat appropriately *[see Warnings and Precautions (5.4)]*.

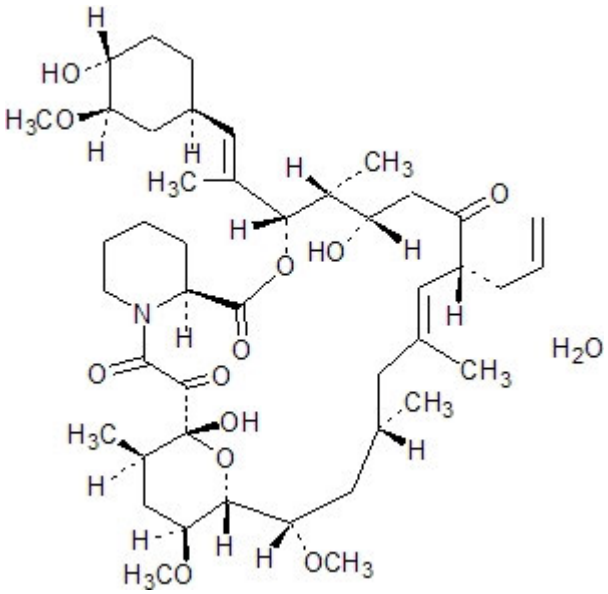
10 OVERDOSAGE

Limited overdosage experience is available. Acute overdosages of up to 30 times the intended dose have been reported. Almost all cases have been asymptomatic and all patients recovered with no sequelae. Acute overdosage was sometimes followed by adverse reactions consistent with those reported with the use of PROGRAF *[see Adverse Reactions (6.1, 6.2)]*, including tremors, abnormal renal function, hypertension, and peripheral edema; in one case of acute overdosage, transient urticaria and lethargy were observed. Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.

11 DESCRIPTION

Tacrolimus, previously known as FK506, is the active ingredient in PROGRAF. Tacrolimus is a calcineurin-inhibitor immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)], 4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,26a*R**]] - 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-*c*][1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.

The chemical structure of tacrolimus is:



Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}•H_2O$ and a formula weight of 822.03. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

PROGRAF is available for oral administration as capsules (tacrolimus capsules USP) containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus USP. Inactive ingredients include croscarmellose sodium NF, hypromellose USP, lactose monohydrate NF, and magnesium stearate NF. The 0.5 mg capsule shell contains ferric oxide NF, gelatin NF and titanium dioxide USP, the 1 mg capsule shell contains gelatin NF and titanium dioxide USP, and the 5 mg capsule shell contains ferric oxide NF, gelatin NF, and titanium dioxide USP.

PROGRAF is also available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus USP in 1 mL for administration by intravenous infusion only. Each mL contains the following inactive

ingredients: dehydrated alcohol USP, 80.0% v/v and polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg. PROGRAF injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use.

PROGRAF Granules is available for oral administration as a suspension containing the equivalent of 0.2 mg or 1 mg of anhydrous tacrolimus USP. Inactive ingredients include croscarmellose sodium NF, hypromellose USP, and lactose monohydrate NF.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (a ubiquitous mammalian intracellular enzyme) is then formed, after which the phosphatase activity of calcineurin is inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT), and nuclear factor kappa-light-chain enhancer of activated B-cells (NF-κB).

Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony-stimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation, as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

12.3 Pharmacokinetics

Tacrolimus activity is primarily due to the parent drug. The pharmacokinetic parameters (mean ± S.D.) of tacrolimus have been determined following intravenous (IV) and/or oral (PO) administration in healthy volunteers, and in kidney transplant, liver transplant, and heart transplant patients (Table 17).

Table 17. Pharmacokinetics Parameters (mean ± S.D.) of Tacrolimus in Healthy Volunteers and Patients

Population	N	Route (Dose)	Parameters					
			C_{max} (ng/mL)	T_{max} (hr)	AUC (ng•hr/mL)	$t_{1/2}$ (hr)	CL (L/hr/kg)	V (L/kg)
Healthy Volunteers	8	IV (0.025 mg/kg/4 hr)	[1]	[1]	652[2] ± 156	34.2 ± 7.7	0.040 ± 0.009	1.91 ± 0.31
	30	PO (5 mg) (granules)	35.6 ± 10.9	1.3 ± 0.5	320[2] ± 164	32.1 ± 5.9	[3]	[3]
		PO (5 mg) (capsules)	28.8 ± 8.9	1.5 ± 0.7	266[2] ± 95	32.3 ± 8.8	[3]	[3]
Kidney Transplant Patients	26	IV (0.02 mg/kg/12 hr)	[1]	[1]	294[2] ± 262	18.8 ± 16.7	0.083 ± 0.050	1.41 ± 0.66
		PO (0.2 mg/kg/day)	19.2 ± 10.3	3.0	203[2] ± 42	[3]	[3]	[3]
		PO (0.3 mg/kg/day)	24.2 ± 15.8	1.5	288[2] ± 93	[3]	[3]	[3]
Liver	17	IV (0.05 mg/kg/12 hr)	[1]	[1]	3300[2] ±	11.7 ±	0.053 ±	0.85 ±

Population	N	Route (Dose)	Parameters					
			C_{max} (ng/mL)	T_{max} (hr)	AUC (ng•hr/mL)	$t_{1/2}$ (hr)	CL (L/hr/kg)	V (L/kg)
Transplant Patients					2130	3.9	0.017	0.30
		PO (0.3 mg/kg/day)	68.5 ± 30.0	2.3 ± 1.5	519[2] ± 179	[3]	[3]	[3]
Heart Transplant Patients	11	IV (0.01 mg/kg/day as a continuous infusion)	[1]	[1]	954[4] ± 334	23.6 ± 9.22	0.051 ± 0.015	[3]
	11	PO (0.075 mg/kg/day)[5]	14.7 ± 7.79	2.1 [0.5-6.0][6]	82.7[7] ± 63.2	[1]	[3]	[3]
	14	PO (0.15 mg/kg/day)[5]	24.5 ± 13.7	1.5 [0.4-4.0][6]	142[7] ± 116	[1]	[3]	[3]

1. Not applicable
2. $AUC_{0\text{-}inf}$
3. Not available
4. $AUC_{0\text{-}t}$
5. Determined after the first dose
6. Median [range]
7. $AUC_{0\text{-}12}$

Due to intersubject variability in tacrolimus pharmacokinetics, individualization of the dosing regimen is necessary for optimal therapy *[see Dosage and Administration (2.6)]*. Pharmacokinetic data indicate that whole blood concentrations rather than plasma concentrations serve as the more appropriate sampling compartment to describe tacrolimus pharmacokinetics.

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. The absolute bioavailability of tacrolimus was 17 ± 10% in adult kidney transplant patients (N = 26), 22 ± 6% in adult liver transplant patients (N = 17), 23 ± 9% in adult heart transplant patients (N = 11) and 18 ± 5% in healthy volunteers (N = 16).

A single dose trial conducted in 32 healthy volunteers established the bioequivalence of the 1 mg and 5 mg capsules. Another single dose trial in 32 healthy volunteers established the bioequivalence of the 0.5 mg and 1 mg capsules. Tacrolimus maximum blood concentrations (C_{max}) and area under the curve (AUC) appeared to increase in a dose-proportional fashion in 18 fasted healthy volunteers receiving a single oral dose of 3, 7, and 10 mg.

In 18 kidney transplant patients, tacrolimus trough concentrations from 3 to 30 ng/mL measured at 10-12 hours post-dose (C_{min}) correlated well with the AUC (correlation coefficient 0.93). In 24 liver transplant patients over a concentration range of 10 to 60 ng/mL, the correlation coefficient was 0.94. In 25 heart transplant patients over a concentration range of 2 to 24 ng/mL, the correlation coefficient was 0.89 after an oral dose of 0.075 or 0.15 mg/kg/day at steady-state.

In a healthy volunteer adult study, the systemic exposure to tacrolimus (AUC) for PROGRAF Granules was approximately 16% higher than that for PROGRAF capsules when administered as single doses. If pediatric patients are converted between formulations, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

Food Effects

The rate and extent of tacrolimus absorption were greatest under fasted conditions. The presence and composition of food decreased both the rate and extent of tacrolimus absorption when administered to 15 healthy volunteers.

The effect was most pronounced with a high-fat meal (848 kcal, 46% fat): mean AUC and C_{max} were decreased 37% and 77%, respectively; T_{max} was lengthened 5-fold. A high-carbohydrate meal (668 kcal, 85% carbohydrate) decreased mean AUC and mean C_{max} by 28% and 65%, respectively.

In healthy volunteers (N = 16), the time of the meal also affected tacrolimus bioavailability. When given immediately following the meal, mean C_{max} was reduced 71%, and mean AUC was reduced 39%, relative to the fasted condition. When administered 1.5 hours following the meal, mean C_{max} was reduced 63%, and mean AUC was reduced 39%, relative to the fasted condition.

In 11 liver transplant patients, PROGRAF administered 15 minutes after a high fat (400 kcal, 34% fat) breakfast, resulted in decreased AUC (27 ± 18%) and C_{max} (50 ± 19%), as compared to a fasted state.

PROGRAF capsules should be taken consistently every day either with or without food because the presence and composition of food decreases the bioavailability of PROGRAF *[see Dosage and Administration (2.1)]*.

Distribution

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a U.S. trial, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12 to 67).

Elimination

Metabolism

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation *in vitro*. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In *in vitro* studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

Excretion

The mean clearance following IV administration of tacrolimus is 0.040, 0.083, 0.053, and 0.051 L/hr/kg in healthy volunteers, adult kidney transplant patients, adult liver transplant patients, and adult heart transplant patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine.

In a mass balance study of IV-administered radiolabeled tacrolimus to 6 healthy volunteers, the mean recovery of radiolabel was 77.8 ± 12.7%. Fecal elimination accounted for 92.4 ± 1.0% and the elimination half-life based on radioactivity was 48.1 ± 15.9 hours whereas it was 43.5 ± 11.6 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.029 ± 0.015 L/hr/kg and clearance of tacrolimus was 0.029 ± 0.009 L/hr/kg. When administered PO, the mean recovery of the radiolabel was 94.9 ± 30.7%. Fecal elimination accounted for 92.6 ± 30.7%, urinary elimination accounted for 2.3 ± 1.1% and the elimination half-life based on radioactivity was 31.9 ± 10.5 hours whereas it was 48.4 ± 12.3 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.226 ± 0.116 L/hr/kg and clearance of tacrolimus was 0.172 ± 0.088 L/hr/kg.

Specific Populations

Pediatric Patients

PROGRAF capsules Pharmacokinetics in Pediatric Patients

Pharmacokinetics of tacrolimus have been studied in liver transplantation patients, 0.7 to 13.2 years of age. Following IV administration of a 0.037 mg/kg/day dose to 12 pediatric patients, mean terminal half-life, volume of distribution and clearance were 11.5 ± 3.8 hours, 2.6 ± 2.1 L/kg and 0.138 ± 0.071 L/hr/kg, respectively. Following oral administration to 9 patients, mean AUC and C_{max} were 337 ± 167 ng·hr/mL and 48.4 ± 27.9 ng/mL, respectively. The absolute bioavailability was 31 ± 24%.

Pharmacokinetics of tacrolimus have also been studied in kidney transplantation patients, 8.2 ± 2.4 years of age. Following IV infusion of a 0.06 mg/kg/day to 12 pediatric patients (8 male and 4 female), mean terminal half-life and clearance were 10.2 ± 5.0 hours and 0.12 ± 0.04 L/hr/kg, respectively. Following oral administration to the same patients, mean AUC and C_{max} were 181 ± 65 ng·hr/mL and 30 ± 11 ng/mL, respectively. The absolute bioavailability was 19 ± 14%.

Whole blood trough concentrations from 31 patients less than 12 years old showed that pediatric patients needed higher doses than adults to achieve similar tacrolimus trough concentrations *[see Dosage and Administration (2.3)]*.

PROGRAF Granules Pharmacokinetics in Pediatric Patients

A multicenter, open-label, single arm, pharmacokinetic study (OPTION, NCT01371331) was conducted using tacrolimus granules for oral suspension in pediatric patients undergoing de novo liver, kidney, or heart transplant. After an initial 24-hour continuous IV infusion of tacrolimus (0.025 mg/kg/hour) for 12 hours to 4 days, oral PROGRAF Granules were dosed at 0.3 mg/kg/day in divided doses twice daily. Tacrolimus whole blood trough concentrations ranged from 5-15 ng/mL for the first month post-transplant, and 5-10 ng/mL thereafter. Two pharmacokinetic (PK) profiles, AUC, C_{max}, T_{max} and C_{trough}, were taken after the first oral dose (Day 1) and at steady state (Day 7). Subsequent oral doses of PROGRAF Granules were adjusted based on clinical evidence of efficacy, the whole-blood trough levels, and/or occurrence of adverse events. Of 52 patients enrolled, thirty-eight (38) had an evaluable PK profile. The mean pediatric age was 6.1 years for heart transplant, 1.1 years for liver transplant and 3.6 years for kidney transplant. Summary results of PK parameters are presented in Table 18.

Table 18. Summary of Whole Blood PK Parameters of Tacrolimus after Administration of PROGRAF Granules in Pediatric Patients

Population	N (age range)		Parameters			
			AUC_{tau} [hr*ng/mL] mean ± SD	**C_{max} [ng/mL]** mean ± SD	**T_{max} [hr]** mean ± SD	**C_{trough} [ng/mL]** mean ± SD
Heart Transplant Patients	12 (0.58-13 years)	Day 1	224.13 ± 114.30	45.61 ± 19.55	2.95 ± 4.33	12.60 ± 13.40
		Day 7	165.17 ± 39.12	32.69 ± 9.78	0.84 ± 0.44	7.57 ± 1.80
Liver Transplant Patients	14 (0.33-12 years)	Day 1	210.56 ± 84.01	25.11 ± 10.78	2.73 ± 1.84	13.41 ± 7.11
		Day 7	195.08 ± 94.63	30.52 ± 19.35	1.71 ± 1.12	9.71 ± 4.03
Kidney Transplant Patients	12 (2.42-11 years)	Day 1	97.40 ± 36.77	18.04 ± 8.10	1.78 ± 0.88	3.54 ± 1.45
		Day 7	208.32 ± 68.75	36.63 ± 13.97	1.09 ± 0.61	8.92 ± 3.59

Renal and Hepatic Impaired Patients

The mean pharmacokinetic parameters for tacrolimus following single administrations to adult patients with renal and hepatic impairment are given in Table 19.

Table 19. Pharmacokinetics in Renal and Hepatic Impaired Adult Patients

Population (No. of Patients)	Dose	AUC_{0-t} (ng·hr/mL)	$t_{1/2}$ (hr)	V (L/kg)	Cl (L/hr/kg)
Renal Impairment (n = 12)	0.02 mg/kg/4 hr IV	393 ± 123 (t = 60 hr)	26.3 ± 9.2	1.07 ± 0.20	0.038 ± 0.014
Mild Hepatic Impairment (n = 6)	0.02 mg/kg/4 hr IV	367 ± 107 (t = 72 hr)	60.6 ± 43.8 Range: 27.8 – 141	3.1 ± 1.6	0.042 ± 0.02
	7.7 mg PO	488 ± 320 (t = 72 hr)	66.1 ± 44.8 Range: 29.5 – 138	3.7 ± 4.7[1]	0.034 ± 0.019[1]
Severe Hepatic Impairment (n = 6, IV)	0.02 mg/kg/4 hr IV (n = 2)	762 ± 204 (t = 120 hr)	198 ± 158 Range: 81 – 436	3.9 ± 1.0	0.017 ± 0.013
	0.01 mg/kg/8 hr IV (n = 4)	289 ± 117 (t = 144 hr)			
(n = 5, PO)[2]	8 mg PO (n = 1)	658 (t = 120 hr)	119 ± 35 Range: 85 – 178	3.1 ± 3.4[1]	0.016 ± 0.011[1]
	5 mg PO (n = 4) 4 mg PO (n = 1)	533 ± 156 (t = 144 hr)			

1. Corrected for bioavailability
2. 1 patient did not receive the PO dose

Patients with Renal Impairment

Tacrolimus pharmacokinetics, following a single IV administration, were determined in 12 patients (7 not on dialysis and 5 on dialysis, serum creatinine of 3.9 ± 1.6 and 12.0 ± 2.4 mg/dL, respectively) prior to their kidney transplant. The pharmacokinetic parameters obtained were similar for both groups. The mean clearance of tacrolimus in patients with renal dysfunction was similar to that in normal volunteers (Table 19) *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

Tacrolimus pharmacokinetics have been determined in six patients with mild hepatic dysfunction (mean Pugh score: 6.2) following single IV and oral administrations. The mean clearance of tacrolimus in patients with mild hepatic dysfunction was not substantially different from that in normal volunteers (see previous table). Tacrolimus pharmacokinetics were studied in 6 patients with severe hepatic dysfunction (mean Pugh score: > 10). The mean clearance was substantially lower in patients with severe hepatic dysfunction, irrespective of the route of administration *[see Dosage and Administration (2.5) and Use in Specific Populations (8.7)]*.

Patients with Cystic Fibrosis

Lower bioavailability of tacrolimus has been reported in patients with cystic fibrosis *[see Dosage and Administration (2.2, 2.3)]*.

Racial or Ethnic Groups

The pharmacokinetics of tacrolimus have been studied following single IV and oral administration of PROGRAF to 10 African-American, 12 Latino-American, and 12 Caucasian healthy volunteers. There were no significant pharmacokinetic differences among the three ethnic groups following a 4-hour IV infusion of 0.015 mg/kg. However, after single oral administration of 5 mg, mean (± SD) tacrolimus C_{max} in African-Americans (23.6 ± 12.1 ng/mL) was significantly lower

than in Caucasians (40.2 ± 12.6 ng/mL) and the Latino-Americans (36.2 ± 15.8 ng/mL) ($p < 0.01$). Mean $AUC_{0\text{-}inf}$ tended to be lower in African-Americans (203 ± 115 ng·hr/mL) than Caucasians (344 ± 186 ng·hr/mL) and Latino-Americans (274 ± 150 ng·hr/mL). The mean (± SD) absolute oral bioavailability (F) in African-Americans (12 ± 4.5%) and Latino-Americans (14 ± 7.4%) was significantly lower than in Caucasians (19 ± 5.8%, $p = 0.011$). There was no significant difference in mean terminal $T_{1/2}$ among the three ethnic groups (range from approximately 25 to 30 hours). A retrospective comparison of African-American and Caucasian kidney transplant patients indicated that African-American patients required higher tacrolimus doses to attain similar trough concentrations *[see Dosage and Administration (2.2)]*.

Male and Female Patients

A formal trial to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted, however, there was no difference in dosing by gender in the kidney transplant trial. A retrospective comparison of pharmacokinetics in healthy volunteers, and in kidney, liver, and heart transplant patients indicated no gender-based differences.

Drug Interaction Studies

Frequent monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when concomitant use of the following drugs with tacrolimus is initiated or discontinued *[see Drug Interactions (7)]*.

- *Telaprevir:* In a single-dose study in 9 healthy volunteers, co-administration of tacrolimus (0.5 mg single dose) with telaprevir (750 mg three times daily for 13 days) increased the tacrolimus dose-normalized C_{max} by 9.3-fold and AUC by 70-fold compared to tacrolimus alone *[see Drug Interactions (7.2)]*.
- *Boceprevir:* In a single-dose study in 12 subjects, co-administration of tacrolimus (0.5 mg single dose) with boceprevir (800 mg three times daily for 11 days) increased tacrolimus C_{max} by 9.9-fold and AUC by 17-fold compared to tacrolimus alone *[see Drug Interactions (7.2)]*.
- *Nelfinavir:* Based on a clinical study of 5 liver transplant recipients, co-administration of tacrolimus with nelfinavir increased blood concentrations of tacrolimus significantly and, as a result, a reduction in the tacrolimus dose by an average of 16-fold was needed to maintain mean trough tacrolimus blood concentrations of 9.7 ng/mL. It is recommended to avoid concomitant use of PROGRAF and nelfinavir unless the benefits outweigh the risks *[see Drug Interactions (7.2)]*.
- *Rifampin:* In a study of 6 normal volunteers, a significant decrease in tacrolimus oral bioavailability (14 ± 6% vs. 7 ± 3%) was observed with concomitant rifampin administration (600 mg). In addition, there was a significant increase in tacrolimus clearance (0.036 ± 0.008 L/hr/kg vs. 0.053 ± 0.010 L/hr/kg) with concomitant rifampin administration *[see Drug Interactions (7.2)]*.
- *Magnesium and Aluminum-hydroxide:* In a single-dose crossover study in healthy volunteers, co-administration of tacrolimus and magnesium-aluminum-hydroxide resulted in a 21% increase in the mean tacrolimus AUC and a 10% decrease in the mean tacrolimus C_{max} relative to tacrolimus administration alone *[see Drug Interactions (7.2)]*.
- *Ketoconazole:* In a study of 6 normal volunteers, a significant increase in tacrolimus oral bioavailability (14 ± 5% vs. 30 ± 8%) was observed with concomitant ketoconazole administration (200 mg). The apparent oral clearance of tacrolimus during ketoconazole administration was significantly decreased compared to tacrolimus alone (0.430 ± 0.129 L/hr/kg vs. 0.148 ± 0.043 L/hr/kg). Overall, IV clearance of tacrolimus was not significantly changed by ketoconazole co-administration, although it was highly variable between patients *[see Drug Interactions (7.2)]*.
- *Voriconazole* (see complete prescribing information for VFEND)*:* Repeat oral dose administration of voriconazole (400 mg every 12 hours for one day, then 200 mg every 12 hours for 6 days) increased tacrolimus (0.1 mg/kg single dose) C_{max} and $AUC\tau$ in healthy subjects by an average of 2-fold (90% CI: 1.9, 2.5) and 3-fold (90% CI: 2.7, 3.8), respectively *[see Drug Interactions (7.2)]*.
- *Posaconazole* (see complete prescribing information for Noxafil)*:* Repeat oral administration of posaconazole (400 mg twice daily for 7 days) increased tacrolimus (0.05 mg/kg single dose) C_{max} and AUC in healthy subjects

by an average of 2-fold (90% CI: 2.01, 2.42) and 4.5-fold (90% CI 4.03, 5.19), respectively *[see Drug Interactions (7.2)]*.

- *Caspofungin* (see complete prescribing information for CANCIDAS)*:* Caspofungin reduced the blood AUC_{0-12} of tacrolimus by approximately 20%, peak blood concentration (C_{max}) by 16%, and 12-hour blood concentration (C_{12hr}) by 26% in healthy adult subjects when tacrolimus (2 doses of 0.1 mg/kg 12 hours apart) was administered on the 10th day of CANCIDAS 70 mg daily, as compared to results from a control period in which tacrolimus was administered alone *[see Drug Interactions (7.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in male and female rats and mice. In the 80-week mouse oral study and in the 104-week rat oral study, no relationship of tumor incidence to tacrolimus dosage was found. The highest dose used in the mouse was 3.0 mg/kg/day (0.9 to 2.2 times the AUC at clinical doses of 0.075 to 0.2 mg/kg/day) and in the rat was 5.0 mg/kg/day (0.265 to 0.65 times the AUC at clinical doses of 0.075 to 0.2 mg/kg/day) *[see Warnings and Precautions (5.1)]*.

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03% - 3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m^2/day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high-dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high-dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment). The relevance of topical administration of tacrolimus in the setting of systemic tacrolimus use is unknown.

The implications of these carcinogenicity studies to the human condition are limited; doses of tacrolimus were administered that likely induced immunosuppression in these animals, impairing their immune system's ability to inhibit unrelated carcinogenesis.

Mutagenesis

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Impairment of Fertility

Tacrolimus, subcutaneously administered to male rats at paternally toxic doses of 2 mg/kg/day (1.6 to 4.3 times the recommended clinical dose range [0.2 to 0.075 mg/kg/day] on a mg/m^2 basis) or 3 mg/kg/day (2.4 to 6.4 times the recommended clinical dose range), resulted in a dose-related decrease in sperm count. Tacrolimus, administered orally at 1.0 mg/kg (0.8 to 2.2 times the clinical dose range) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre- and post-implantation loss and increased numbers of undelivered and nonviable pups. When administered at 3.2 mg/kg (2.6 to 6.9 times the clinical dose range based on body surface area), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

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 survivals were 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 loss 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[1]				
	N	MEAN	SD	MEDIAN	Treatment Difference with Group C (99.2% CI[2])
(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					

1. 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.
2. 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[1])	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				

1. 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[1]) 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)

1. 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.

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)[1]		
	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)			

1. 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])		1.9% (-5.2%, 9.0%)

1. 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.

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

Time	Median (P10-P90[1]) 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)

1. 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)[1]		
	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)

1. 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 the 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 are often 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 (2.3)]*. 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 loss 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[1])	-8.4% (-22.7%, 6.0%)	

1. 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 U.S., 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)]*.

14.4 Lung Transplantation

The efficacy and safety of PROGRAF-based immunosuppression in primary lung transplantation were assessed in a non-interventional (observational) study using data from the U.S. Scientific Registry of Transplant Recipients (SRTR). The study analyzed outcomes based on discharge immunosuppression treatment regimen in recipients of a primary lung transplant between 1999 and 2017 who were alive at the time of discharge. In adult patients receiving tacrolimus immediate-release products in combination with MMF (n=15,478) or tacrolimus immediate-release products in combination with AZA (n=4,263), the one-year graft survival estimates from time of discharge were 90.9% and 90.8%, respectively. In pediatric patients receiving tacrolimus immediate-release products in combination with MMF (n= 450) or tacrolimus immediate-release products in combination with AZA (n=72), the one-year graft survival estimates from time of discharge were 91.7% and 84.7%, respectively.

15 REFERENCES

1. “OSHA Hazardous Drugs.” OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 PROGRAF (tacrolimus) Capsules, USP

Strength	**0.5 mg** (containing the equivalent of 0.5 mg anhydrous tacrolimus USP)	**1 mg** (containing the equivalent of 1 mg anhydrous tacrolimus USP)	**5 mg** (containing the equivalent of 5 mg anhydrous tacrolimus USP)
Shape/color	oblong/light yellow	oblong/white	oblong/grayish red
Branding on capsule cap/body	f 607	f 617	f 657
100 count bottle	**NDC 0469-0607-73**	**NDC 0469-0617-73**	**NDC 0469-0657-73**
10 blister cards of 10 capsules		**NDC 0469-0617-11**	**NDC 0469-0657-11**

Note: PROGRAF capsules USP are not filled to maximum capsule capacity. Capsule contains labeled amount.

Store and Dispense

Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

16.2 PROGRAF (tacrolimus) Injection

(for Intravenous infusion only)

NDC 0469-3016-01 Product Code 301601
5 mg/mL (equivalent of 5 mg of anhydrous tacrolimus USP per mL) supplied as a sterile solution in a 1 mL ampule, in boxes of 10 ampules

Store and Dispense

Store between 5°C and 25°C (41°F and 77°F).

16.3 PROGRAF Granules (tacrolimus for oral suspension)

Strength	**0.2 mg** (containing the equivalent of 0.2 mg anhydrous tacrolimus USP)	**1 mg** (containing the equivalent of 1 mg anhydrous tacrolimus USP)
Shape/color	White granules	White granules
1 carton containing 50 packets	**NDC 0469-1230-50**	**NDC 0469-1330-50**

Store and Dispense

Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

16.4 Handling and Disposal

Tacrolimus can cause fetal harm. PROGRAF capsules should not be opened or crushed. Wearing disposable gloves is recommended during dilution of the injection or when preparing the oral suspension in the hospital and when wiping any spills. Avoid inhalation or direct contact with skin or mucous membranes of the powder or granules contained in PROGRAF capsules and PROGRAF Granules, respectively. If such contact occurs, wash the skin thoroughly with soap

and water; if ocular contact occurs, rinse eyes with water. In case a spill occurs, wipe the surface with a wet paper towel. Follow applicable special handling and disposal procedures[1].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

17.1 Administration

Advise the patient or caregiver to:

- Inspect their PROGRAF medicine when they receive a new prescription and before taking it. If the appearance of the capsule is not the same as usual, or if dosage instructions have changed, advise patients to contact their healthcare provider as soon as possible to make sure that they have the right medicine. Other tacrolimus products cannot be substituted for PROGRAF.
- Take PROGRAF at the same 12-hour intervals every day to achieve consistent blood concentrations.
- Take PROGRAF consistently either with or without food because the presence and composition of food decreases the bioavailability of PROGRAF.
- Not to eat grapefruit or drink grapefruit juice in combination with PROGRAF *[see Drug Interactions (7.2)]*.
- If the patient is receiving PROGRAF Granules, advise that the dose should be given immediately after preparation and not to save the dose for later. Advise the caregiver to carefully read the Instructions for Use.

17.2 Development of Lymphoma and Other Malignancies

Inform patients they are at increased risk of developing lymphomas and other malignancies, particularly of the skin, due to immunosuppression. Advise patients to limit exposure to sunlight and ultraviolet (UV) light by wearing protective clothing and using a broad spectrum sunscreen with a high protection factor *[see Warnings and Precautions (5.1)]*.

17.3 Increased Risk of Infection

Inform patients they are at increased risk of developing a variety of infections, including opportunistic infections, due to immunosuppression and to contact their physician if they develop any symptoms of infection such as fever, sweats or chills, cough or flu-like symptoms, muscle aches, or warm, red, painful areas on the skin *[see Warnings and Precautions (5.2)]*.

17.4 New Onset Diabetes After Transplant

Inform patients that PROGRAF can cause diabetes mellitus and should be advised to contact their physician if they develop frequent urination, increased thirst, or hunger *[see Warnings and Precautions (5.4)]*.

17.5 Nephrotoxicity

Inform patients that PROGRAF can have toxic effects on the kidney that should be monitored. Advise patients to attend all visits and complete all blood tests ordered by their medical team *[see Warnings and Precautions (5.5)]*.

17.6 Neurotoxicity

Inform patients that they are at risk of developing adverse neurologic reactions including seizure, altered mental status, and tremor. Advise patients to contact their physician should they develop vision changes, delirium, or tremors *[see Warnings and Precautions (5.6)]*.

17.7 Hyperkalemia

Inform patients that PROGRAF can cause hyperkalemia. Monitoring of potassium levels may be necessary, especially with concomitant use of other drugs known to cause hyperkalemia *[see Warnings and Precautions (5.7)]*.

17.8 Hypertension

Inform patients that PROGRAF can cause high blood pressure which may require treatment with antihypertensive therapy. Advise patients to monitor their blood pressure *[see Warnings and Precautions (5.8)]*.

17.9 Drug Interactions

Instruct patients to tell their healthcare providers when they start or stop taking any medicines, including prescription medicines and nonprescription medicines, natural or herbal remedies, nutritional supplements, and vitamins. Advise patients to avoid grapefruit and grapefruit juice *[see Drug Interactions (7)]*.

17.10 Pregnancy, Lactation and Infertility

Inform women of childbearing potential that PROGRAF can harm the fetus. Instruct male and female patients to discuss with their healthcare provider family planning options including appropriate contraception. Also, discuss with pregnant patients the risks and benefits of breastfeeding their infant *[see Use in Specific Populations (8.1, 8.2, 8.3)]*.

Encourage female transplant patients who become pregnant and male patients who have fathered a pregnancy, exposed to immunosuppressants including tacrolimus, to enroll in the voluntary Transplantation Pregnancy Registry International. To enroll or register, patients can call the toll free number 1-877-955-6877 or https://www.transplantpregnancyregistry.org/ *[see Use in Specific Populations (8.1)]*.

Based on animal studies, PROGRAF may affect fertility in males and females *[see Nonclinical Toxicology (13.1)]*.

17.11 Myocardial Hypertrophy

Inform patients to report symptoms of tiredness, swelling, and/or shortness of breath (heart failure).

17.12 Immunizations

Inform patients that PROGRAF can interfere with the usual response to immunizations and that they should avoid live vaccines. *[see Warnings and Precautions (5.14)]*.

Capsules and Intravenous Injection manufactured by:
Astellas Ireland Co., Ltd.
Killorglin, County Kerry, Ireland

Granules for oral suspension manufactured by:
Astellas Pharma Tech Co., Ltd.
Toyama, Japan

Marketed by:
Astellas Pharma US, Inc.
Northbrook, IL 60062

291762-PRG

Patient Information

PROGRAF® (PRO-graf) (tacrolimus) capsules, for oral use

PROGRAF® (PRO-graf) Granules (tacrolimus for oral suspension)

Read this Patient Information before you start taking PROGRAF and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about PROGRAF?

PROGRAF can cause serious side effects, including:

- **Increased risk of cancer.** People who take PROGRAF have an increased risk of getting some kinds of cancer, including skin and lymph gland cancer (lymphoma).
- **Increased risk of infection.** PROGRAF is a medicine that affects your immune system. PROGRAF can lower the ability of your immune system to fight infections. Serious infections can happen in people receiving PROGRAF that can cause death. **Call your healthcare provider right away if you have any symptoms of an infection, including:**
  - fever
  - sweats or chills
  - cough or flu-like symptoms
  - muscle aches
  - warm, red, or painful areas on your skin

What is PROGRAF?

- PROGRAF is a prescription medicine used with other medicines to help prevent organ rejection in people who have had a kidney, liver, heart, or lung transplant.
- PROGRAF capsules and PROGRAF GRANULES are types of tacrolimus immediate-release drugs and they are not the same as tacrolimus extended-release tablets or tacrolimus extended-release capsules. Your healthcare provider should decide what medicine is right for you.

Who should not take PROGRAF?

Do not take PROGRAF if you:

- are allergic to tacrolimus or any of the ingredients in PROGRAF. See the end of this leaflet for a complete list of ingredients in PROGRAF.

What should I tell my healthcare provider before taking PROGRAF?

Before taking PROGRAF, tell your healthcare provider about all of your medical conditions, including if you:

- plan to receive any vaccines. People taking PROGRAF should not receive live vaccines.
- have or have had liver, kidney, or heart problems.
- are pregnant or plan to become pregnant. PROGRAF can harm your unborn baby.
  - If you are able to become pregnant, you should use effective birth control before and during treatment with PROGRAF. Talk to your healthcare provider before starting treatment with PROGRAF about birth control methods that may be right for you.
  - Males who have female partners who are able to become pregnant should also use effective birth control before and during treatment with PROGRAF. Talk to your healthcare provider before starting treatment with PROGRAF about birth control methods that may be right for you.
  - There is a pregnancy registry for females who become pregnant and males who have fathered a pregnancy during treatment with PROGRAF. The purpose of this registry is to collect information about the health of you and your baby. To enroll in this voluntary registry, call 1-877-955-6877 or go to https://www.transplantpregnancyregistry.org/.
- are breastfeeding or plan to breastfeed. PROGRAF passes into your breast milk. You and your healthcare provider should decide if you will breastfeed while taking PROGRAF.
- plan to have children. PROGRAF may affect the ability to have children in females and males (fertility problems).

Tell your healthcare provider about all the medicines you take, and when you start a new medicine or stop taking a medicine, including prescription and over-the-counter medicines, vitamins, natural, herbal, or nutritional supplements.

Especially tell your healthcare provider if you take:

- sirolimus (RAPAMUNE): You should not take PROGRAF if you take sirolimus.
- cyclosporine (GENGRAF, NEORAL, and SANDIMMUNE)
- medicines called aminoglycosides that are used to treat bacterial infections
- ganciclovir (CYTOVENE IV, VALCYTE)
- amphotericin B (ABELCET, AMBISOME)
- cisplatin
- antiviral medicines called nucleoside reverse transcriptase inhibitors
- antiviral medicines called protease inhibitors
- water pill (diuretic)
- medicine to treat high blood pressure

- nelfinavir (VIRACEPT)
- telaprevir (INCIVEK)
- boceprevir
- ritonavir (KALETRA, NORVIR, TECHNIVIE, VIEKIRA PAK, VIEKIRA XR)
- letermovir (PREVYMIS)
- ketoconazole
- itraconazole (ONMEL, SPORANOX)
- voriconazole (VFEND)
- clarithromycin (BIAXIN, BIAXIN XL, PREVPAC)
- rifampin (RIFADIN, RIFAMATE, RIFATER, RIMACTANE)
- rifabutin (MYCOBUTIN)
- amiodarone (NEXTERONE, PACERONE)

Ask your healthcare provider or pharmacist if you are not sure if you take any of the medicines listed above.
PROGRAF may affect the way other medicines work, and other medicines may affect how PROGRAF works.
Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take PROGRAF?

- Take PROGRAF exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much PROGRAF to take and when to take it.
  Your healthcare provider may change your PROGRAF dose if needed. **Do not** stop taking or change your dose of PROGRAF without talking to your healthcare provider.
- Take PROGRAF with or without food.
- Take PROGRAF the same way every day. For example, if you choose to take PROGRAF with food, you should always take PROGRAF with food.
- Take PROGRAF at the same time each day, 12 hours apart. For example, if you take your first dose at 7:00 a.m., you should take your second dose at 7:00 p.m.
- Taking PROGRAF at the same time each day helps to keep the amount of medicine in your body at a steady level.
- If you take too much PROGRAF, call your healthcare provider or go to the nearest hospital emergency room right away.

PROGRAF capsules:

- **Do not** open or crush PROGRAF capsules.

PROGRAF Granules:

- Children who have trouble swallowing capsules can be given PROGRAF Granules.
- Give the dose of PROGRAF Granules right after preparing. Do not save prepared PROGRAF Granules as a liquid to take at a later time.
- **See the Instructions for Use at the end of this Patient Information** for detailed instructions about how to mix and give PROGRAF Granules as a liquid in a glass cup or oral syringe.
- If you get the granules or prepared oral suspension on your skin, wash the area well with soap and water.
- If you get the granules or prepared oral suspension in your eyes, rinse with plain water.

What should I avoid while taking PROGRAF?

- While you take PROGRAF you should not receive any live vaccines.
- Limit the amount of time you spend in sunlight and avoid exposure to ultraviolet (UV) light, such as tanning machines. Wear protective clothing and use a sunscreen with a high sun protection factor (SPF).
- **Do not** eat grapefruit or drink grapefruit juice during treatment with PROGRAF.

What are the possible side effects of PROGRAF?

PROGRAF may cause serious side effects, including:

- See **"What is the most important information I should know about PROGRAF?"**
- **problems from medicine errors.** People who take PROGRAF have sometimes been given the wrong type of tacrolimus product. **Tacrolimus extended-release medicines are not the same as PROGRAF capsules or granules** and cannot be substituted for each other. **Check your PROGRAF when you get a new prescription and before you take it to make sure you have received PROGRAF capsules or PROGRAF Granules.**
- Check with the pharmacist and call your healthcare provider if you think you were given the wrong medicine.
- **high blood sugar (diabetes).** Your healthcare provider may do blood tests to check for diabetes while you take PROGRAF. Call your healthcare provider right away if you have any symptoms of high blood sugar, including:
  - frequent urination
  - increased thirst or hunger
  - blurred vision
  - confusion
  - drowsiness
  - loss of appetite
  - fruity smell on your breath
  - nausea, vomiting, or stomach pain
- **kidney problems.** Kidney problems are a serious and common side effect of PROGRAF. Your healthcare

provider may do blood tests to check your kidney function while you take PROGRAF.

- **nervous system problems.** Nervous system problems are a serious and common side effect of PROGRAF. Call your healthcare provider right away if you get any of these symptoms while taking PROGRAF. These could be signs of a serious nervous system problem:
  - headache
  - confusion
  - seizures
  - changes in your vision
  - changes in behavior
  - coma
  - tremors
  - numbness and tingling
- **high levels of potassium in your blood.** Your healthcare provider may do blood tests to check your potassium level while you take PROGRAF.
- **high blood pressure.** High blood pressure is a serious and common side effect of PROGRAF. Your healthcare provider will monitor your blood pressure while you take PROGRAF and may prescribe blood pressure medicine for you, if needed. Your healthcare provider may instruct you to check your blood pressure at home.
- **changes in the electrical activity of your heart (QT prolongation).**
- **heart problems (myocardial hypertrophy).** Tell your healthcare provider right away if you get any of these symptoms of heart problems while taking PROGRAF:
  - shortness of breath
  - chest pain
  - feel lightheaded
  - feel faint
- **severe low red blood cell count (anemia).**

The most common side effects of PROGRAF in people who have received a kidney, liver, heart, or lung transplant are:

- infections in general, including cytomegalovirus (cmv) infection
- tremors (shaking of the body)
- constipation
- diarrhea
- headache
- stomach pain
- trouble sleeping
- nausea
- high blood sugar (diabetes)
- low levels of magnesium in your blood
- low levels of phosphate in your blood
- swelling of the hands, legs, ankles, or feet
- weakness
- pain
- high levels of fat in your blood
- high levels of potassium in your blood
- low red blood cell count (anemia)
- low white blood cell count
- fever
- numbness or tingling in your hands and feet
- inflammation of your airway (bronchitis)
- fluid around your heart

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of PROGRAF. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PROGRAF?

PROGRAF capsules

- Store PROGRAF capsules at room temperature between 68°F to 77°F (20°C to 25°C).

PROGRAF Granules

- Store PROGRAF Granules packets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep PROGRAF and all medicines out of the reach of children.

General information about the safe and effective use of PROGRAF.

- Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use PROGRAF for a condition for which it was not prescribed. Do not give PROGRAF to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about PROGRAF that is written for health professionals.
- This Patient Information leaflet summarizes the most important information about PROGRAF. If you would like more information, talk to your healthcare provider.

What are the ingredients in PROGRAF?

Active ingredient: tacrolimus

Inactive ingredients:

PROGRAF capsules: croscarmellose sodium, hypromellose, lactose monohydrate, and magnesium stearate. The 0.5 mg capsule shell contains ferric oxide, gelatin, and titanium dioxide. The 1 mg capsule shell contains gelatin and titanium dioxide. The 5 mg capsule shell contains ferric oxide, gelatin, and titanium dioxide.
PROGRAF Granules: croscarmellose sodium, hypromellose, and lactose monohydrate.

Capsules manufactured by: **Astellas Ireland Co., Ltd.** Killorglin, County Kerry, Ireland
PROGRAF Granules manufactured by: **Astellas Pharma Tech Co., Ltd.** Toyama, Japan
Marketed by: **Astellas Pharma US, Inc.** Northbrook, IL 60062

291762-PRG

Instructions for Use

PROGRAF® Granules
(PRO-graf)
(tacrolimus for oral suspension)

Your healthcare provider has prescribed PROGRAF® Granules, which comes in individual packets that will need to be mixed with water before giving the medicine to your child.

Read this Instructions for Use and the Patient Information for the first time and each time you get a refill of PROGRAF Granules (tacrolimus for oral suspension). There may be new information.

This Instructions for Use does not take the place of talking to your child's healthcare provider about their medical condition or treatment. Ask the healthcare provider if you have any questions about how to mix or give a dose of PROGRAF Granules the right way.

Important information:
These instructions are for preparing PROGRAF Granules only.
These instructions should not be used for PROGRAF capsules.

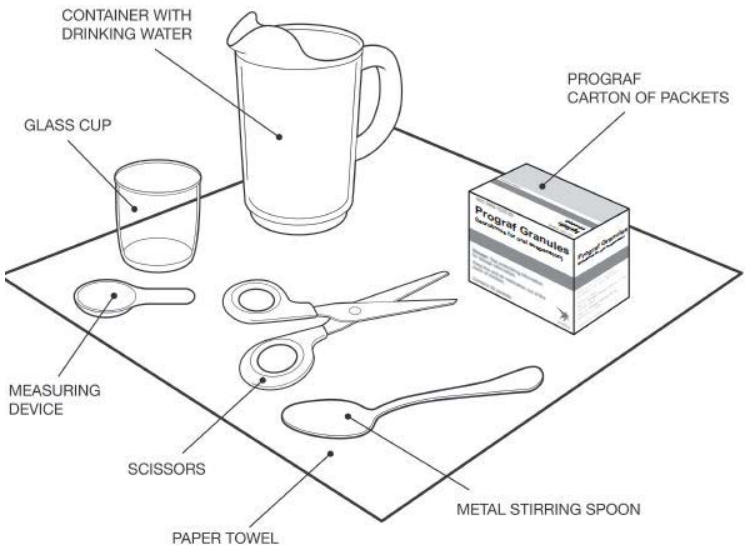
- Mix PROGRAF Granules in water to make an oral suspension.
- Give all of the prepared oral suspension to your child right away after preparing. **Do not** save the prepared oral suspension for later use.
- **Use glass or metal materials** to prepare your child's dose of PROGRAF Granules.
    - **Do not** use any plastic (PVC) materials to prepare PROGRAF Granules. The granules will stick to a plastic container and your child may not receive their full dose.
- **Do not** breathe in (inhale) or let the granules in PROGRAF or the prepared oral suspension come in contact with your skin or eyes.
    - If you get the granules or the prepared oral suspension on your skin, wash the area well with soap and water.
    - If you get the granules or the prepared oral suspension in your eyes, rinse with plain water.

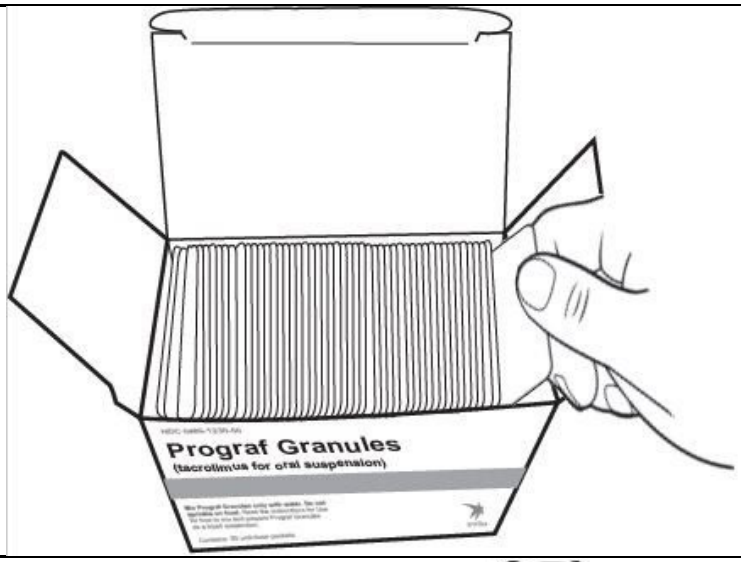
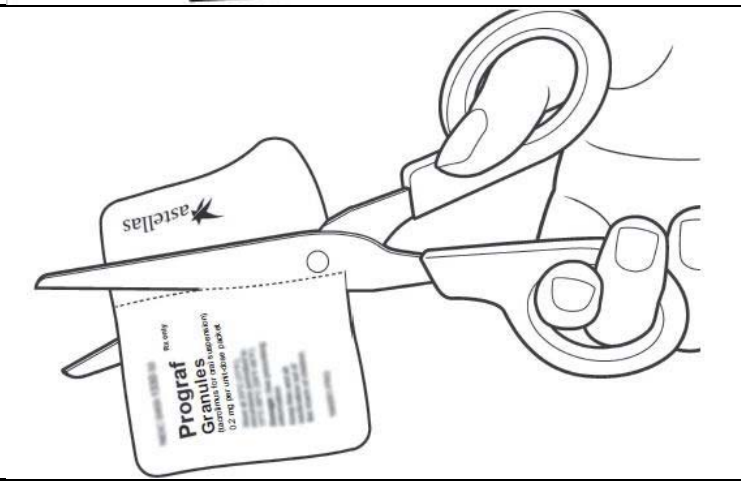
If you spill the granules, wipe the surface with a wet paper towel. If you spill the prepared oral suspension, dry the area with a dry paper towel and then wipe the area with a wet paper towel. Throw away the paper towels in the trash and wash your hands well with soap and water.

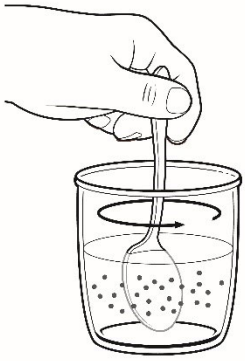
For each dose of PROGRAF Granules mixed with water that will be given using a glass cup, you will need the following supplies (See Figure A):

- Carton containing PROGRAF Granules packets. **Follow the instructions on the carton for the number of packets your child's healthcare provider has prescribed for each dose.**
- paper towels
- pair of scissors
- **metal** stirring spoon
- measuring device
- 1 small clean **glass** cup (plastic containers should not be used)
- container with drinking water

Figure A



Step 1	Choose a clean flat work surface. Place a clean paper towel on the work surface. Place the supplies to prepare the dose on the paper towel.	
Step 2	Wash and dry your hands.	
Step 3	Remove the prescribed number of PROGRAF Granules packets from the carton.	
Step 4	Using a pair of scissors, cut along the dotted line on 1 PROGRAF Granules packet to open it.	

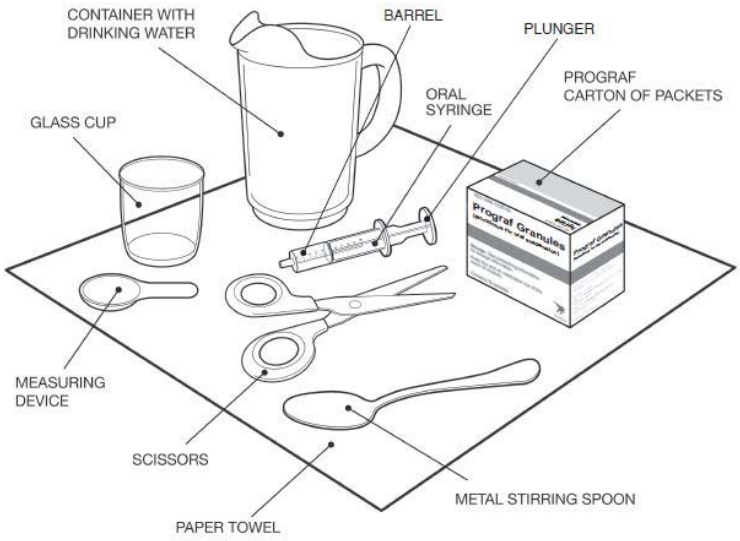
Step 5	Empty all of the granules in the packet into the glass cup. Check for any remaining granules in the packet and empty these into the glass cup.	
Step 6	If more than 1 packet of PROGRAF Granules is needed for your child's prescribed dose, repeat Steps 4 and 5 using the number of packets needed for the prescribed dose.	
Step 7	Add 1 to 2 tablespoons (15 to 30 milliliters) of room temperature drinking water to the glass cup containing the granules.	
Step 8	Gently stir the granules and water in the glass cup with a metal stirring spoon. The granules will not completely dissolve. You will see granules that are suspended in the water.	

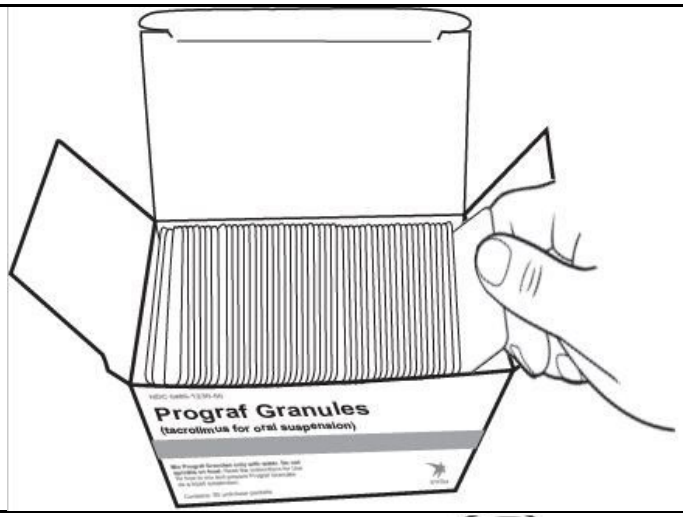
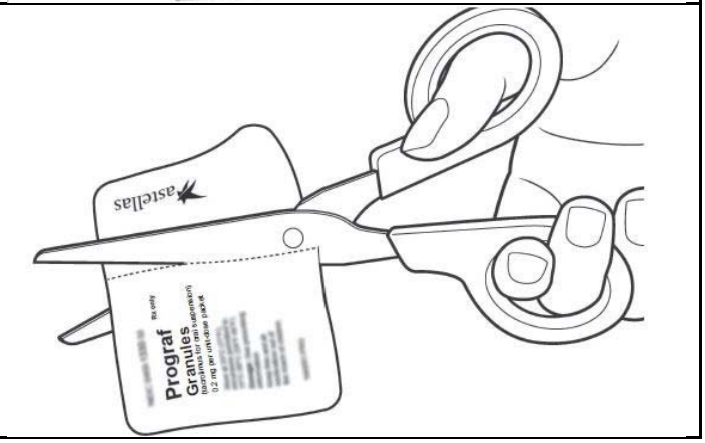
Step 9	Give the granules and water suspension in the glass cup to your child. Make sure your child drinks all of the medicine in the cup. Give all of the medicine to your child right away after preparing. **Do not** save the medicine for later use.	
Step 10	To make sure all of the medicine is given to your child, refill the glass cup with the same amount of water used in Step 7.	
Step 11	Gently swirl the glass cup to mix any remaining granules.	
Step 12	Give all of the medicine in the cup to the child.	
Step 13	Wash the glass cup. Throw away the paper towel and clean the work surface. Wash your hands.	

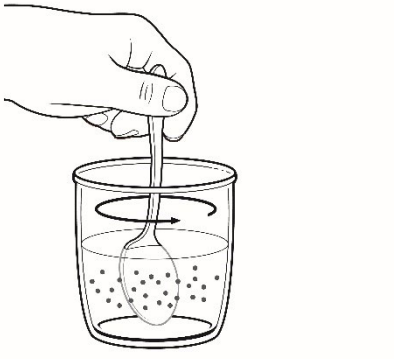
For each dose of PROGRAF Granules (tacrolimus for oral suspension) mixed with water that will be drawn up and given using an oral syringe, you will need the following supplies (See Figure B):

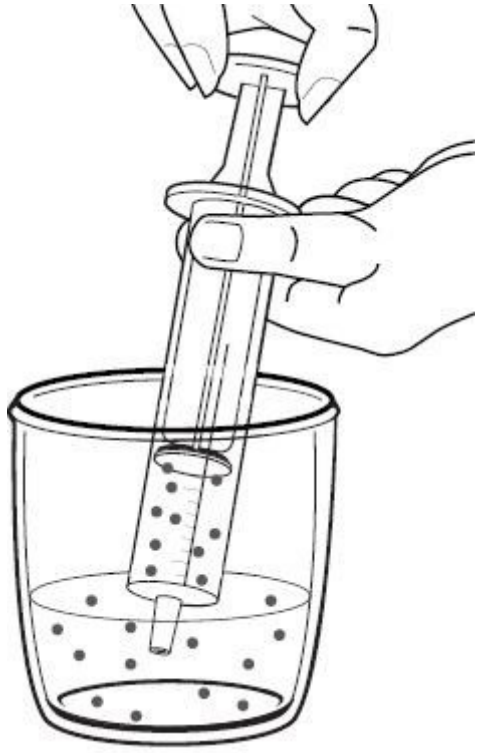
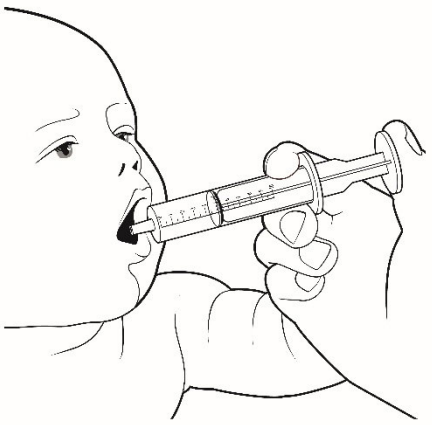
- Carton containing PROGRAF Granules packets. **Follow the instructions on the carton for the number of packets your child's healthcare provider has prescribed for each dose.**
- paper towels
- pair of scissors
- **metal** stirring spoon
- measuring device
- 1 small clean **glass** cup (plastic containers should not be used)
- container with drinking water
- **1 non-PVC** oral syringe (ask your pharmacist for the oral syringe you should use)

Figure B



Step 1	Choose a clean flat work surface. Place a clean paper towel on the work surface. Place the supplies to prepare the dose on the paper towel.	
Step 2	Wash and dry your hands.	
Step 3	Remove the prescribed number of PROGRAF Granules packets from the carton.	
Step 4	Using a pair of scissors, cut along the dotted line on 1 PROGRAF Granules packet to open it.	

Step 5	Empty all of the granules in the packet into the glass cup. Check for any remaining granules in the packet and empty these into the glass cup.	
Step 6	If more than 1 packet of PROGRAF Granules is needed for your child's prescribed dose, repeat Steps 4 and 5 using the number of packets needed for the prescribed dose.	
Step 7	Add 1 to 2 tablespoons (15 to 30 milliliters) of room temperature drinking water to the glass cup containing the granules.	
Step 8	Gently stir the granules and drinking water in the glass cup with a metal stirring spoon. The granules will not completely dissolve. You will see granules that are suspended in the drinking water.	

Step 9	Insert the tip of the oral syringe into the glass cup. Pull back on the plunger of the oral syringe to draw up the suspension.	
Step 10	Place the tip of the oral syringe in your child's mouth along the inner cheek. Slowly push the plunger all the way down to give your child **all** of the medicine in the oral syringe. Repeat Steps 9 and 10 until the glass cup is empty. Give all of the medicine to your child right away after preparing. **Do not** save the medicine for later use.	
Step 11	To make sure all of the medicine is given to your child, refill the glass cup with the same amount of drinking water used in Step 7.	
Step 12	Gently swirl the glass cup to mix any remaining granules.	
Step 13	Repeat Steps 9 and 10 until the glass cup is empty.	
Step 14	Rinse the plunger and barrel of the syringe well with drinking water and dry well before storing the oral syringe.	
Step 15	Wash the glass cup. Throw away the paper towel and clean the work surface. Wash your hands.	

How should I store PROGRAF Granules packets?

Store PROGRAF Granules packets at room temperature between 68°F to 77°F (20°C to 25°C).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use.

Keep PROGRAF Granules and all medicine out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

PROGRAF Granules manufactured by:
Astellas Pharma Tech Co., Ltd.
Toyama, Japan

Marketed by:
Astellas Pharma US, Inc.
Northbrook, IL 60062

291762-PRG

Revised: July 2021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50708s053, 50709s045, 210115s005

MULTI-DISCIPLINE REVIEW

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2) Supplemental NDA
Application Number(s)	NDA 50708/S-053 NDA 50709/S-045 NDA 210115/S-005
Priority or Standard	Priority
Submit Date(s)	December 15, 2020
Received Date(s)	December 15, 2020
PDUFA Goal Date	June 15, 2021
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM) Office of Immunology and Inflammation (OII)
Review Completion Date	See electronic stamp date
Established/Proper Name	Tacrolimus
(Proposed) Trade Name	Prograf
Pharmacologic Class	Immunosuppressant, calcineurin inhibitor (CNI)
Code name	
Applicant	Astellas Pharma US
Dosage form	NDA 50708/S-053: capsule NDA 50709/S-045: injection NDA 210115/S-005: granules for oral suspension
Applicant proposed Dosing Regimen	Adult: initial 0.075 mg/kg/day, target trough concentrations: Month 1-3: 10-15 ng/mL Month 4-12: 8-12 ng/mL Pediatric: initial 0.3 mg/kg/day, target trough concentrations: Weeks 1-2: 10-20 ng/mL Week 2 to Month 12: 10-15 ng/mL
Applicant Proposed Indication(s)/Population(s)	Prophylaxis of rejection in adult and pediatric patients receiving allogeneic lung transplant
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	88039007 |Transplant of lung (procedure)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Prophylaxis of rejection in adult and pediatric patients receiving allogeneic lung transplant
Recommended SNOMED CT Indication Disease Term for each Indication	88039007 |Transplant of lung (procedure)|
Recommended Dosing Regimen	Same as the Applicant proposed Dosing Regimen

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Susan Rhee, PharmD
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Nonclinical Team Leader	N/A
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Office of Clinical Pharmacology Team Leader(s)	Jianmeng Chen
Clinical Reviewer	Ergun Velidedeoglu
Clinical Team Leader	Ergun Velidedeoglu
Statistical Reviewer	Tae Hyun Jung
Statistical Team Leader	Clara Kim
Cross-Disciplinary Team Leader	Ergun Velidedeoglu
Division Director (OB)	Mark Levenson
Deputy Division Director (Signatory)	Ozlem Belen

Additional Reviewers of Application

OPDP	Carrie Newcomer, James Dvorsky
OMPI	Mary Carroll, Marcia Williams, LaShawn Griffiths
OSE/DEPI	Yan Li, Efe Eworuke, Monique Falconer

OPDP=Office of Prescription Drug Promotion
OMPI= Office of Medical Policy Initiatives
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	N/A		Sections:	Select one: ___ Authored ___ Approved
	Signature:			
Nonclinical Supervisor	N/A		Sections:	Select one: ___ Authored ___ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Clinical Pharmacology Team Leader	Jianmeng Chen	OTS/OCP/DIIP	Section: 6	Select one: ___ Authored _X_ Approved
	Signature: Jianmeng Chen -S Digitally signed by Jianmeng Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianmeng Chen -S, 0.9.2342.19200300.100.1.1=2000743816 Date: 2021.07.16 07:47:46 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Ergun Velidedeoglu	OII/DRTM	Sections:1, 2, 3, 7, 8.2, 11	Select one: __X_ Authored ___ Approved
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Clinical Team Leader	Ergun Velidedeoglu	OII/DRTM	Sections: 1, 2, 3, 7, 8.2, 11	Select one: _X__ Authored _X_ Approved
	Signature: Huseyin Velidedeoglu -S Digitally signed by Huseyin Velidedeoglu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000245776, cn=Huseyin Velidedeoglu -S Date: 2021.07.15 18:13:14 -04'00'			
Deputy Division Director (Signatory)	Ozlem Belen	OII/DRTM	Sections: 1.2, 1.3, 17	Select one: _X__ Authored _X__ Approved, All
	Signature: Ozlem A. Belen -S Digitally signed by Ozlem A. Belen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ozlem A. Belen -S, 0.9.2342.19200300.100.1.1=1300167984 Date: 2021.07.15 19:03:17 -04'00'			
Statistical Reviewer	Tae Hyun Jung	OTS/OB/DB7	Sections: 8.1, 8.3	Select one: _X_ Authored ___ Approved
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Statistical Team Leader	Clara Kim	OTS/OB/DB7	Sections: 8.1, 8.3	Select one: ___ Authored _X_ Approved
	Signature: Clara Y. Kim -S Digitally signed by Clara Y. Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Clara Y. Kim -S, 0.9.2342.19200300.100.1.1=1300382748 Date: 2021.07.16 09:40:10 -04'00'			
Division Director (OB)	Mark Levenson	OTS/OB/DB7	Sections: 8.1, 8.3	Select one: ___ Authored _X__ Approved
	Signature: Mark S. Levenson -S Digitally signed by Mark S Levenson -S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=1300384235 cn=Mark S Levenson -S Date: 2021 07 16 09:44:40 04'00'			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
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
CNI	calcineurin inhibitor
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CS	corticosteroid
CsA	cyclosporine
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
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 Conference on Harmonisation
IND	Investigational New Drug
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
MMF	mycophenolate mofetil

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
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
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
SRTR	Scientific Registry of Transplant Recipients
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Tacrolimus is a calcineurin inhibitor (CNI) class, macrolide immunosuppressant produced by the fungus-like bacteria “Streptomyces tsukubaensis.Tacrolimus inhibits T-lymphocyte activation. CNIs are the main component of most immunosuppressive regimens administered to transplant recipients. There are two CNIs approved for the prophylaxis of rejection in transplant recipients, cyclosporine and tacrolimus. Although cyclosporine was discovered and approved prior to tacrolimus, tacrolimus (Prograf® and generics) has become the CNI of choice in most transplant recipients. Currently, Prograf is indicated for the prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic liver, kidney or heart transplants, in combination with other immunosuppressants.

Prograf® (tacrolimus) has been on the US market for 27 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. Another dosage form (tacrolimus for oral suspension) was approved in 2018 (NDA 210115).

Tacrolimus was originally approved as immediate-release oral capsule and injection dosage forms under the proprietary name Prograf, in 1994 (NDA 50708 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 the US.

End stage lung disease is a serious and life-threatening condition. Lung transplantation is the only treatment option for most of these patients. Lung transplantation is an orphan disease with fewer than 3000 new transplantations per year and about 15000 lung transplant recipients currently alive in the US. There are only 30 to 50 pediatric lung transplantationss performed in the US per year. There is no immunosuppressive drug product approved for lung transplant recipients; however, 85% of these patients are treated off-label, with tacrolimus, mycophenolate mofetil (MMF), and corticosteroids per the 2018 US Annual Data Report published by the Scientific Registry of Transplant Recipients (SRTR) [Valapour 2020].

The purpose of the current supplemental NDA is to add the lung transplantation indication to the Prograf® labeling. Orphan Drug Designation for tacrolimus for the

prevention of rejection in lung transplantation was granted on September 12, 2019. The Applicant submitted real-world evidence (RWE), based on U.S. Scientific Registry of Transplant Recipients (SRTR) data along with relevant published literature in support of this sNDA. The RWE is based on real-world data (RWD) generated from an analysis of treatment and outcomes of lung transplant recipients who were administered tacrolimus. This sNDA was granted Priority Review since there are currently no FDA-approved immunosuppressant drug products for lung transplant recipients.

Off-label Tacrolimus use in Lung Transplantation

Decades of experimental studies and clinical attempts were required to reach successful outcomes in lung transplantation. The main hurdles were technical problems involving healing of the bronchial anastomosis, high immunogenicity of the lung with need for augmented immunosuppression, and the substantial risk of pulmonary infections in the lung allograft [Venuta 2017].

Prior to human lung transplantation attempts, extensive research was done in animal models. Originally it was not possible to achieve lung allograft survival beyond a few days in animals. Following years of work, the greatest success was achieved in dogs in 1961 by using methotrexate for immunosuppression which made it possible to prolong lung allograft survival beyond 12 days for the first time [Venuta 2017].

The first clinical lung transplantation attempt in humans was reported by Hardy and Webb in 1963 [Hardy 1963]. Immunosuppressive regimen of this patient consisted of prednisone, azathioprine, and cytoablative irradiation focused on the thymic region [Panchabhai 2018]. The patient survived 18 days and died of renal failure and infection. Between 1963 and 1978 approximately 38 lung, lung lobe or combined heart and lung transplants were attempted, with no long-term success. Only one patient was discharged from the hospital in 1968 in Belgium with subsequent survival of 10 months [Venuta 2017]. The vast majority of patients died in the third postoperative week from disruption of the bronchial anastomosis. It became clear that the major determinant for the future success of lung transplantation was related to the establishment of an adequate bronchial arterial supply to the transplanted lung allograft bronchus and the prevention of bronchial necrosis and disruption of the bronchial anastomoses. At the time, all of the lung transplant recipients were maintained on azathioprine and corticosteroids as the immunosuppressants.

Cyclosporine was discovered in 1968 as a product of Tolypocladium inflatum, a fungus isolated from Norwegian soil and was approved by the FDA for liver transplantation in 1983. In lung allo- and auto- transplantations performed in dogs, the detrimental effect of corticosteroids on bronchial anastomotic healing was discovered. When cyclosporine became available, lung transplantations in dogs demonstrated that, unlike corticosteroids, cyclosporine did not interfere with bronchial anastomotic healing [Lima 1981 and Goldberg 1983].

In 1981 Bruce Reitz and his colleagues at Stanford University performed a heart and lung transplantation (HLTx) on a 45 year old woman who became the first long-term HLTx survivor, thanks to the improved surgical technique and the use of cyclosporine [Reitz 2011]. Joel Cooper and colleagues reported the first long-term survivor of lung transplantation in 1983, and that patient was also treated with cyclosporine. In their 1986 NEJM publication [Toronto Lung Transplant Group 1986] Cooper and colleagues state "*From these studies, we concluded that routine use of corticosteroids for immunosuppression in the early period after the transplantation significantly contributes to poor bronchial healing; the substitution of cyclosporine for corticosteroids reduces these complications*." Both patients described in the 1986 NEJM publication were treated with cyclosporine and intravenous azathioprine. Azathioprine was substituted with corticosteroids after Day 21, a time, when substantial bronchial anastomotic healing has occured. Both the nonclinical and the clinical lung transplantation outcomes using cyclosporine, cleary prove the contribution of cyclosporine to success which otherwise would not be possible.

Lung transplantation in pediatric patients began in the mid-1980s. Lung transplantation is a highly specialized therapy for end-stage lung disease in children and it is performed at a small number of transplant centers in the US (19 centers, with 8 centers that performed more than 1 pediatric lung transplant in a year) [Valapour 2020].

After the FDA approval of tacrolimus in 1994 for liver transplantation, off-label use in lung transplantation increased over time, gradually replacing cyclosporine as the CNI of choice.The nonclinical and clinical development history of lung transplantation as a viable therapeutic option, clearly demonstrates that it would not have been possible to achieve successful lung transplantation outcomes if the CNIs had not been discovered. Prior to the use of cyclosporine, all lung allografts were lost within a matter of days because of bronchial anastomotic dehiscence caused by the initial high dose of corticosteroids which had to be administred to prevent rejection. When cyclosporine was used to replace the early postoperative corticosteroid treatment, it became possible to prevent the fatal bronchial anastomotic complications. Subsequently, cyclosporine was gradually replaced by tacrolimus which became the CNI of choice both for the approved and off-label indications in transplantation. Today, patient survival rates for lung transplant recipients are 88.8% at 1 year; 59.2% at 5 years and 33.1% at 10 years [Valapour 2021] which would not have beeen possible to achieve without the CNIs. In today's clinical practice, tacrolimus + MMF + corticosteroids with or without induction immunosuppression is the standard of care (SOC) in lung transplantation and in other types of solid organ transplantations. Since lung transplantation outcomes would be catastrophic in the absence of CNIs, it is not ethical to design placebo controlled, randomized trials in support of the efficacy of CNIs in lung transplantation. The historical evolution of lung transplantation clearly demonstrates the contribution of the CNIs to the overall efficacy of the immunosuppressive regimen which is also

supported by similar efficacy and safety data from other types of organ transplants in which, tacrolimus is the main component of the immunosuppressive regimen. All of these factors make the current supplemental NDA ideally suited for the use of RWD to generate RWE in support of efficacy and safety of tacrolimus in lung transplantation. Support for the starting dose and the target trough concentration range is provided by published clinical practice guidelines reflecting the practice in multiple transplant centers, other published studies and also by extrapolation from the dosing information for heart transplantation included in the Prograf package insert.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Summary

The Applicant has provided substantial evidence of effectiveness for tacrolimus in combination with MMF and CS, or in combination with azathioprine and CS, in the prophylaxis of rejection in lung transplantation. This assessment is based on Study F506-CL-3001 as an adequate and well-controlled study along with other clinical studies (see below) serving as confirmatory evidence of effectiveness. The remainder of this section of the review summarizes evidence for the effectiveness of tacrolimus in lung transplantation as a component of a triple immunosuppressive regimen and the contribution of tacrolimus to the overall efficacy of the regimen.

Clinical context

Prior to the availability of cyclosporine as an immunosuppressive agent, historical data demonstrated that graft and overall survival among lung transplant recipients was typically only several weeks post-transplantation. For example, in a non-interventional (observational) study of 36 patients receiving lung transplantation in the late 1960s and early 1970s, the median survival was less than two weeks[1] and no patients survived to one year [Veith 1974]. Immunosuppressive treatment at that time consisted mainly of azathioprine and CS; CNIs (cyclosporine or tacrolimus) weren't yet available. Subsequently, in the 1980's, graft and overall survival times of 14 months and 26 months were reported in the first two cases of patients receiving a CNI (cyclosporine) as part of their post-transplant immunosuppressive regimen [Toronto Lung Transplant Group 1986]. Although some improvements in surgical techniques and supportive care occurred over the interval, these dramatically longer survival times can be attributed directly to the improved effectiveness of immunosuppressive therapy [Veith 1974, European Multicentre Trial Group 1983 and Toronto Lung Transplant Group 1986].

[1] FDA analysis based on [Veith 1974].

Adequate and well-controlled study

The review team, with the support of the RWE subcommittee, determined that Study F506-CL-3001, with comparison to historical controls, constitutes an adequate and well-controlled study, and together with a) confirmatory evidence from randomized controlled clinical trials in the setting of other solid organ transplants, and b) published reports indicating the independent contribution of tacrolimus in a multi-drug immunosuppressive regimen, the study supports approval of an indication for tacrolimus in lung transplantation in combination with other immunosuppressants.

Substantial evidence of effectiveness based on adequate and well-controlled clinical investigations is required for approval of a drug under section 505(c) of the Federal Food, Drug, and Cosmetic Act. In many cases, two adequate and well-controlled clinical investigations are needed. However, when scientifically appropriate, evidence from a single adequate and well-controlled clinical investigation with confirmatory evidence can be sufficient to meet the substantial evidence standard. FDA regulations at 21 CFR 314.126 outline the characteristics of an adequate and well-controlled clinical study. Among other factors, these regulations recognize five types of controls, including historical controls. Although historically controlled studies typically involve a treatment group with drug assignment according to a protocol (as in a single-arm clinical trial), the regulations do not require such a design when comparing outcomes of treatment and historical control groups.

A distinctive aspect of Study F506-CL-3001 is its non-interventional ("observational") design, meaning that patients in the treatment arm received the drug of interest in everyday medical practice rather than being assigned the drug according to a research protocol. Given that treatment assignment in a non-interventional study is based on clinical judgment rather than a protocol-based assignment, confounding and other sources of bias can create challenges in establishing causal inference for the purpose of supporting an effectiveness determination for regulatory decisions. Nonetheless, FDA recognizes that a non-interventional study—depending on details of the clinical context, data sources (including methods of data collection), study design, and magnitude of the treatment effect—may in certain circumstances meet the regulatory requirements for an adequate and well-controlled study under 21 CFR 314.126.

We have determined that Study F506-CL-3001, with a non-interventional study design, satisfies the regulatory requirements for an adequate and well-controlled study under 21 CFR 314.126. The study is based on data from the SRTR, operating under contract from the Health Resource and Services Administration (HRSA) in the Department of Health and Human Services (HHS). The SRTR has a well-established and robust operational structure for collecting rigorous data on all US solid-organ transplant recipients, as required by the National Organ Transplantation Act of 1984 [Leppke 2013]. The accuracy of SRTR data is enhanced by the capture of predefined data

elements on each patient regarding transplantation and graft survival, and is supplemented by other information, including from the Social Security Administration's Death Master File as a trusted repository of mortality data. Based on the sources of data and steps involved with data processing (including data quality verification) [Leppke 2013], the review team found the assessments of study variables, such as the endpoints of interest (death or graft failure at one year), to be relevant and reliable. Given additional study features of complete capture of patients undergoing transplant, and the complete capture of relevant clinical information, the review team found data from the SRTR to be fit-for-use.

Study F506-CL-3001 was designed and conducted according to a protocol with clear research objectives and a statistical analysis plan. The sponsor analyzed data from the SRTR on all patients receiving single- or double-lung transplantation in the US during 1999 to 2017, with reliable classification of each patient's diagnosis as well as objective and well-defined clinical endpoints of death or graft failure. In addition, patients included in the SRTR analyses were not limited to a selected population, such as only volunteer participants who were willing or able to be enrolled in a trial. Similarly, the inclusion of patients wasn't limited to only selected study sites. Instead, as a compulsory registry [Hanto 2003], the data represent the most generalizable U.S. population of lung transplant recipients that could be recruited, and data on all such patients are captured. Accordingly, limitations related to a non-representative study population do not apply.

Analysis of data in the SRTR showed one-year graft and overall survival of 85-90% or better for a tacrolimus-containing immunosuppressive regimen of either tacrolimus + MMF + CS or tacrolimus + azathioprine + CS. Although Study F506-CL-3001 did not include a specified control group, these outcomes are highly unlikely to have occurred spontaneously or by chance, given the well-documented natural history of a transplanted lung with no or minimal immunosuppressive therapy. As such, the outcomes were compared to historical controls in the absence of an immunosuppressive regimen, where no graft or overall survival was observed at one year and survival was largely limited to several weeks [Hardy 1963 and Veith 1974]. When the treatment group in Study F506-CL-3001 is compared with the historical controls, and in conjunction with the other considerations described above, the study can be considered adequate and well-controlled.

The division acknowledges that given the lack of contemporaneous data collection, differences may exist between the treatment and the historical control groups. The SRTR data go back to 1999 and some differences would be expected between patients in the SRTR and historical controls due to changes in baseline characteristics of patients receiving transplantation, surgical techniques, and supportive medical care over time. Nonetheless, the clinical benefit seen with the tacrolimus-containing immunosuppressive regimen studied is so large compared to historical controls that differences in baseline characteristics, surgical technique, and/or supportive care

between groups are highly unlikely to explain the outcome differences, and therefore do not change the conclusion of effectiveness.

In summary, given the collection of well-defined and reliable data, as well as the fact that all lung transplant patients were captured, the SRTR provides robust data similar to that which would have been collected in a single-arm trial with a comparison to the same historical controls. Study F506-CL-3001 was a well-planned and well-executed study demonstrating clinically meaningful increases in one-year graft and patient survival that would otherwise not occur after lung transplantation and can be considered an adequate and well-controlled study when results for the treated patients are compared to historical controls. The remainder of this section discusses confirmatory evidence as well as specific citations supporting the independent contribution of tacrolimus in a multi-drug immunosuppressive regimen.

Confirmatory evidence

FDA approval of tacrolimus (Prograf) for adult and pediatric liver, kidney, and heart transplant recipients was supported by substantial evidence of effectiveness from adequate and well-controlled randomized clinical trials for each of these indications using non-inferiority trial designs that tested multi-drug immunosuppressive regimens, all of which included a CNI (tacrolimus or cyclosporine) [Prograf Prescribing Information, Section 14]. Alloimmune response to these transplanted organs is mechanistically similar, regardless of the organ involved, and rejection is known to occur in the absence of therapy. Therefore, and based on these related uses, it is scientifically reasonable to conclude that tacrolimus as part of an immunosuppressive regimen should decrease and delay rejection in lung transplantation, consistent with the findings of the SRTR study.

Contribution of tacrolimus to the immunosuppressive regimen

In addition to mechanistic considerations, the independent contribution of a CNI to the efficacy of immunosuppressive regimens is supported by clinical trial data. Specifically, immunosuppressive regimens consisting of MMF + CS were used in the 1990s for kidney transplant recipients. In a trial of kidney transplant recipients maintained on a two-drug MMF + CS regimen, 48% (47/98) of patients enrolled developed acute rejection by six months post-transplantation [Vincenti 2001]. In contrast, in a report of 75 patients maintained on a MMF + CS regimen and a CNI (cyclosporine), rejection occurred in 12% of recipients [Vincenti 1999]. These two reports provide evidence of the specific and significant contribution of CNIs to the overall efficacy of commonly used

immunosuppressive regimens.[2] Notably, the immunosuppressive regimens in the cited reports, as well as the types of organs transplanted, are not identical to those used in the SRTR study. Nonetheless, the similarity of the regimens to those used in the SRTR study as well as the similarity between kidney and lung transplantation are sufficient to support the finding that CNIs contribute to graft and overall survival in the setting of an immunosuppressive regimen in lung transplantation.

Finally, evidence from randomized trials comparing tacrolimus + MMF + CS versus CsA + MMF + CS in lung transplantation suggests similar effectiveness of tacrolimus and cyclosporine in MMF-containing three-drug regimens. One trial found "one-year and two-year survival rates were similar in the two groups" [Treede 2012], and another trial reported "no significant difference in incidence of acute rejection was observed between the 2 groups [and] survival and incidence of infection were similar" [Zuckerman 2003]. The similar effectiveness of tacrolimus + MMF + CS and CsA + MMF + CS supports the contribution of tacrolimus to the three-drug regimen in lung transplant regimens, based on the rationale that, as in kidney transplantation described above, an MMF + CS regimen would be expected to be insufficient in lung transplantation as well.[3] Accordingly, it is reasonable to conclude that tacrolimus provides comparable additivity to MMF + CS as does CsA.

[2] Other clinical trials support a similar conclusion regarding the contribution of CsA to a regimen comprised of azathioprine + CS [European Trial Group 1983; Canadian Trial Group 1983; Opelz 1986].

[3] Similar effectiveness of tacrolimus compared to cyclosporine is also supported by two randomized trials comparing these agents among lung transplant recipients who also received azathioprine + CS. One trial reported that 3/38 (7.9%) patients in the tacrolimus group died one year after transplantation compared to 6/36 (17%) patients in the CsA group, and acute rejection occurred less often in the tacrolimus group [Griffith 1994]. A second trial involving 74 patients reported survival post-transplantation for tacrolimus and CsA, respectively, of 83% and 71% at one year, and 76% and 66% at two years [Keenan 1995].

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Tacrolimus is the most commonly used immunosuppressant in all types of solid organ transplantations including the off-label use in lung transplantation. Tacrolimus is currently approved for heart, kidney and liver transplantations both in adults and pediatric patients and has been on the US market since 1994. In the absence of CNIs (cyclosporine and tacrolimus) it would not have been possible to achieve today's success rates in any type of solid organ transplantation including lung transplantation. The data provided in this submission, which are derived from the SRTR, a well-established and robust operational structure for collecting rigorous data on all US solid-organ transplant recipients, establishes the efficacy of tacrolimus for the prophylaxis of rejection in adult and pediatric patients receiving allogeneic lung transplant. The safety profile of tacrolimus is well characterized as described in the product labeling. All transplant recipients under immunosuppressive therapy are at increased risk of infections and malignancies. This is an acceptable trade off for maintaining the viability of the allograft. Lung transplantation provides both a survival benefit [Vock 2017]and quality of life benefit [Santana 2009] to end stage lung disease patients. Therefore, tacrolimus has a clearly favorable benefit/risk profile for this patient population. The approval of tacrolimus will provide much needed access to this therapy for adult and pediatric patients receiving allogeneic lung transplant.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• End stage lung disease is a serious and life-threatening condition. Lung transplantation is the only treatment option for most of these patients. Lung transplantation is an orphan disease with fewer than 3000 new transplantations per year and about 15000 lung transplant recipients currently alive in the US.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are no approved immunosuppressant products to be used in lung transplant recipients. Based on the Scientific registry of Transplant Recipients (SRTR) data, more than 80% of lung transplant recipients are discharged from the hospital on a tacrolimus based regimen, used off-label. Most commonly used regimen consists of tacrolimus + MMF + corticosteroids.	
Benefit	• As explained in different sections of this review, including Evidence of Effectiveness section (Section 1.2), in the absence of a CNI (including tacrolimus) as part of the immunosuppressive regimen, it would not be possible to achieve, lung transplant survival beyond a few weeks.	
Risk and Risk Management	• N/A	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Lung transplantation is the only option available for patients with treatment resistant end-stage lung disease. Lung transplant patients constitute a rare disease population (14,000 currently alive and 2500 new transplants per year in US).

2.2. Analysis of Current Treatment Options

There are no approved immunosuppressant drug products for lung transplant recipients. Per the SRTR (National Registry) data, currently 83% of lung transplant recipients are on a Tacrolimus + Mycophenolate Mofetil (MMF) + corticosteroid (cs) immunosuppressive regimen (off-label) with 50-60% graft survival rate at 5 years. The following products have been approved for use in kidney transplant recipients as induction or maintenance immunosuppressants for prevention, or treatment of acute rejection. These products are also being used off-label in lung transplant recipients with varying proportions. 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.

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.

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.

3 Regulatory Background

3.1. 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. Tacrolimus for oral suspension dosage form was approved in 2018 (NDA 210,115).

As evident from the regulatory history, the active moiety (tacrolimus) has been on the US market for 27 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 including lung transplantation.

3.2. Summary of Presubmission/Submission Regulatory Activity

- In August 2019, Astellas submitted a Written Response Only (WRO) meeting request to discuss a supplemental New Drug Application (sNDA) to add a new indication for Prograf for the prophylaxis of rejection in lung transplantation based on RWE.

- The Applicant's submission and the suitability of RWE in support of an efficacy supplement for lung transplantation indication was discussed at the September 26, 2019 RWE subcommittee meeting and was found appropriate.

- FDA provided answers to the sponsor's questions on October 3, 2019 (WRO Meeting Minutes). FDA responses included comments on the the selected data source, proposed statistical analysis plan (SAP) for primary and secondary efficacy outcomes, safety analysis, and the methodology and format of the output to support an sNDA. These responses also reflected the recommendations made during the September 26, 2019 RWE subcommittee meeting by the Committee members.

- The Applicant asked additional questions in their December 5, 2019, Meeting Package. A teleconference was held on February 26, 2020 to answer the applicant's questions. The Applicant's questions included whether a starting dose of (b) (4) would be appropriate for adult patients. The FDA responded that this would be a review issue. The requirement of an initial pediatric study plan (IPSP) was among the dicussed subjects. However, shortly after the meeting, on March 9, 2020, Astellas informed the review division that orphan-drug designation for tacrolimus was granted for the indication of prevention of rejection in lung transplantation. The Division communicated that since tacrolimus has an orphan drug designation for this indication, Astellas is exempt from the PREA requirements (March 13, 2020 meeting minutes).

- A pre supplemental NDA meeting (teleconference) was held on August 21 , 2020. The purpose of the meeting was to discuss the adequacy of the plan and content of the submission which utilizes RWE. Agreements were reached on the proposed primary endpoint, pediatric data and labeling for the pediatric indication and statistical issues including submission of the data fro FDA review.

- Current sNDA was submitted on December 15, 2020.

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

4.1. Office of Scientific Investigations (OSI)

The review of the data did not indicate data integrity issues and OSI inspection was not deemed necessary for this application.

4.2. Product Quality

No new product quality data were submitted or required to support this submission.

4.3. Clinical Microbiology

No new microbiology data were submitted or required to support this submission.

4.4. Devices and Companion Diagnostic Issues

No new device or companion diagnostics data were submitted or required to support this submission.

5 Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted or required to support this submission.

6 Clinical Pharmacology

6.1.Executive Summary

This supplemental NDA contains a database from Scientific Registry of Transplant Recipients based on real world data, but dosing regimen and trough concentration were not recorded in the database. The Applicant conducted a literature review to summarize the dosing regimen and targeted whole blood trough concentrations that were currently used by different transplant centers. Clinical pharmacology review was focused on the literature review to support the dose recommendation, targeted whole blood trough concentration, and a labeling statement for dosing in lung transplantation patients with cystic fibrosis.

The proposed dose of tacrolimus for adult patients receiving lung transplantation is 0.075 mg/kg/day divided into two doses every 12 hours orally with a targeted whole blood trough concentration of 10-15 ng/mL from Month 1 to Month 3 and 8-12 ng/mL from Month 4 to Month 12. The proposed dose of tacrolimus for pediatric patients receiving lung transplantation is 0.3 mg/kg/day capsules or oral suspension, divided in two doses, every 12 hours orally with a targeted whole blood trough concentration of 10-20 ng/mL from Week 1 to Week 2 and 10-15 ng/mL from Week 2 to Month 12. The proposed starting dose and targeted whole blood trough concentration were similar to the current clinical practice and the use of tacrolimus in patients receiving heart transplantation. Previously published exposure response analysis also supported the targeted whole blood trough concentration.

In patients with cystic fibrosis, tacrolimus bioavailability was 20% to 50% lower compared to patients without cystic fibrosis. Therefore, patients with cystic fibrosis may require higher doses due to lower bioavailability.

In patients who cannot tolerate oral administration, the proposed intravenous (IV) infusion dosing regimen is 0.01-0.03 mg/kg/day. IV infusion 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.

Based on clinical pharmacology review, the published literatures and clinical guidelines supported the approval of tacrolimus in patients receiving lung transplantation.

6.2.Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The pharmacokinetics of tacrolimus in patients receiving lung transplantation had been characterized in several publications. A PK comparison between patients receiving lung transplant and patients receiving heart transplant is given Table 1.

Table 1 Comparison of Pharmacokinetics in Patients Receiving Lung Transplant and Heart Transplant

Population	N	Route (Dose)	Parameters		
			C_{max} (ng/mL)	T_{max} (hr)	AUC (ng•hr/mL)
Heart Transplant Patients*	11	IV (0.01 mg/kg/day as a continuous infusion)	NA	NA	954 ± 334
	11	PO (0.075 mg/kg/day)	14.7 ± 7.79	2.1 [0.5-6.0]	82.7 ± 63.2
	14	PO (0.15 mg/kg/day)	24.5 ± 13.7	1.5 [0.4-4.0]	142 ± 116
Lung Transplant Patients[4, 5]	11	PO (6.1 mg/day) Non-CF patients	30.6 [11.6–43.5]	1.5 [1–3]	170 [80–240]
	11	PO (12 mg/day) CF patients	23.4 [10.6–76.8]	1.5 [0.5–5]	160 [100–270]
	40	PO (6.0 mg/day) Non-CF patients	NA	NA	153 ± 55
	38	PO (9.4 mg/day) CF patients	NA	NA	153 ± 46

*Prograf Label

The PK characteristics in patients receiving lung transplantation and heart transplantation are similar.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposed the following dosing regimen in adult and pediatric patients receiving lung transplantation.

[4] Knoop et al., Tacrolimus Pharmacokinetics and Dose Monitoring After Lung Transplantation for Cystic Fibrosis and Other Conditions. American Journal of Transplantation 2005; 5: 1477–1482.
[5] Monchaud et al., Population Pharmacokinetic Modelling and Design of a Bayesian Estimator for Therapeutic Drug Monitoring of Tacrolimus in Lung Transplantation. Clin Pharmacokinet 2012; 51 (3): 175-186.

Lung Transplantation in Adults		
With azathioprine or MMF	0.075 mg/kg/day[1] capsules, divided in two doses, every 12 hours	Month 1-3: 10-15 ng/mL Month 4-12: 8-12 ng/mL
Lung Transplantation in Pediatrics		
	0.3 mg/kg/day[1, 2, 3] capsules or oral suspension, divided in two doses, every 12 hours	Weeks 1-2: 10-20 ng/mL Week 2 to Month 12: 10-15 ng/mL

[1] Patients with cystic fibrosis may require higher doses due to lower bioavailability.
[2] Dose at 0.1 mg/kg/day if antibody induction treatment is administered.
[3] The dose may decrease as the child grows older.

In patients who cannot tolerate oral administration, the proposed intravenous (IV) infusion dosing regimen is 0.01-0.03 mg/kg/day. IV infusion 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 proposed starting dose and targeted whole blood trough concentration in patients receiving lung transplantation were reasonable and were supported by current clinical practice, experience in other indications (e.g. heart transplantation), and published exposure response analysis for efficacy and safety (see section 6.3.2).

Therapeutic Individualization

Patients with cystic fibrosis may have a reduced extent of absorption of orally administered tacrolimus resulting in the need for higher doses to achieve target tacrolimus trough concentrations. Monitor tacrolimus trough concentrations and adjust the dose accordingly.

Outstanding Issues

None.

6.3.Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Tacrolimus is a calcineurin phosphatase inhibitor. The inhibition of calcineurin results in the inhibition of T-lymphocyte activation and proliferation, as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

The pharmacokinetics of tacrolimus has been characterized in healthy volunteers, patients receiving kidney transplantation, liver transplantation, and heart transplantation. The absolute bioavailability of tacrolimus was 17 ± 10% in adult kidney transplant patients (N = 26), 22 ± 6%

in adult liver transplant patients (N = 17), 23 ± 9% in adult heart transplant patients (N = 11) and 18 ± 5% in healthy volunteers (N = 16). The rate and extent of tacrolimus absorption were greatest under fasted conditions. The presence and composition of food decreased both the rate and extent of tacrolimus absorption.

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A). The mean clearance following IV administration of tacrolimus is 0.040, 0.083, 0.053, and 0.051 L/hr/kg in healthy volunteers, adult kidney transplant patients, adult liver transplant patients, and adult heart transplant patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine.

6.3.2. Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The Applicant proposed an oral starting dose of 0.075 mg/kg/day and a targeted whole blood trough concentration of 10-15 ng/mL from Month 1 to 3 and 8-12 ng/mL from Month 4-12 in adult patients receiving lung transplantation.

The proposed starting dose and targeted whole blood trough concentration in patients receiving lung transplantation were supported by current clinical practice, experience in other indications (e.g. heart transplantation), and published exposure response analysis for efficacy and safety.

1) Current Clinical Practice

Similar dosing regimens have been reported in literatures and adopted in clinical practice. A summary of starting oral dose and targeted whole blood trough concentration is given in Table 2.

Table 2 Summary of Initial Oral Tacrolimus Dosing Recommendations and Target Whole Blood Trough Concentration Range in Randomized Studies, Nonrandomized Studies, and Published Single-center Guidelines

Reference	Starting Oral Dose	Target Blood Concentration
Treede et al., 2001	0.1 – 0.3 mg/kg/day	12 – 15 ng/mL[#]
Treede et al., 2012	0.05 – 0.3 mg/kg/day	10 – 15 ng/mL for the first 3 months and 8 – 12 ng/mL thereafter
Zuckermann et al., 2003	0.1 – 0.3 mg/kg day	12 – 15 ng/mL during first month and 9 – 12 ng/mL thereafter
Keenan et al., 1995	0.15 mg/kg/day	10 – 20 ng/mL[$]
Bhorade et al., 2011	0.08 mg/kg/day[&]	5 – 15 ng/mL
Hachem et al., 2007	Not reported	5 – 15 ng/mL

Reference	Starting Oral Dose	Target Blood Concentration
Kolaitis et al., 2019	Not reported	Month 0 - 3: 10 - 14 ng/mL Month 3 - 6: 10 - 12 ng/mL Month 6 - 24: 8 - 10 ng/mL > 24 months: 6 - 8 ng/mL
Sikma et al., 2017	0.1 mg/kg/day	9 - 15 ng/mL$
Clinical Guidelines for Transplant Medications, 2019	0.06 - 0.1 mg/kg/day	Month 0 - 3: 10 - 12 ng/mL Month 4 - 12: 8 - 10 ng/mL > 12 months: 6 - 8 ng/mL > 12 months with eGFR < 50 mL/min/1.73 m^2: 4 - 6 ng/mL
Lung Transplantation Management Guidelines, 2016	1 mg bid	Month 1 - 12: 10 - 15 ng/mL Month 12 - 24: 8 - 12 ng/mL > 24 months and CKD: 6 - 10 ng/mL
Neurohr et al., 2009	Not reported	Month 0 - 12: 12 - 15 ng/mL; > 12 months: 9 - 12 ng/mL

#immunofluorescence absorption method
$Abbott IMx
&day 90 posttransplant
CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.
(source: adopted from Table 2 and Table 3 in section 2.7.2 summary of clinical pharmacology)

2) Experience in heart transplantation

The proposed dosing regimen and target trough concentration are similar to the approved ones for heart transplantation. A comparison between the two dosing regimens are listed in Table 3 below.

Table 3 Comparison of Starting Dose and Targeted Whole Blood Trough Concentration in Adult Patients Receiving Heart Transplantation and Lung Transplantation

Heart Transplant		
With azathioprine or MMF	0.075 mg/kg/day capsules, divided in two doses, every 12 hours	Month 1-3: 10-20 ng/mL Month ≥ 4: 5-15 ng/mL
Lung Transplant		
With azathioprine or MMF	0.075 mg/kg/day capsules, divided in two doses, every 12 hours	Month 1-3: 10-15 ng/mL Month 4-12: 8-12 ng/mL

MMF: mycophenolate mofetil

3) Exposure response analysis for efficacy and safety

The targeted trough concentration was supported by current clinical practice as well as published literatures. Rye et al. conducted a Kaplan Meir survival analysis in lung transplant patients[6]. The study showed a tacrolimus trough concentration of 9 ng/ml or less at 1 month was associated with lower rejection-free survival (P = 0.009), and a time-averaged tacrolimus trough concentration of 10 ng/ml or less within 1 month post transplantation was an independent risk factor for poor patient survival (hazard ratio: 4.904; 95% confidence interval: 1.930-12.459; P= 0.001). Sikma et al. evaluated the relationship between tacrolimus trough concentration with incidence of acute kidney injury (AKI) in lung transplant patients and showed AKI in the first week after transplantation was related to supra-therapeutic tacrolimus concentrations (> 15 ng/mL).[7] These two publications provided supportive evidence for the lower boundary and upper boundary of targeted whole blood trough concentrations, respectively.

Overall, the proposed dosing regimen and targeted whole blood trough concentration were similar to the current clinical practice in patients receiving lung transplantation and the approved dosing regimen in patients receiving heart transplantation. Also, the published exposure response analysis also support the targeted whole blood trough concentration.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes. The bioavailability (BA) of tacrolimus in patients with cystic fibrosis (CF) was significantly lower than patients without CF. In one report, targeting the same trough concentration, patients with CF required one fold higher dose (12mg/d) than patients without CF (6.1mg/d).[8] The observed AUC, C_{trough}, C_{max} and T_{max} were similar between patients with CF and patients without CF despite the difference in dose. This study suggested that the BA (extent of absorption) was about 50% lower in patient with CF, and CF has no impact on the rate of tacrolimus absorption (T_{max}). Similarly, Walker et al. reported a 20% to 30% lower bioavailability in patients with CF (n = 4) compared to patients without CF (n = 8).[9] Monchaud et al. conducted a population pharmacokinetic analysis in 78 patients receiving lung transplantation, the estimated BA was 37% lower in patients with CF (n = 38) compared to patients without CF (n = 40).[10] According to these published data, patients with CF may require higher doses due to lower bioavailability.

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[6] Ryu et al., Low early posttransplant serum tacrolimus levels are associated with poor patient survival in lung transplant patients. Annals of Thoracic Medicine - Volume 14, Issue 3, July-September 2019
[7] Sikma et al., High tacrolimus blood concentrations early after lung transplantation and the risk of kidney injury. European Journal of Clinical Pharmacology volume 73, pages573–580(2017)
[8] Knoop et al., Tacrolimus Pharmacokinetics and Dose Monitoring After Lung Transplantation for Cystic Fibrosis and Other Conditions. American Journal of Transplantation 2005; 5: 1477–1482
[9] Walker et al., Clinical Use and Bioavailability of Tacrolimus in Heart-Lung and Double Lung Transplant Recipients With Cystic Fibrosis. Transplantation Proceedings, 30, 1519–1520 (1998)
[10] Monchaud et al, Population Pharmacokinetic Modelling and Design of a Bayesian Estimator for Therapeutic Drug Monitoring of Tacrolimus in Lung Transplantation. Clin Pharmacokinet 2012; 51 (3): 175-186

Is an alternative dosing regimen or management strategy required for children?

The efficacy and safety of tacrolimus in pediatric lung transplantation patients are based on real world data (See section 8.1.2.2). The Applicant proposed an oral dosing regimen and a targeted trough concentration in pediatric patients receiving lung transplantation. This proposal was also consistent with current clinical practice and similar to the approved dosing regimen in pediatric patient receiving heart transplantation (Table 4).

Table 4 Comparison of Starting Dose and Targeted Whole Blood Trough Concentration in Pediatric Patients Receiving Heart Transplantation and Lung Transplantation

Heart Transplant		
	0.3 mg/kg/day[$] capsules or oral suspension, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL
Lung Transplant		
	0.3 mg/kg/day[$, #] capsules or oral suspension, divided in two doses, every 12 hours	Weeks 1-2: 10-20 ng/mL Week 2 to Month 12: 10-15 ng/mL

[$] Dose at 0.1 mg/kg/day if antibody induction treatment is administered.
[#] Patients with cystic fibrosis may require higher doses due to lower bioavailability.

Pediatric patients, in general, need higher tacrolimus doses (in the unit of mg/kg) compared to adults: the higher dose requirements may decrease as the child grows older.

Is an IV dosing regimen reasonable in lung transplantation patients?

In patients who cannot tolerate oral administration, the Applicant proposed an IV infusion dose of 0.01-0.03 mg/kg/day in adult patients receiving lung transplantation. The proposed dosing regimen was implemented in a previously published randomized clinical trial.[11] Considering the 20% BA of tacrolimus capsule, this IV infusion dosing regimen is approximately equivalent to an oral administration dose of 0.05 to 0.15 mg/kg/day and close to the proposed oral dosage of 0.075 mg/kg/day. Therefore, the proposed IV dosing regimen is reasonable. In addition, based on the approved label, 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. The proposed IV infusion dose of 0.01-0.03 mg/kg/day in adult patients receiving lung transplantation is consistent with the approved IV doses in other

[11] Treede H, Glanville AR, Klepetko W, Aboyoun C, Vettorazzi E, Lama R, et al. Tacrolimus and cyclosporinee have differential effects on the risk of development of bronchiolitis obliterans syndrome: Results of a prospective, randomized international trial in lung transplantation. J Heart Lung Transplant. 2012;31:797-804.

indications. Overall, based on current clinical practice, PK characteristics of tacrolimus, and the experience in other indications, the proposed IV dosing regimen is reasonable.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant submited this sNDA to add a new indication to the Prograf labeling for the prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic lung transplants. The evidence in support of labeling changes is based on a sponsor-conducted clinical study F506-CL-3001 – a study providing RWE from a analysis of treatment and outcomes in the SRTR database for patients who have received a lung transplant and were administered tacrolimus, with results then compared to historical controls.

The SRTR is a national transplant registry operated under a federal contract by Hennepin Healthcare Research Institute. The SRTR standard analysis files (SAFs) contain data on all lung transplant candidates, recipients and donors in the US from 1987 onward. The SRTR is made available under a Data Use Agreement to external researchers and includes the outcomes of graft failure, retransplants and deaths for all transplant recipients. The primary source of data contained in the SRTR SAF is from the Organ Procurement and Transplantation Network (OPTN) operated under federal contract by the United Network for Organ Sharing. These data are supplemented with data from the Centers for Medicare & Medicaid Services and the National Technical Information Service's Death Master File.

The Applicant designed Study F506-CL-3001 as a non-interventional (observational) study for the analysis of treatment and outcomes for patients who received a lung transplant in the US. When these results were compared to historical controls the study can be considered adequate and well controlled. The full title of this study is "*Retrospective Study of Treatment and Outcomes for Lung Transplant Patients in the United States using the Scientific Registry of Transplant Recipients (SRTR)*." Confirmatory evidence comes from randomized controlled trials in other solid organ transplants. Additional support for the application comes from existing journal publications as evidence for the effectiveness of tacrolimus in lung transplantation as a component of a triple immunosuppressive regimen and the contribution of tacrolimus to the overall efficacy of the regimen.

Listing of Clinical Trials Relevant to this NDA/BLA
Other than Study F506-CL-3001 there are no clinical studies conducted by the Applicant in support of this efficacy supplement.

Table 5 Listing of Clinical Studies

Study Identifier/ Type of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Eligible for Analysis	Diagnosis of Patients	Study Status; Type of Report
F506-CL-3001 Safety, Efficacy	**Primary:** • describe the use of tacrolimus IR and other immunosuppressive agents over time in lung transplanted patients in the US • describe the incidence of transplant-related outcomes over time in lung transplanted patients in the US **Secondary:** • evaluate the real-world effectiveness of tacrolimus IR + MMF in lung transplantation • evaluate the safety of tacrolimus IR + MMF in lung transplantation Exploratory: • evaluate the contribution of individual agents (specifically tacrolimus IR) over time	Cohort study using real-world data in patients who received a primary lung transplant (not retransplant) between 01 Jan 1999 and 31 Dec 2017 as identified in the SRTR database.	Tacrolimus IR or CsA in combination with either MMF or AZA	25355 adult subjects 725 pediatric subjects (< 18 years old)	Patients who received a primary single- or double-lung transplant (not retransplant) in the SRTR registry between 01 Jan 1999 and 31 Dec 2017 and did not have a history of previous organ transplant, multi-organ transplant or living donor transplant; did not die during index hospitalization; did not have graft failure prior to discharge; did not have discharge date missing or > 1 year from transplant and did not have missing maintenance immunosuppression information at discharge.	Complete; Final CSR

7.2.Review Strategy

The submission of RWD to support the sNDA to add the lung transplant indication to the product labeling is consistent with the framework for FDA's RWE program. The evidence in support of labeling changes is based on RWE generated from data from a Study F506-CL-3001, a non-interventional study that included an analysis of treatment and outcomes, collected from the SRTR, for patients who received a lung transplant and were administered tacrolimus and compared with historical controls. Confirmatory evidence comes from randomized controlled trials in other solid organ transplants. Additional support for the application comes from existing journal publications as evidence for the effectiveness of tacrolimus in lung transplantation as a component of a triple immunosuppressive regimen and the contribution of tacrolimus to the overall efficacy of the regimen. Tacrolimus is a narrow therapeutic index (NTI) drug and is used with therapeutic drug monitoring (TDM) in all approved and off-label indications. The SRTR database used in Study F506-CL-3001 of tacrolimus does not include dosing information or blood trough concentrations for tacrolimus; therefore, the Applicant uses results from published clinical studies and guidelines to support an initial dose regimen and whole blood tacrolimus trough concentration range in the Prograf labeling. The Applicant has also submitted limited safety data from the SRTR to the extent available or collected. The SRTR collects very limited safety information such as malignancies. The Applicant also performed a search of their own database for potential safety issues as well as a literature search.

The efficacy review strategy for this sNDA consists of verifying the efficacy analyses of the Applicant as described in the SAP and the protocol of Study F506-CL-3001 by using the submitted datasets. Safety review mainly relies on existing safety information in the product labeling for other indications and the information gained from the labeled and off-label use of tacrolimus for various types of organ transplants including publications on the off-label use in lung transplantation. The Applicant's analysis of safety based on limited safety data available in the SRTR database and also in the Company safety database will be used as supportive safety data for the pursued lung transplant indication.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Studies Used to Support Efficacy

8.1.1. Clinical Context

Prior to the availability of cyclosporine as an immunosuppressive agent, historical data demonstrated that graft and overall survival among lung transplant recipients was typically only several weeks post-transplantation. For example, in a non-interventional (observational) study of 36 patients receiving lung transplantation in the late 1960s and early 1970s, the median survival was less than two weeks[12] and no patients survived to one year [Veith 1974]. Immunosuppressive treatment at that time consisted mainly of azathioprine and CS; CNIs (cyclosporine or tacrolimus) were not yet available. Subsequently, in the 1980's, graft and overall survival times of 14 months and 26 months were reported in the first two cases of patients receiving a cyclosporine (another CNI) as part of their post-transplant immunosuppressive regimen [Toronto Lung Transplant Group 1986]. Although some improvements in surgical techniques and supportive care occurred over the interval, these dramatically longer survival times can be attributed directly to the improved effectiveness of immunosuppressive therapy [Hardy 1963, Veith 1974, Toronto Lung Transplant Group 1986 and Griffith 1994].

8.1.2. Adequate and Well Controlled Study

Substantial evidence of effectiveness based on adequate and well-controlled clinical investigations is required for approval of a drug under section 505(c) of the Federal Food, Drug, and Cosmetic Act. In many cases, two adequate and well-controlled clinical investigations are needed. However, when scientifically appropriate, evidence from a single adequate and well-controlled clinical investigation with confirmatory evidence can be sufficient to meet the substantial evidence standard. FDA regulations at 21 CFR 314.126 outline the characteristics of an adequate and well-controlled clinical study. Historically controlled studies usually involve a treatment group with drug assignment according to a protocol (as in a single-arm clinical trial), the regulations do not require such a design when comparing outcomes of treatment and historical control groups.

A distinct aspect of Study F506-CL-3001 is its non-interventional ("observational") design, meaning that patients in the treatment arm received the drug of interest in everyday medical practice rather than being assigned the drug according to a research protocol. Given that treatment assignment in a non-interventional study is based on clinical judgment rather than a protocol-based assignment, confounding and other sources of bias

[12] FDA analysis based on [Veith 1974].

can create challenges in establishing causal inference for the purpose of supporting an effectiveness determination for regulatory decisions. However, the review team recognizes that a non-interventional study—depending on details of the clinical context, data sources (including methods of data collection), study design, and magnitude of the treatment effect—can provide robust findings comparable to a clinical trial and meet the regulatory requirements for an adequate and well-controlled study under 21 CFR 314.126.

The review team, with the support of the RWE subcommittee, determined that Study F506-CL-3001, with comparision to historical controls, satisfies the regulatory requirements for an adequate and well-controlled study under 21 CFR 314.126. The study is based on data from the SRTR, operating under contract from the Health Resource and Services Administration (HRSA) in the Department of Health and Human Services (HHS). The SRTR has a well-established and robust operational structure for collecting rigorous data on all US solid-organ transplant recipients, as required by the National Organ Transplantation Act of 1984 [Leppke 2013]. The accuracy of SRTR data is enhanced by the capture of predefined data elements on each transplant patient regarding transplantation and graft survival, and is supplemented by other information, including from the Social Security Administration's Death Master File as a trusted repository of mortality data. Based on the sources of data and steps involved with data processing (including data quality verification) [Leppke 2013], the review team found the assessments of study variables, such as the endpoints of interest (death or graft failure at one year), to be relevant and reliable.

Study F506-CL-3001 was designed and conducted according to a protocol with clear research objectives and a statistical analysis plan. The sponsor analyzed data from the SRTR on all patients receiving single- or double-lung transplantation in the US during 1999 to 2017, with reliable classification of each patient's diagnosis as well as objective and well-defined clinical endpoints of death or graft failure. In addition, patients included in the SRTR analyses were not limited to a selected population and the inclusion of patients wasn't limited to only selected study sites. As a compulsory registry [Hanto 2003], the data represent the most generalizable U.S. population of lung transplant recipients that could be recruited, and data on all such patients are captured. Accordingly, limitations related to a non-representative study population do not apply.

Analysis of data in the SRTR showed one-year graft and overall survival of 85-90% or better for a tacrolimus-containing immunosuppressive regimen of either tacrolimus + MMF + CS or tacrolimus + azathioprine + CS. Although Study F506-CL-3001 did not include a specified control group, these outcomes are highly unlikely to have occurred spontaneously or by chance, given the well-documented natural history of a transplanted lung with no or minimal immunosuppressive therapy. As such, the outcomes were compared to historical controls in the absence of combination immunosuppressant therapy, where no graft or overall survival was observed at one year and survival was largely limited to several weeks

[Veith 1974]. When the treatment group in Study F506-CL-3001 is compared with the historical controls, the study can be considered adequate and well-controlled.

Given the lack of contemporaneous data collection, differences may exist between the treatment and the historical control groups. The SRTR data go back to 1999 and some differences would be expected between patients in the SRTR and historical controls due to changes in baseline characteristics of patients receiving transplantation, surgical techniques, and supportive medical care over time. Nonetheless, the clinical benefit seen with the tacrolimus-containing immunosuppressive regimen studied is so large compared to historical controls that differences in baseline characteristics, surgical technique, and/or supportive care between groups are highly unlikely to explain the outcome differences, and therefore do not change the conclusion of effectiveness.

8.1.3. Non-Interventional Study of Treatment and Outcomes for Lung Transplant Patients in the United States using the Scientific Registry of Transplant Recipients (SRTR) (Study F506-CL-3001)

Study Design

Study F506-CL-3001 used the SRTR database to evaluate the use of tacrolimus and other immunosuppressive agents for lung transplantation and transplantation-related outcomes.The study included patients who received a primary lung transplantation (single-lung and double-lung transplantation but not retransplantation) from January 1, 1999 to December 31, 2017. Although the study assessed the use of immunosuppressive agents other than tacrolimus, the efficacy of tacrolimus was not compared to that of these immunosuppressive agents. The outcomes were compared to historical controls in the absence of combination immunosuppressant therapy, where no graft or overall survival was observed at one year and survival was largely limited to several weeks [Hardy 1963 and Veith 1974]. When the treatment group in Study F506-CL-3001 is compared with the historical controls, the study can be considered adequate and well-controlled.

Study Endpoints

The primary efficacy endpoint was a composite endpoint of graft failure (GF) or death (due to any cause) within 1 year (365 days) after transplantation.

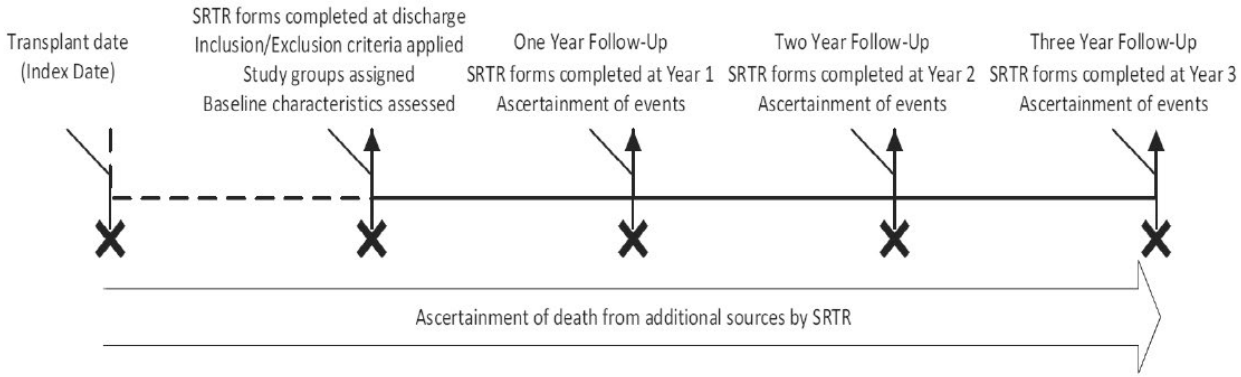
The secondary endpoints included the following:

- GF or death at 2 and 3 years of follow-up
- Patient death
- GF
- Any rejection
- Treated rejection
- Bronchiolitis obliterans syndrome (BOS)
- Composite endpoints

- Death, GF, any rejection
- Death, GF, any treated rejection
- Death, GF, BOS
- Death, GF, BOS or any rejection
- Death, GF, BOS or any treated rejection

Study Assessments
Data for transplant recipients are collected at discharge posttransplant, 6 months posttransplant, 12 months posttransplant and annually thereafter. The schedule of assessments is provided in Figure 1.

Figure 1. Study Schematic



Source: applicant's analysis data reviewer's guide (p.4)

Statistical Analysis Plan

Sample size consideration
The study identified 28,553 adult and 849 pediatric lung transplantation recipients during 1999 and 2017. Because the SRTR captures data of all transplantation patients in the United States, even without a precision based sample size calculation, the FDA considered the sample size to be adequate to support the planned analyses and to yield estimates with sufficient precision.

Analysis Populations
The analysis population for the evalulation of efficacy was the intention-to-treat (ITT) population based on the immunosuppressive regimen at discharge from the hospital after lung transplantation. The adult and pediatric populations consisted of patients ≥18 years old and <18 years old, respectively, at the time of transplantation.

Patients who had received a primary lung transplantation during January 1, 199 and December 31, 2017 were included in the study population. The following patients were excluded from the

study population.

- Patients with a history of organ transplantation prior to and including the date of lung transplantation
- Transplant recipients of a multiorgan transplantation or organ from a living donor
- Transplant recipients who had died during the index hospitalization or had GF on or prior to discharge
- Transplant recipients with missing discharge date, discharge date more than 1-year posttransplant, or missing maintenance immunosuppression information at discharge

Analysis of Primary Efficacy Endpoints

The primary efficacy endpoint was the cumulative incidence of graft failure or death within one-year posttransplant. A cumulative incidence was estimated by Kaplan-Meier estimate and the 95% confidence interval (CI) was derived using a log transformation. Applicant conducted three different analyses (primary, sensitivity, and post hoc). All analyses excluded patients who experienced death or graft failure during hospitalization for transplantation.

The primary analysis included time from transplantation date (index date) to estimate the cumulative incidence. However, the analysis only included events that occurred after patients were discharged. In other words, the the time-to-event data were left-truncated at discharge. Therefore, patients entered the risk set on discharge date.

The sensitivity analysis included time and events that occurred after discharge date (= index date) in calculating the cumulative incidence. All patients were included in the risk set from discharge date.

The post-hoc analysis, conducted only for the TAC IR + MMF group, was similar to the primary analysis. However, this analysis reassigned the event date of four events that occurred before Day 7 to Day 10 posttransplantation. Day 10 was when the first event in the TAC IR + AZA group occurred. The primary analysis was sensitive to these early events that occurred when the risk set was small. Hospitalization data did not distinguish discharge from transfers, which affected the size of the risk set and ultimately the estimate. (See Section 8.3 Statistical Issues.)

Analysis of Secondary Efficacy Endpoints

All secondary efficacy endpoints with the exception of graft failure, used the same primary analysis method described in the primary efficacy endpoint. For graft failure, Applicant used the Aalen-Johansen estimate of cumulative incidence to account for competing risk.

8.1.4. Study Results

Compliance with Good Clinical Practices

Based on the rigor of the regulatory oversight of the SRTR, a well-established and robust operational structure for collecting data on all US solid-organ transplant recipients as required by the National Organ Transplantation Act of 1984, the review team did not deem it necessary to request inspections by the Office of Scientific Investigations (OSI) for this submission.

Financial Disclosure

Per the Form 3454, submitted on June 24, 2021, signed by Mary Jo Pritza, Sr. Director Regulatory Affairs, Astellas has not entered into any financial arrangement with the listed clinical investigators (b) (4) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

8.1.4.1. Adult Lung Transplantation Recipeints

Patient Disposition

A total of 29,772 patients were identified as having received a single-lung or double-lung transplantation from January 1, 1999 to December 31, 2017. Of these, 25,355 adult (≥18 years old) patients met the analysis inclusion criteria . The majority of adults patients received TAC IR + MMF (61%) followed by TAC IR + AZA (17%) as a maintenance therapy at discharge. A number of patients received regimens that used cyclosporine A (CsA): CsA + MMF (5%) and CsA + AZA (8%). A total of 2,436 patients (10%) received another regimen, categorized as “Other” in Table 6. Table 6 summarizes the number and proportion of patients by each immunosuppression regimen.

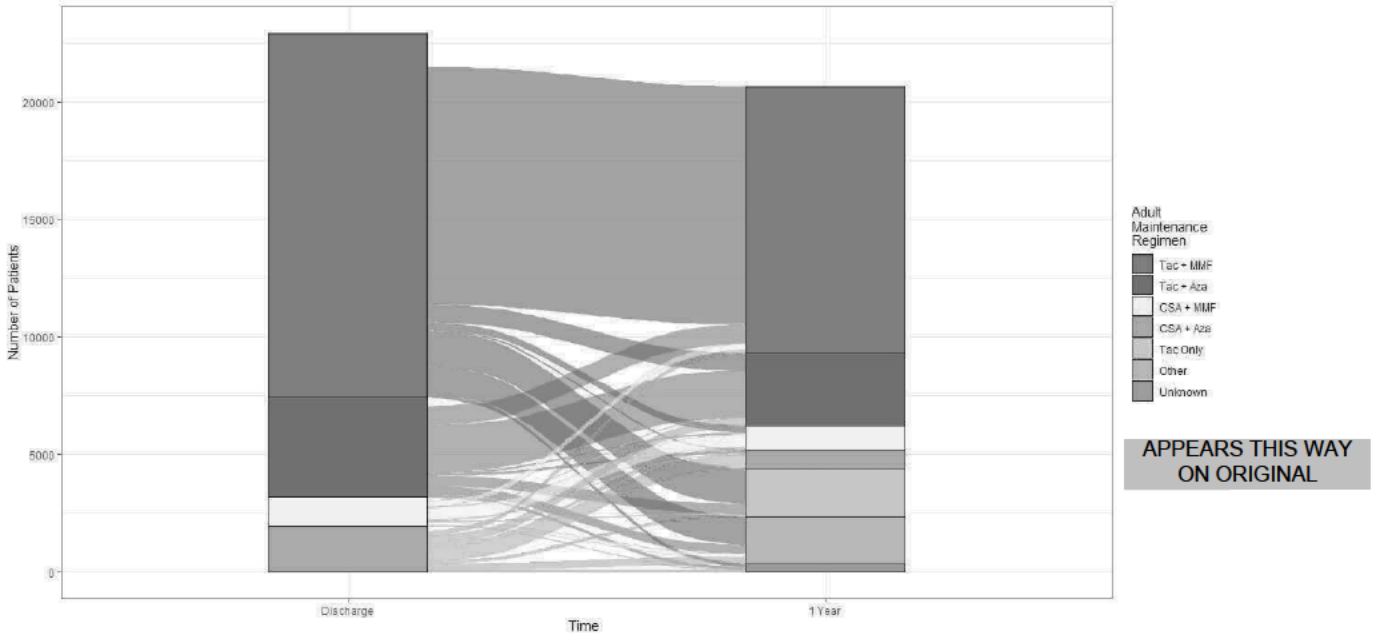
Table 6. Patient Disposition in Adult Patients

	Total	TAC IR + MMF	TAC IR + AZA	CsA + MMF	CsA + AZA	Other
Number (%) of patients	25355 (100%)	15478 (61%)	4263 (17%)	1219 (5%)	1959 (8%)	2436 (10%)

Source: reviewer’s analysis

Most patients who received TAC IR + MMF at discharge remained on TAC IR + MMF at 1-year posttransplantation (72%). However, 5% and 11% of the patients who received TAC IR + MMF at discharge switched to TAC + AZA, and TAC only, respectively, at 1-year posttransplantation (Figure 2).

Figure 2. Changes in Immunosuppression Regimen in Adult Patients at 1-year Posttransplantation



Source: reviewer's figure replicated from *CDRG Changes in Immunosuppresive Meds Report Figure 4.1 (p.5)*

Protocol Violations/Deviations

Protocol violations or deviations were not applicable in this registry study.

Demographic and Other Baseline Characteristics

In total, adult lung transplantation recipients were on average 53 years old, 57.3% male, and 89.7% White (Table 7). In patients receiving tacrolimus products, double-lung transplantation was more common than single-lung transplantation. Pulmonary fibrosis was the most common diagnosis in these patients, followed by chronic obstructive pulmonary disease (COPD) and cystic fibrosis. The median length of hospitalization for TAC IR + MMF group and TAC IR + AZA group patients were 16 and 14 days, respectively. The usage of tacrolimus increased over time; during 2010-2017, 71.6% of the total lung transplantation patients received TAC IR + MMF at discharge.

Table 7. Demographic Characteristics of Adult Lung Transplantation Recipients

Baseline Characteristic	Immunosuppression Regimen Exposure Groups				
	Total Cohort (n = 25355)	TAC IR + MMF (n = 15478)	TAC IR + AZA (n = 4263)	CsA + MMF (n = 1219)	CsA + AZA (n = 1959)
Age at transplant (years)					
Mean	53.4	55.5	53.3	53.0	51.3
Median	58	59	57	56	55
Sex, n (%)					
Male	14526 (57.3)	9055 (58.5)	2408 (56.5)	677 (55.5)	1052 (53.7)
Female	10829 (42.7)	6423 (41.5)	1855 (43.5)	542 (44.5)	907 (46.3)
Race, n (%)					

White	22745 (89.7)	13825 (89.3)	3779 (88.6)	1101 (90.3)	1821 (93.0)
Black	2101 (8.3)	1286 (8.3)	416 (9.8)	106 (8.7)	115 (5.9)
Asian	349 (1.4)	264 (1.7)	46 (1.1)	7 (0.6)	6 (0.3)
Native American	77 (0.3)	54 (0.3)	9 (0.2)	9 (0.2)	5 (0.3)
Pacific Islander	19 (0.1)	14 (0.1)	2 (0.0)	0	3 (0.2)
Multiracial	63 (0.2)	35 (0.2)	11 (0.3)	3 (0.2)	9 (0.5)
Lung transplant procedure, n (%)					
Double	16190 (63.9)	10278 (66.4)	2775 (65.1)	558 (45.8)	1011 (51.6)
Single	9165 (36.1)	5200 (33.6)	1488 (34.9)	661 (54.2)	948 (48.4)
Transplant era, n (%)					
1999 - 2005	6284 (24.8)	1664 (10.8)	1427 (33.5)	861 (70.6)	1494 (76.3)
2006 - 2009	5024 (19.8)	2738 (17.7)	1305 (30.6)	168 (13.8)	259 (13.2)
2010 - 2017	14047 (55.4)	11076 (71.6)	1531 (35.9)	190 (15.6)	206 (10.5)
LAS at transplant, median (Q1, Q3)	39.9 (34.7, 50.5)	40 (34.8, 50.9)	39.4 (34.5, 48.6)	39.5 (34.7, 53.1)	38.2 (34.2, 44.5)
Diagnosis group, n (%)					
COPD	9529 (37.6)	5092 (32.9)	1743 (40.9)	621 (50.9)	1102 (56.3)
Pulmonary hypertension	966 (3.8)	593 (3.8)	163 (3.8)	35 (2.9)	66 (3.4)
Cystic fibrosis	3198 (12.6)	1890 (12.2)	595 (14.0)	125 (10.3)	300 (15.3)
Pulmonary fibrosis	11621 (45.8)	7900 (51.0)	1755 (41.2)	431 (35.4)	477 (24.3)
Unknown	41 (0.2)	3 (0.0)	7 (0.2)	7 (0.6)	14 (0.7)
Length of hospital stay after transplant, days, median (Q1, Q3)	15 (11, 25)	16 (11, 25)	14 (10, 21)	17 (11, 28)	13 (9, 20)
Clinical laboratory values at transplant, median (Q1, Q3)					
Serum creatinine, mg/dL	0.8 (0.7, 1)	0.8 (0.7, 1)	0.8 (0.7, 1)	0.8 (0.7, 1)	0.8 (0.7, 1)
eGFR, mL/min/1.73 m2	94.2 (78.7, 105.5	93.9 (79.1, 105.0)	94.4 (78.9, 106.3)	94.2 (77.5, 105.4)	95.1 (79.3, 106.4)
Total bilirubin, mg/dL	0.5 (0.3, 0.7)	0.5 (0.3, 0.7)	0.5 (0.3, 0.7)	0.5 (0.4, 0.7)	0.5 (0.3, 0.7)
Lung total ischemia time, hours: median (Q1, Q3)	4.9 (3.9, 6)	4.9 (3.9, 6)	4.8 (3.8, 5.9)	4.6 (3.5, 5.9)	4.8 (3.8, 5.9)

Note: LAS: lung allocation score
Source: reviewer's analysis and Applicant's study report (p.34, Table 1)

Efficacy Results – Primary Efficacy Endpoint

The review of efficacy focuses on the two regimens that include tacrolimus, TAC IR + MMF and TAC IR + AZA. Immunosuppressive regimens were not compared to each other because of the differences in risk factors at baseline.

In the TAC IR + MMF group, the cumulative incidence of death or graft failure at 1-year posttransplant was 14.2% (95% CI: 7.8, 20.2) (Table 8). The primary analysis method (left-truncation) is sensitive to events that occur when the risk set is small. The first event occurred at Day 4 posttranplantation, only 44 patients had been discharged and included in the risk set. Therefore, the cumulative incidence and its CI were relatively higher and wider than those from

the following sensitivity and post-hoc analysis. The CI was wide during the entire follow-up period. (Figure 3).

Table 8. Estimates of Cumulative Incidence of Death or Graft Failure Outcomes from 1-year Posttransplantation (primary, post hoc) and Postdischarge (sensitivity)

Group	Analysis	# of Patients at Risk	# of Events	Cumulative Incidence % (95% CI)
TAC IR + MMF	Primary	15478	1272	14.2 (7.8, 20.2)
	Sensitivity	15478	1398	9.1 (8.6, 9.5)
	Post-hoc	15478	1272	8.6 (8.1, 9.1)
TAC IR + AZA	Primary	4263	365	8.8 (7.9, 9.6)
	Sensitivity	4263	390	9.2 (8.3, 10.0)

Source: applicant's study report (p.48, Table 6)
Note: post hoc analysis is not available (NA) in TAC IR + AZA group

The sensitivity analysis resulted in the cumulative incidence of 9.1% (95% CI: 8.6, 9.5) at 1-year postdischarge. Because all patients entered the risk set from the discharge date, the cumulative incidence was lower than that from the primary analysis even though the first event occurred at Day 4. Figure 4 presents the cumulative incidence through 1 year postdischarge.

Applicant's post-hoc analysis reassigned the event date of the early four events to Day 10 posttransplantation. This modification increased the number of patients in the risk set from 44 to 2,354 patients when the first event occurred, thereby decreased the cumulative incidence of death or graft failure at 1-year posttransplant from 14.2% to 8.6% (95% CI: 8.1, 9.1). Figure 5 presents the cumulative incidence through 1-year posttransplantation. Table 9 presents information (day of discharge, day of event and event type) of the four patients who experienced an event before Day 7.

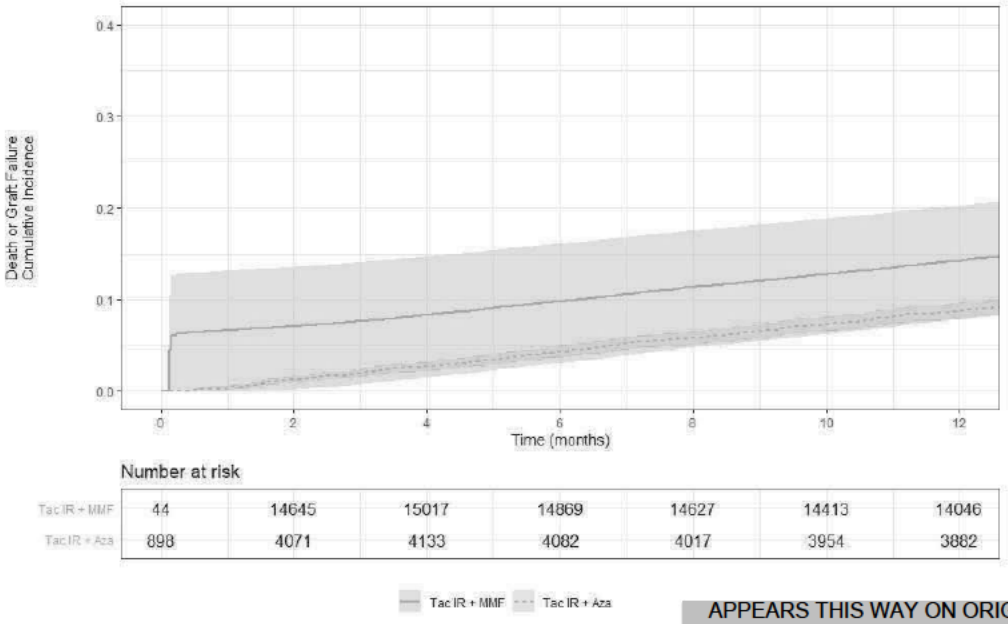
Table 9. Day of discharge and transplant of early four events in TAC IR + MMF group

ID	Day of Discharge	Day of Event	Event
(b) (6)	2	4	Graft failure
	2	4	Death
	2	5	Death
	5	7	Death

Note: patient ID is substituted for alphabet; Day 0 was day of transplant
Source: reviewer's table

In the TAC IR + AZA group, the cumulative incidence of death or graft failure at 1-year posttransplant was 8.8% (95% CI: 7.9, 9.6) (Table 8). Applicant did not conduct the post hoc analysis in this exposure group because the risk set was relatively large (n= 898) when the first event occurred at Day 10. The sensitivity analysis resulted in a cumulative incidence of 9.2% (95% CI: 8.3, 10.0) at 1-year postdischarge.

Figure 3. Primary Analysis (Adult): Cumulative Incidence of Death or Graft Failure through 1-year Posttransplantation



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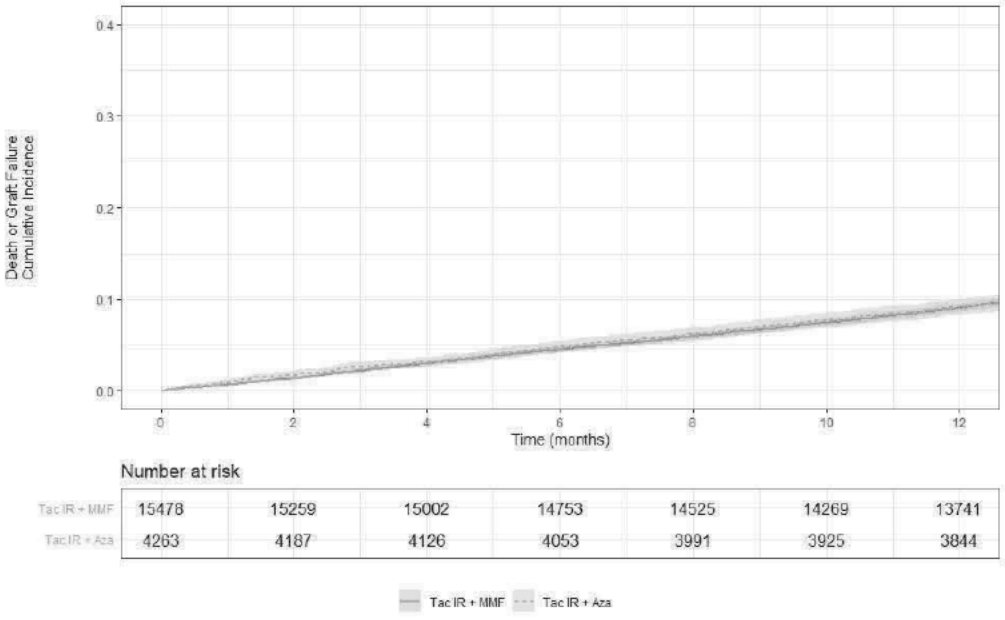
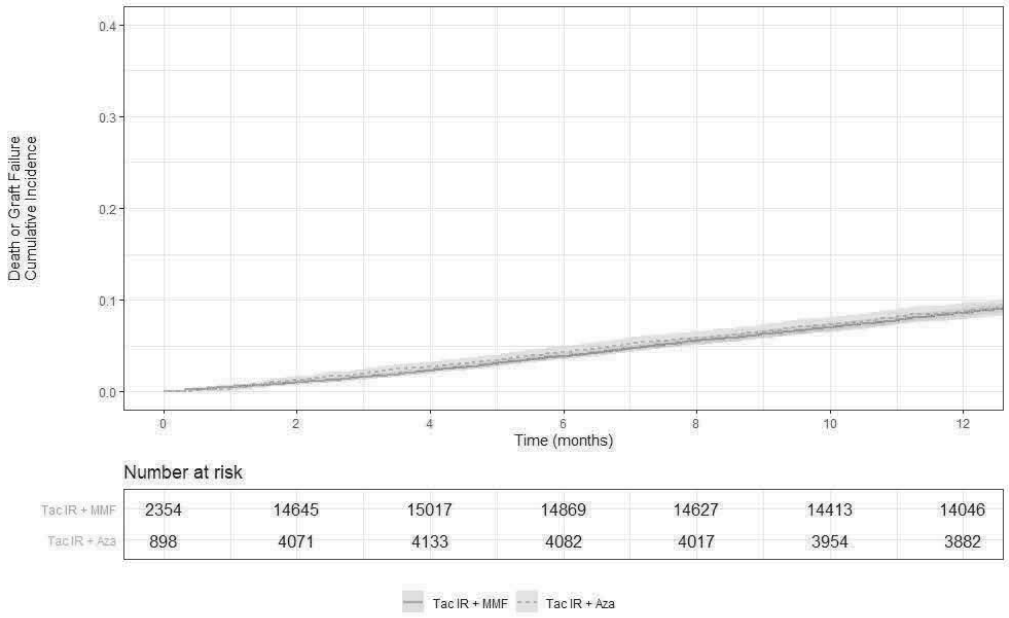
Source: reviewer's analysis

Figure 4. Sensitivity Analysis (Adult): Cumulative Incidence of Death or Graft Failure through 1-year Postdischarge



Source: reviewer's analysis

Figure 5. Post-hoc Analysis (Adult): Cumulative Incidence of Death or Graft Failure through 1-year Posttransplantation



Source: reviewer's analysis

Secondary Efficacy Endpoints

Composite endpoint of death or graft failure at 2- and 3-year posttransplantation

The cumulative incidences of a composite endpoint of graft failure or death at 2-year and 3-year posttranplant in the TAC IR + MMF patients were 22.7% (95% CI: 16.9, 28.1) and 30.5% (95% CI: 25.3, 35.4), respectively (Table 10).

For the TAC IR + AZA group, the cumulative incidences of a composite endpoint of graft failure or death were 17.7% (95% CI: 16.5, 18.9) and 25.5% (95% CI: 24.1, 26.8) at 2-year and 3-year posttransplantation, respectively (Table 10).

Table 10. Estimates of Cumulative Incidence of a Composite Endpoint of Death or Graft Failure at 2-years and 3-years Posttransplantation

Group	Time	# of Patients at Risk	# of Events	Cumulative Incidence % (95% CI)
TAC IR + MMF	Year 2	14046	1306	22.7 (16.9, 28.1)
	Year 3	10946	1036	30.5 (25.3, 35.4)
TAC IR + AZA	Year 2	3882	375	17.7 (16.5, 18.9)
	Year 3	3388	315	25.5 (24.1, 26.8)

Source: reviewer's analysis and Applicant's study report (p.48, Table 6)

Death and graft failure at 1, 2, and 3 years posttransplant

The cumulative incidence of death at 1-year posttransplantation was 11.9% (95% CI: 6.9, 16.6) and 8.3% (95% CI: 7.4, 9.1) in the TAC IR + MMF and TAC IR + AZA groups, respectively. The cumulative incidence of graft failure at 1-year posttransplantation was 4.8% (95% CI: 2.0, 11.8) and 2.7% (95% CI: 2.2, 3.2) in the TAC IR + MMF and TAC IR + AZA groups, respectively.

Results of cumulative incidences of death and of graft failture at 2-year and 3-year posttransplantation are summarized in the Table 11 below.

Table 11. Estimates of Cumulative Incidence of Death and Cumulative Incidence of Graft Failture at 1-, 2- and 3-Year Posttransplantation

Group	Outcome	Years Posttranplantation	# of Patients At risk	# of Events	Cumulative Incidence % (95% CI)
TAC IR + MMF	Death	1	15478	1229	11.9 (6.9, 16.6)
		2	14249	1244	20.1 (15.5, 24.4)
		3	11278	1012	27.8 (23.6, 31.7)
	Graft Failure†	1	15478	372	4.8 (2.0, 11.8)
		2	14046	583	8.6 (5.3, 14.0)
		3	10946	497	12.4 (8.9, 17.1)
TAC IR + AZA	Death	1	4263	346	8.3 (7.4, 9.1)
		2	3917	350	16.6 (15.4, 17.7)
		3	3465	301	23.9 (22.6, 25.2)
	Graft Failure†	1	4263	110	2.7 (2.2, 3.2)
		2	3882	186	7.1 (6.4, 7.9)
		3	3388	146	10.7 (9.8, 11.7)

Source: reviewer's analysis and Applicant's study report (p.48, Table 6)
†The Aalen-Johansen CR estimate

8.1.4.2. Pediatric Lung Transplant Recipients

Patient Disposition

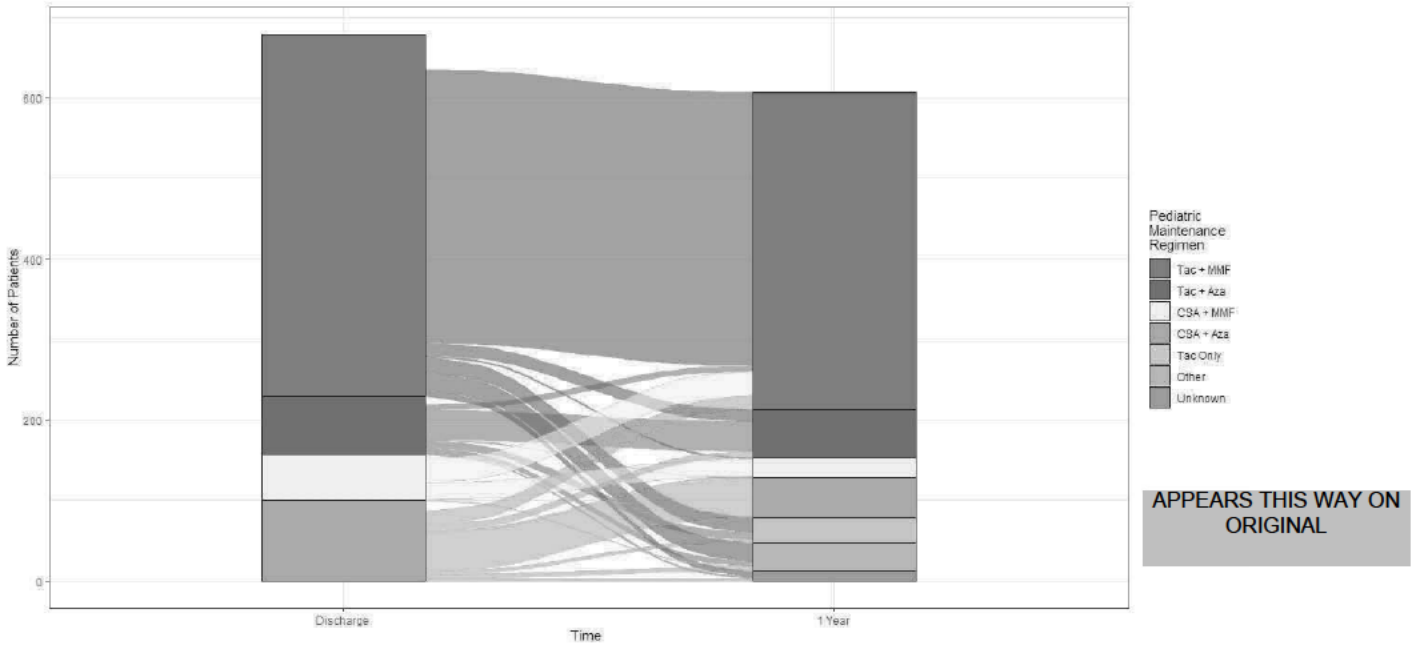
A total of 725 pediatric patients were included in the analysis. Similar to the adult patient population, the majority of the pediatric patients received tacrolimus products in combination with either MMF (62%) or AZA (10%). A number of patients received regimens that used cyclosporine A (CsA): CsA + MMF (8%) and CsA + AZA (14%). Approximately 6% of the patients received another regimen, categorized as "Other" in Table 12. Table 12 summarizes the number and proportion of patients by each immunosuppression regimen. Approxmiately 84% of the pediatric patients who received TAC IR + MMF at discharge remained on TAC IR + MMF, 4% switched to TAC + AZA, and 5% switched to TAC only at 1-year posttransplant (Figure 6).

Table 12. Patient Disposition in Pediatric Patients

	Total	TAC IR + MMF	TAC IR + AZA	CsA + MMF	CsA + AZA	Other
Number (%) of patients	725 (100%)	450 (62%)	72 (10%)	57 (8%)	100 (14%)	46 (6%)

Source: reviewer's analysis

Figure 6. Changes in Immunosuppression Regimen in Pediatric Patients at 1-year Posttransplantation



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Source: reviewer's figure replicated from *CDRG Changes in Immunosuppresive Meds Report Figure 4.2 (p.6)*

Protocol Violations/Deviations

Protocol violations or deviations were not applicable in this registry study.

Demographic and Other Baseline Characteristics

In total, pediatric lung transplantation recipients were on average 12 years old, 59.3% female, and 90.9% White (Table 13). Most patients who received tacrolimus products in combination with MMF or AZA, received a double-lung transplantation. Cystic fibrosis was the most common diagnosis in these patients. However, a large number of patients did not have diagnoses information. The median of length of hospitalization for TAC IR + MMF and TAC IR + AZA groups were both 19 days. The usage of tacrolimus in combination with MMF increased over time whereas the usage in combination with AZA decreased.

Table 13. Demographic Characteristics of Pediatric Lung Transplantation Recipients

Baseline Characteristic	Immunosuppression Regimen Exposure Groups				
	Total Cohort (n = 725)	TAC IR + MMF (n = 450)	TAC IR + AZA (n = 72)	CsA + MMF (n = 57)	CsA + AZA (n = 100)
Age at transplant (years)					
Mean	11.6	11.5	13.9	11.4	10.5
Median	14	13	16	13	13
Sex, n (%)					
Male	295 (40.7)	191 (42.4)	24 (33.3)	21 (36.8)	43 (43.0)
Female	430 (59.3)	259 (57.6)	48 (66.7)	36 (63.2)	57 (57.0)
Race, n (%)					
White	659 (90.9)	409 (90.9)	67 (93.1)	53 (93.0)	91 (91.0)
Black	43 (5.9)	26 (5.8)	4 (5.6)	2 (3.5)	5 (5.0)
Asian	12 (1.7)	8 (1.8)	1 (1.4)	1 (1.8)	2 (2.0)
Native American	5 (0.7)	5 (1.1)	0	0	0
Pacific Islander	1 (0.1)	1 (0.2)	0	0	0
Multiracial	5 (0.7)	1 (0.2)	0	1 (1.8)	2 (2.0)
Lung transplant procedure, n (%)					
Double	720 (99.3)	448 (99.6)	72 (100.0)	56 (98.2)	100 (100.0)
Single	5 (0.7)	2 (0.4)	0	1 (1.8)	0
Transplant era, n (%)					
1999 - 2005	246 (33.9)	51 (11.3)	39 (54.2)	43 (75.4)	89 (89.0)
2006 - 2009	177 (24.4)	122 (27.1)	22 (30.6)	12 (21.1)	11 (11.0)
2010 - 2017	302 (41.7)	277 (61.6)	11 (15.3)	2 (3.5)	0
LAS at transplant, median (Q1, Q3)	37.1 (34.6, 44.8)	36.8 (34.4, 45.0)	39.5 (36.1, 45.2)	34.7 (33.3, 35.8)	36.7 (35.8, 38.3)
Diagnosis group, n (%)					
COPD	9 (1.2)	6 (1.3)	2 (2.8)	0	0
Pulmonary hypertension	45 (6.2)	35 (7.8)	0	3 (5.3)	3 (3.0)
Cystic fibrosis	327 (45.1)	182 (40.4)	48 (66.7)	28 (49.1)	50 (50.0)
Pulmonary fibrosis	73 (10.1)	55 (12.2)	5 (6.9)	4 (7.0)	4 (4.0)
Unknown	271 (37.4)	172 (38.2)	17 (23.6)	22 (38.6)	43 (43.0)
Length of hospital stay after transplant, days, median (Q1, Q3)	19 (13, 30)	19 (14, 30)	19 (13, 28.2)	15 (9, 19)	19 (13, 37)
Clinical laboratory values at transplant, median (Q1, Q3)					
Serum creatinine, mg/dL	0.4 (0.3, 0.6)	0.4 (0.3, 0.6)	0.4 (0.4, 0.6)	0.5 (0.4, 0.6)	0.4 (0.4, 0.5)

eGFR, mL/min/1.73 m2	NA	NA	NA	NA	NA
Total bilirubin, mg/dL	0.3 (0.2, 0.6)	0.3 (0.2, 0.6)	0.4 (0.2, 0.5)	0.4 (0.2, 0.5)	0.4 (0.3, 0.5)
Lung total ischemia time, hours: median (Q1, Q3)	5.4 (4.5, 6.2)	5.5 (4.5, 6.3)	5.0 (4.3, 6.2)	5.7 (4.8, 6.6)	5.3 (4.8, 6)

Note: LAS: lung allocation score
Source: reivewer's analysis and Applicant's study report (p.34, Table 1)

Efficacy Results – Primary Efficacy Endpoint
Similarly to the adult population, the review of pediactric population focuses on the two regimens that include tacrolimus, TAC IR + MMF and TAC IR + AZA. Immunosuppressive regimens were not compared to each other because of the differences in risk factors at baseline.

In the TAC IR + MMF group, the cumulative incidence of death or graft failure at 1-year posttransplant was 7.7% (95% CI: 5.2, 10.1) (Table 14).
The sensitivity analysis resulted in a cumulative incidence of 8.3% (95% CI: 5.7, 10.8) at 1-year postdischarge. Applicant did not conduct the post-hoc analysis in the pediatric patients.

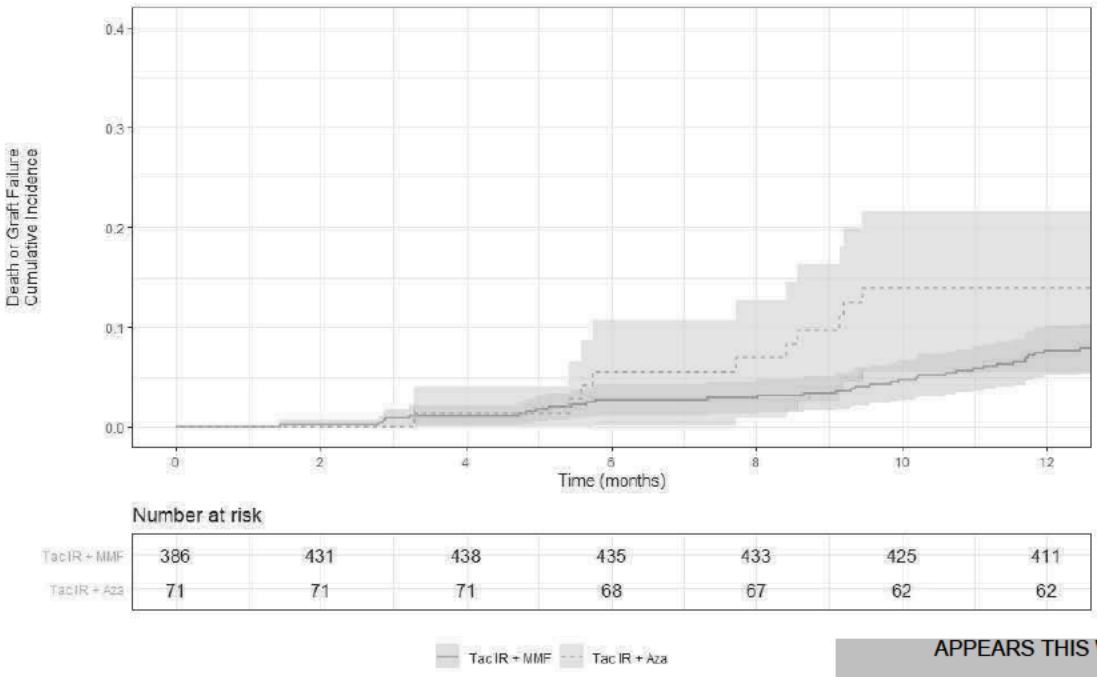
In the TAC IR + AZA group, the cumulative incidence of death or graft failure at 1-year posttransplantation was 13.9 (95% CI: 5.5, 21.5) (Table 14). The sensitivity analysis resulted in a cumulative incidence of 15.3% (95% CI: 6.5, 23.2) at 1-year postdischarge.

Table 14. Estimates of Cumulative Incidence of Death or Graft Failure 1-year Posttransplant (primary) and Postdischarge (sensitivity)

Group	Analysis	# of Patients at Risk	# of Events	Cumulative Incidence % (95% CI)
TAC IR + MMF	Primary	450	34	7.7 (5.2, 10.1)
	Sensitivity	450	37	8.3 (5.7, 10.8)
TAC IR + AZA	Primary	72	10	13.9 (5.5, 21.5)
	Sensitivity	72	11	15.3 (6.5, 23.2)

Source: reviewer's analysis and Applicant's study report (p.66, Table 14)

Figure 7. Primary Analysis (Pediatric): Cumulative Incidence of Death or Graft Failure through 1-year Posttransplant



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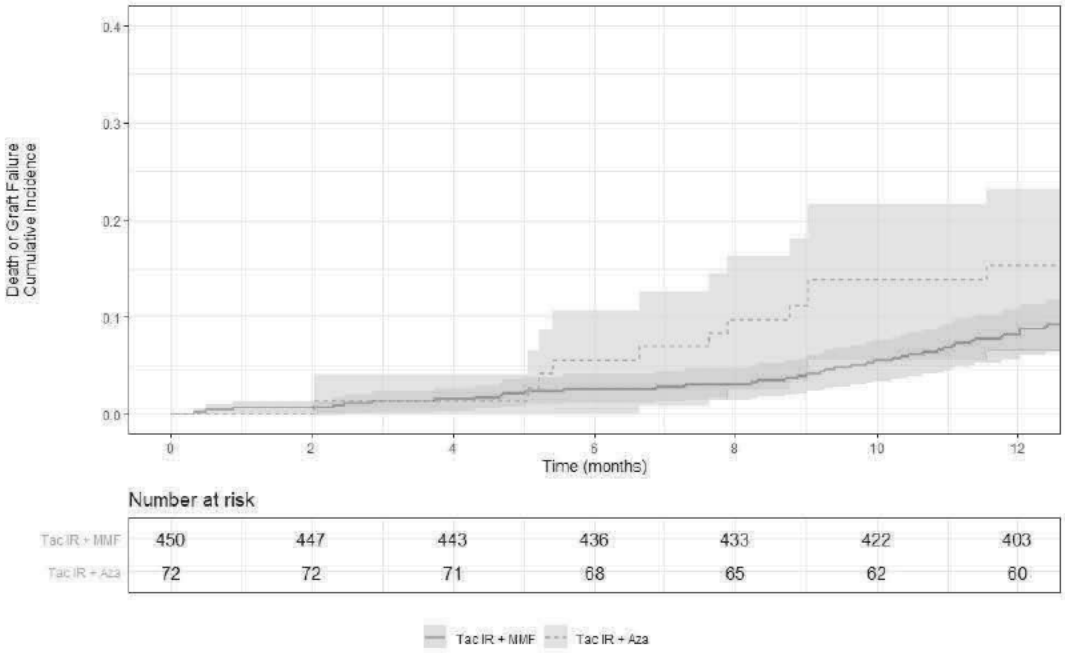
Source: reviewer's analysis

Figure 8. Sensitivity Analysis (Pediatric): Cumulative Incidence Death or Graft Failure through 1-year Postdischarge



Source: reviewer's analysis

Secondary Efficacy Endpoints

Composite endpoint of death or graft failure through 2- and 3-year posttransplantation
The cumulative incidences of a composite endpoint of graft failure or death at 2-year and 3-year posttranplant in the TAC IR + MMF patients were 20.9% (95% CI: 17.0, 24.7) and 31.7% (95% CI: 27.1, 36.1), respectively (Table 15).

For the TAC IR + AZA group, the cumulative incidences of a composite endpoint of graft failure or death were 31.0% (95% CI: 19.4, 41.0) and 45.4% (95% CI: 32.4, 55.9) at 2-year and 3-year posttransplantation, respectively (Table 15).

Table 15. Estimates of Cumulative Incidence of a Composite Endpoint of Death or Graft Failure at 2-years and 3-years Posttransplantation

Group	Time	# of Patients at Risk	# of Events	Cumulative Incidence % (95% CI)
TAC IR + MMF	Year 2	411	56	20.9 (17.0, 24.7)
	Year 3	319	42	31.7 (27.1, 36.1)
TAC IR + AZA	Year 2	62	12	31.0 (19.4, 41.0)
	Year 3	48	10	45.4 (32.4, 55.9)

Source: reviewer's analysis and Applicant's study report (p.66, Table 14)

Death and graft failure at 1-, 2-, and 3 years posttransplantation
The cumulative incidence of death at 1-year posttransplantation was 7.4% (95% CI: 5.0, 9.8) and 12.5% (95% CI: 4.5, 19.8) in the TAC IR + MMF and TAC IR + AZA groups, respectively. The cumulative incidence of graft failure at 1-year posttransplantation was 4.5% (95% CI: 2.9, 6.9) and 9.7% (95% CI: 4.8, 19.7) in the TAC IR + MMF and TAC IR + AZA groups, respectively.

Results of cumulative incidences of death and of graft failture at 2-year and 3-year posttransplantation are summarized in the Table 16 below.

Table 16. Estimates of Cumulative Incidence of Death and Cumulative Incidence of Graft Failture at 1-, 2- and 3-Year Posttransplantation

Group	Outcome	Years Posttranplantation	# of Patients At risk	# of Events	Cumulative Incidence % (95% CI)
TAC IR + MMF	Death	1	450	33	7.4 (5.0, 9.8)
		2	417	50	19.1 (15.3, 22.7)
		3	333	38	28.7 (24.2, 32.9)
	Graft Failure†	1	450	20	4.5 (2.9, 6.9)
		2	411	45	15.1 (12.1, 19.0)
		3	319	32	23.4 (19.6, 27.9)

TAC IR + AZA	Death	1	72	9	12.5 (4.5, 19.8
		2	63	13	30.8 (19.2, 40.7)
		3	49	9	43.5 (30.7, 53.9)
	Graft Failure†	1	72	7	9.7 (4.8, 19.7)
		2	62	9	22.6 (14.7, 34.8)
		3	48	8	34.1 (24.6, 47.2)

Source: reviewer's analysis and Applicant's study report (p.66, Table 14)
†The Aalen-Johansen CR estimate

Contribution of Tacrolimus to the Immunosuppressive Regimen

In addition to mechanistic considerations, the independent contribution of a CNI to the efficacy of immunosuppressive regimens is supported by clinical trial data. Specifically, immunosuppressive regimens consisting of MMF + CS were used in the 1990s for kidney transplant recipients. In a trial of kidney transplant recipients maintained on a two-drug MMF + CS regimen, 48% (47/98) of patients enrolled developed acute rejection by six months post-transplantation [Vincenti 2001]. In contrast, in a report of 75 patients maintained on a MMF + CS regimen and a CNI (cyclosporine), rejection occurred in 12% of recipients [Vincenti 1999]. These two reports provide evidence of the specific and significant contribution of CNIs to the overall efficacy of commonly used immunosuppressive regimens.[13] Notably, the immunosuppressive regimens in the cited reports, as well as the types of organs transplanted, are not identical to those used in the SRTR study. Nonetheless, the similarity of the regimens to those used in the SRTR study as well as the similarity between kidney and lung transplantation are sufficient to support the finding that CNIs contribute to graft and overall survival in the setting of an immunosuppressive regimen in lung transplantation.

Finally, evidence from randomized trials comparing tacrolimus + MMF + CS versus CsA + MMF + CS in lung transplantation suggests similar effectiveness of tacrolimus and cyclosporine in MMF-containing three-drug regimens. One trial found "one-year and two-year survival rates were similar in the two groups" [Treede 2012], and another trial reported "no significant difference in incidence of acute rejection was observed between the 2 groups [and] survival and incidence of infection were similar" [Zuckerman 2003]. The similar effectiveness of tacrolimus + MMF + CS and CsA + MMF + CS supports the contribution of tacrolimus to the three-drug regimen in lung transplant regimens, based on the rationale that, as in kidney transplantation described above, an MMF + CS regimen would be expected to be insufficient in lung transplantation as

[13] Other clinical trials support a similar conclusion regarding the contribution of CsA to a regimen comprised of azathioprine + CS [European Multicentre Trial Group 1983; Canadian Multicentre Trial Group 1983; Opelz 1986].

well.[14] Accordingly, it is reasonable to conclude that tacrolimus provides comparable additivity to MMF + CS as does CsA.

8.1.5. Confirmatory Evidence

FDA approval of tacrolimus (Prograf) for adult and pediatric liver, kidney, and heart transplant recipients was supported by substantial evidence of effectiveness from adequate and well-controlled randomized clinical trials for each of these indications using non-inferiority trial designs that tested multi-drug immunosuppressive regimens, all of which included a CNI (tacrolimus or cyclosporine) [Prograf Prescribing Information]. Alloimmune response to these transplanted organs is mechanistically similar, regardless of the organ involved, and rejection is known to occur in the absence of therapy. Therefore, and based on these related uses, it is scientifically reasonable to conclude that tacrolimus as part of an immunosuppressive regimen should decrease and delay rejection in lung transplantation, consistent with the findings of the SRTR study.

8.1.6. Integrated Assessment of Effectiveness

Not applicable for the current sNDA

8.2. Review of Safety

8.2.1. Safety Review Approach

Tacrolimus was first approved for marketing in Japan in 1993 and in US in 1994. In the US, the approved indications in both adult and pediatric patients are prophylaxis and treatment of allograft rejection in kidney, heart and liver transplantation. Per the Applicant's analysis, the estimated worldwide exposure is 6.7 million patient-years since 1993. The safety profile for tacrolimus is well-established and risks are well-characterized. Identified risks associated with tacrolimus treatment and corresponding risk minimization measures are included in the approved Prograf package insert. The main adverse effects associated with tacrolimus (and CNIs in general) include new onset diabetes after transplant (NODAT), neurological effects (including increased risk of posterior reversible encephalopathy) and kidney dysfunction. Other adverse effects associated with immunosuppression in general, include serious infections and malignancy. Based on animal studies, tacrolimus may affect fertility in males and females and may cause fetal harm when administered to pregnant women. All of these risks are described in the Prograf package insert. Safety review mainly relies on existing

[14] Similar effectiveness of tacrolimus compared to cyclosporine is also supported by two randomized trials comparing these agents among lung transplant recipients who also received azathioprine + CS. One trial reported that 3/38 (7.9%) patients in the tacrolimus group died one year after transplantation compared to 6/36 (17%) patients in the CsA group, and acute rejection occurred less often in the tacrolimus group [Griffith 1994]. A second trial involving 74 patients reported survival post-transplantation for tacrolimus and CsA, respectively, of 83% and 71% at one year, and 76% and 66% at two years [Keenan 1995].

extensive safety information gained from the labeled and off-label use of tacrolimus for various types of organ transplants including publications on the off-label use in lung transplantation. Along with the existing safety information on tacrolimus in the product labeling and in the published literature, the Applicant's analysis of safety, based on limited safety data available in the SRTR database and in the Company safety database are used as supplementary safety data for the pursued lung transplant indication. All this available safety data constitute the main material for the safety review. Due to the nature of the transplanted organ (lung) a potential increase in lung infections compared to other types of organ transplantations is expected.

8.2.2. Review of the Safety Database

Overall Exposure

The current sNDA submission is based on RWD. The Applicant has not performed any clinical studies for the indication of lung transplantation. However, limited safety data is routinely collected by the SRTR on all organ transplant recipients including lung transplant recipients. The Applicant collected the available safety data in the SRTR as part of the lung transplantation study (Study F506-CL-3001). This safety data is from 26080 lung transplant patients (adult and pediatric) included in the SRTR for the study period. Of the total 25355 adult lung transplant recipients, 15748 received tacrolimus immediate release (IR) + mycophenolate mofetil (MMF), 4263 received tacrolimus IR + azathioprine (AZA). Of the total 725 pediatric lung transplant recipients, 450 received tacrolimus IR + MMF, 72 received tacrolimus IR + AZA. The Applicant also submitted safety data analysis from five (5) published randomized controlled trials (RCTs) (Table below).

Table 17. Randomized Controlled Studies in Patients with Lung Transplants

Studies	Population Under Study	Study Design	Number of Patients
[Treede et al, 2012]†	Primary lung transplant adult recipients (ages 18-66 years old)	Randomized, prospective, open-label, multicenter, investigator-driven, superiority study of de novo Tac vs CsA, with both study arms given MMF and prednisolone after lung	124 patients randomized to Tac and 125 to CsA
[Hachem et al, 2007]	Lung transplant adult recipients	Randomized, single-center, controlled study Tac vs CsA in combination with AZA and prednisone after lung transplantation	44 patients randomized to Tac and 46 to CsA
[Zuckermann et al, 2003]	Primary lung transplant adult recipients	Prospective, 2-center, open-label, randomized study Combination of CsA, MMF and steroids compared with Tac, MMF and steroids as primary therapy after primary lung transplantation	37 patients randomized to Tac and 37 to CsA

[Treede et al, 2001]†	Lung transplant adult recipients	Prospective, open-label, randomized, 2-center study comparing: Tac in combination with MMF and steroids vs CsA in combination with MMF and steroids after lung transplantation	26 patients randomized to Tac and 24 to CsA
[Keenan et al, 1995]	Primary lung transplant adult recipients	Randomized, single-center, controlled study Tac vs CsA as the primary immunosuppressive agent after lung transplantation	66 patients randomized to Tac and 67 to CsA

AZA: azathioprine; **CsA**: cyclosporine A; **MMF**: mycophenolate mofetil; **Tac**: tacrolimus.
† Treede et al [2012] consists of patients enrolled from Jan 2001 until Jun 2003. Treede et al [2001] consists of patients enrolled from Sep 1997 through Apr 1999.

Published observational studies generally did not report detailed exposure data other than the regimens used for treatment, therefore cannot be reliavbly used in support of safety and will not be discussed in this review.

Adequacy of the safety database:

Tacrolimus is currently approved for different solid organ transplantations and has been on the US market since 1994. The safety profile of tacrolimus for the approved indications is reflected in the product labeling. The additional safety information for the lung transplant indication obtained from the SRTR, published literature and the company safety database is adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There are no data integrity or submission quality issues with this submission.

Categorization of Adverse Events

Study F506-CL-3001
For analysis of adverse events (AEs) during treatment with tacrolimus for prevention of rejection after lung transplantation, the Applicant analyzed the Study F506-CL-3001 data for the following safety endpoints: hospitalization for infection, malignancy and posttransplant lymphoproliferative disease (PTLD), new onset of diabetes after transplant (NODAT), renal dysfunction, cause of death and cause of graft failure. In this registry study, there was no systematic collection of all AEs experienced by the patients; therefore, no information is available about other AEs. Due to the limited timeframe of follow-up, the majority of graft failures are caused by rejection or are unknown.

Published RCTs
Per the Applicant's analysis of the RCTs comparing tacrolimus and CsA in patients treated after lung transplant showed that limited safety data were provided in the literature. An overview of the safety data is provided in the table below. The AEs described in the RCTs were similar to those known to be associated with tacrolimus in other solid organ transplant patients and

included renal dysfunction, infections and NODAT.

8.2.4. Safety Results

Deaths and Graft Failures

Study F506-CL-3001 Adult Patients:
For adult patients in the tacrolimus IR + MMF group, the most common causes of death in the first year posttransplant included respiratory and infection (approximately 25% each). At 3 years posttransplant, respiratory was reported as the cause in 27.2% of deaths, followed by infection (17.8%) and rejection (15.4%). Rejection was the most common cause of graft failure (GF) in patients in the tacrolimus IR + MMF group (42.5% in year 1); however, for a substantial proportion of patients with GF (41.4%) the cause was unknown. At 3 years posttransplant, rejection was the cause of 61.0% of GF in the tacrolimus IR + MMF group.

Study F506-CL-3001 Pediatric Patients:
For pediatric patients in the tacrolimus IR + MMF group, the most common causes of death in the first year posttransplant included respiratory AEs and infection. At 3 years posttransplant, rejection was reported as the cause in 29.8% of deaths, followed by respiratory (28.9%) and infection (10.7%). Rejection was the most common cause of GF in patients in the tacrolimus IR + MMF group (30.0% in year 1); however, for a larger proportion of patients with GF (45.0%), the cause was unknown. At 3 years posttransplant, rejection was the cause of 66.0% of GF in the tacrolimus IR + MMF group.

Serious Adverse Events

Not applicable in this registry analysis study.

Dropouts and/or Discontinuations Due to Adverse Effects

Not applicable in this registry analysis study.

Significant Adverse Events

Not applicable in this registry analysis study.

Treatment Emergent Adverse Events and Adverse Reactions

Not applicable in this registry analysis study.

Laboratory Findings

Not applicable in this registry analysis study.

Vital Signs

Not applicable in this registry analysis study.

Electrocardiograms (ECGs)

Not applicable in this registry analysis study.

QT

Not applicable in this registry analysis study.

Immunogenicity

Not applicable in this registry analysis study.

8.2.5. Analysis of Submission-Specific Safety Issues

SRTR Study F506-CL-3001
As explained earlier, the Applicant analyzed the Study F506-CL-3001 data for the following safety endpoints: hospitalization for infection, malignancy and PTLD, NODAT, renal dysfunction, cause of death and cause of graft failure. Due to the limited data collection on safety in the SRTR, these are the only safety analyses that can be done withn the SRTR data. Deaths and graft loses are already discussed in previous sections of this review and the remaining safety endpoints are discussed below for the adult and pediatric patients separately.

Study F506-CL-3001 Adult Patients:
Of the safety outcomes evaluated, the most common complication posttransplant in adult lung transplant recipients (all treatment groups together) was hospitalization for infection. In the first year posttransplant, 15.0% of patients developed renal complications and 16.6% developed NODAT; at 3 years posttransplant, the incidences were 31.3% and 24.7%, respectively. The cumulative incidence of patients who developed a malignancy was 1.8% at 1 year posttransplant and 5.1% at 3 years posttransplant. In adult patients, the incidence of hospitalization for infection, NODAT and renal dysfunction generally decreased across transplant eras. The incidence of malignancy across transplant eras decreased in the first year posttransplant but remained constant at 2 and 3 years posttransplant.

For the tacrolimus IR + MMF exposure group, the cumulative incidence at 1 , 2 and 3 years posttransplant for all safety endpoints were comparable or lower than those estimated for the total cohort, as well as the other exposure groups. Hospitalization for infection was the most common complication. At 1 year posttransplant, the cumulative incidences of renal dysfunction and NODAT were 11.9% and 15.0%, respectively; at 3 years posttransplant, cumulative incidences were 25.6% and 22.2%, respectively.

Table 18. Estimates of Cumulative Incidence of Safety Outcomes in Lung Transplant Recipients by Immunosuppression Regimens in Adult Patients (F506-CL-3001 Study Report, Table 10)

Outcome	Year†	TAC IR + MMF			TAC IR + AZA			CsA + MMF			CsA + AZA		
		At Risk (n)	Events (n)	Cumulative Incidence % (95% CI)	At Risk (n)	Events (n)	Cumulative Incidence % (95% CI)	At Risk (n)	Events (n)	Cumulative Incidence % (95% CI)	At Risk (n)	Events (n)	Cumulative Incidence % (95% CI)
Hospitalization for infection													
	1	15478	4055	**26.2** (25.5, 26.9)	4263	1082	25.4 (24.1, 26.7)	1219	441	36.2 (33.5, 38.9)	1959	732	37.4 (35.2, 39.5)
	2	13582	5319	**39.2** (38.4, 39.9)	4147	1584	38.2 (36.7, 39.7)	1194	584	48.9 (46.1, 51.7)	1940	957	49.3 (47.1, 51.5)
	3	11804	5504	**46.6** (45.8, 47.4)	4019	1785	44.4 (42.9, 45.9)	1166	646	55.4 (52.6, 58.2)	1928	1083	56.2 (54.0, 58.4)
NODAT													
	1	12697	1909	**15.0** (14.4, 15.7)	3642	854	23.4 (22.1, 24.8)	1055	156	14.8 (12.6, 16.9)	1782	264	14.8 (13.2, 16.5)
	2	11141	2144	**19.2** (18.6, 19.9)	3552	1037	29.2 (27.7, 30.7)	1035	216	20.9 (18.4, 23.3)	1767	359	20.3 (18.4, 22.2)
	3	9739	2161	**22.2** (21.5, 22.9)	3454	1130	32.7 (31.2, 34.2)	1010	241	23.9 (21.3, 26.4)	1756	421	24.0 (22.0, 26.0)
Renal dysfunction													
	1	15478	1835	**11.9** (11.3, 12.4)	4263	802	18.8 (17.6, 20.0)	1219	306	25.1 (22.7, 27.5)	1959	431	22.0 (20.2, 23.8)
	2	13582	2630	**19.4** (18.7, 20.0)	4147	1251	30.2 (28.8, 31.5)	1194	472	39.5 (36.8, 42.3)	1940	639	32.9 (30.9, 35.0)
	3	11804	3026	**25.6** (24.9, 26.3)	4019	1486	37.0 (35.5, 38.4)	1166	556	47.7 (44.9, 50.5)	1928	766	39.7 (37.6, 41.9)
Overall malignancy (CR)													
	1	15478	250	**1.5** (1.3, 1.8)	4263	76	1.8 (1.4, 2.2)	1219	27	2.2 (1.5, 3.3)	1959	60	3.1 (2.4, 4.0)
	2	13852	274	**3.3** (3.0, 3.7)	3831	82	3.7 (3.2, 4.4)	1030	18	3.7 (2.8, 5.0)	1695	30	4.6 (3.8, 5.7)
	3	10649	208	**4.9** (4.4, 5.4)	3289	69	5.5 (4.8, 6.2)	857	24	5.8 (4.6, 7.3)	1463	31	6.2 (5.3, 7.4)
PTLD (CR)													
	1	15478	114	**0.7** (0.6, 0.8)	4263	35	0.8 (0.6, 1.1)	1219	16	1.3 (0.8, 2.2)	1959	42	2.2 (1.6, 2.9)
	2	13961	51	**1.0** (0.9, 1.2)	3858	14	1.2 (0.9, 1.5)	1039	3	1.6 (1.0, 2.5)	1710	7	2.5 (1.9, 3.3)
	3	10853	27	**1.2** (1.0, 1.4)	3360	10	1.4 (1.1, 1.8)	876	7	2.2 (1.5, 3.2)	1485	9	3.0 (2.3, 3.8)

For hospitalization, NODAT and renal dysfunction, the crude cumulative incidence percent was the number of events in 0 – 1 year, 0 – 2 years, 0 – 3 years posttransplant divided by the total number of recipients. The events from 1 year were counted in years 2 and 3 and likewise for year 2. For the 2010 - 2017 era, all recipients were included in the 1 year results, transplants in 2016 were excluded from the 3 years results and transplants in 2017 were excluded from 2 years and 3 years results; this was also reflected in the overall results. Patients
who were diabetic at transplant were not at risk for NODAT.

For overall malignancy (CR) and PTLD (CR), the Aalen-Johansen competing risk estimate of cumulative incidence is

presented; death or graft failure is the competing risk. For year 1, the number at risk is all recipients and for years 2 and 3 the number at risk is the number at the earliest event in the year, the cumulative incidence percent is from the last event in the year, and the number of events is the total number of events over the year.

AZA: azathioprine; CI: confidence interval; CR: competing risk; CsA: cyclosporine A; IR: immediate release; MMF: mycophenolate mofetil; NODAT: new onset diabetes after transplant; PTLD: posttransplant lymphoproliferative disease; TAC: tacrolimus.
† Year(s) posttransplant from the time of transplant.

Study F506-CL-3001 Pediatric Patients:
Of the safety outcomes evaluated, the most common complication posttransplant in pediatric lung transplant recipients (all treatment cohorts) was hospitalization for infection, with an incidence of 62.5% at 3 years. In the first year posttransplant, 7.7% of patients developed renal complications and 15.3% developed NODAT; at 3 years posttransplant, the cumulative incidences were 17.5% and 24.1%, respectively. The cumulative incidence of patients who developed a malignancy was 4.5% at 1 year posttransplant and 6.1% at 3 years posttranplant. In pediatric patients, incidences of hospitalization for infection, NODAT and renal dysfunction decreased across transplant eras. The incidence of malignancy generally decreased across transplant eras at 1, 2 and 3 years posttransplant (CDRG malignancy PTLD report. Almost all events of malignancy were PTLD.

For the tacrolimus IR + MMF exposure group, the cumulative incidence at 1, 2 and 3 years posttransplant for all safety endpoints were comparable to or lower than those estimated for the total cohort and the other exposure groups. Hospitalization for infection was the most common complication. At 1 year posttransplant, the cumulative incidences of renal dysfunction and NODAT were 4.2% and 9.9%, respectively; at 3 years posttransplant, the cumulative incidences were 9.2% and 15.5%, respectively.

Table 19. Estimates of Cumulative Incidence of Safety Outcomes in Lung Transplant Recipients by Immunosuppression Regimen in Pediatric Patients

Outcome	Year†	TAC IR + MMF			TAC IR + AZA			CsA + MMF			CsA + AZA		
		At Risk (n)	Events (n)	Cumulative Incidence % (95% CI)	At Risk (n)	Events (n)	Cumulative Incidence % (95% CI)	At Risk (n)	Events (n)	Cumulative Incidence % (95% CI)	At Risk (n)	Events (n)	Cumulative Incidence % (95% CI)
Hospitalization for infection													
	1	450	145	32.2 (27.9, 36.5)	72	35	48.6 (37.1, 60.2)	57	17	29.8 (17.9, 41.7)	100	44	44.0 (34.3, 53.7)
	2	411	200	48.7 (44.0, 53.3)	71	44	62.0 (50.8, 73.2)	56	32	57.1 (44.3, 70.0)	100	58	58.0 (48.3, 67.7)
	3	381	224	58.8 (54.2, 63.3)	71	49	69.0 (58.3, 79.7)	56	37	66.1 (53.8, 78.4)	100	72	72.0 (63.2, 80.8)
NODAT													
	1	364	36	9.9 (6.8, 13.0)	53	19	35.8 (22.9, 48.8)	43	10	23.3 (10.6, 35.9)	92	16	17.4 (9.6, 25.1)
	2	333	46	13.8 (10.3, 17.4)	53	22	41.5 (28.2, 54.8)	42	13	31.0 (17.1, 44.8)	92	25	27.2 (18.1, 36.3)

	3	310	48	15.5 (11.8, 19.2)	53	24	45.3 (31.9, 58.7)	42	14	33.3 (19.2, 47.4)	92	29	31.5 (22.0, 41.0)
Renal dysfunction													
	1	450	19	4.2 (2.4, 6.1)	72	9	12.5 (4.9, 20.1)	57	6	10.5 (2.6, 18.5)	100	15	15.0 (8.0, 22.0)
	2	411	31	7.5 (5.1, 10.0)	71	15	21.1 (11.7, 30.6)	56	10	17.9 (7.9, 27.8)	100	24	24.0 (15.6, 32.4)
	3	381	35	9.2 (6.5, 11.9)	71	20	28.2 (17.8, 38.6)	56	12	21.4 (10.8, 32.1)	100	33	33.0 (23.8, 42.2)
Overall malignancy (CR)													
	1	450	20	4.5 (2.9, 6.9)	72	0	0.0 (NA, NA)	57	5	8.8 (3.8, 20.2)	100	6	6.4 (2.9, 13.9)
	2	394	2	5.0 (3.3, 7.5)	62	0	0.0 (NA, NA)	46	2	12.3 (6.2, 24.7)	87	0	6.4 (2.9, 13.9)
	3	306	3	5.7 (3.9, 8.4)	48	3	4.3 (1.4, 13.0)	40	0	12.3 (6.2, 24.7)	76	1	7.4 (3.6, 15.2)
PTLD (CR)													
	1	450	20	4.5 (2.9, 6.9)	72	0	0.0 (NA, NA)	57	5	8.8 (3.8, 20.2)	100	6	6.4 (2.9, 13.9)
	2	394	1	4.7 (3.1, 7.2)	62	0	0.0 (NA, NA)	46	2	12.3 (6.2, 24.7)	87	0	6.4 (2.9, 13.9)
	3	307	3	5.5 (3.7, 8.1)	48	3	4.3 (1.4, 13.0)	40	0	12.3 (6.2, 24.7)	76	1	7.4 (3.6, 15.2)

For hospitalization, NODAT and renal dysfunction, the crude cumulative incidence percent was the number of events in 0 – 1 year, 0 – 2 years and 0 – 3 years posttransplant divided by the total number of recipients. The events from 1 year were counted in years 2 and 3 and likewise for year 2. Patients who were diabetic at transplant were not at risk for NODAT.

For overall malignancy (CR) and PTLD (CR), the Aalen-Johansen competing risk estimate of cumulative incidence is presented; death or graft failure is the competing risk. For year 1, the number at risk is all recipients and for years 2 and 3, the number at risk is the number at the earliest event in the year, the cumulative incidence percent is from the last event in the year and the number of events is the total number of events over the year.

AZA: azathioprine; CI: confidence interval; CR: competing risk; CsA: cyclosporine A; IR: immediate release; MMF: mycophenolate mofetil; NA: not available; NODAT: new onset diabetes after transplant; PTLD: posttransplant lymphoproliferative disease; TAC: tacrolimus.

† Year(s) posttransplant from the time of transplant.

8.2.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No safety concerns other than those included in the product labeling have been identified in

the postmarket setting.

8.2.7. Integrated Assessment of Safety

The use of immunosuppressive regimens changed over the study period, which was further characterized by 3 transplant eras (1999 - 2005, 2006 - 2009 and 2010 - 2017). For the exposure groups of interest, CsA and azathioprine were more common earlier in the period and their use steadily decreased, while tacrolimus IR and MMF use was less common earlier in the period and subsequently increased. In both adult and pediatric patient populations, tacrolimus IR and MMF were the most common nonsteroidal immunosuppressive agents with, respectively, reported use at discharge of 84.1% and 65.1% in adult patients and 76.6% and 69.4% in pediatric patients.

During the 2010 - 2017 transplant era, approximately 79% of adult patients and > 90% of pediatric patients received tacrolimus IR + MMF at hospital discharge. Almost all (> 99%) pediatric patients were recipients of double-lung transplants across transplant eras, while the number of adult patient recipients of double-lung transplants increased from approximately 50% to 70% across transplant eras. Other increasing trends across transplant eras in adult lung transplant recipients included diagnoses of pulmonary fibrosis (with decreases in COPD diagnosis) and a shift in the age at transplant to an increasing proportion of patients in the 65+ year age group. Use of induction agents increased in each new transplant era and there was a trend toward longer lung ischemia times for both adult and pediatric patients.

One-year graft survival results in lung transplant recipients receiving tacrolimus-based regimens are now similar to survival rates in liver and heart transplant patients. At 3 years posttransplant, the results after lung transplant are worse than liver, heart or kidney transplant [OPTN, 2020a]. A major factor contributing to GF beyond 1 year after lung transplant is the increasing rate of BOS. In the total cohort of adult lung transplant recipients, the incidence of BOS increased from 7.3% in the first year posttransplant to 27.5% at 3 years posttransplant. Similar increase in the incidence of BOS was observed in pediatric patients, which increased from 7.9% in the first year posttransplant to 32.1% at 3 years posttransplant.

Of the safety outcomes evaluated, hospitalization for infection was most common in both adult and pediatric lung transplant recipients. The risk of pulmonary infection is higher in the lung transplant population as compared to other solid organ transplants (e.g., kidney, liver, heart) [Dulek et al, 2019]. The risk of infection was common across the treatment regimens studied. Although the tacrolimus IR + MMF exposure group had the lowest rate of rejection, this group did not have an increased rate of infection or malignancy.

Other safety events evaluated in this study including malignancy, lymphoproliferative disease, NODAT and renal dysfunction are also seen in other solid organ transplant

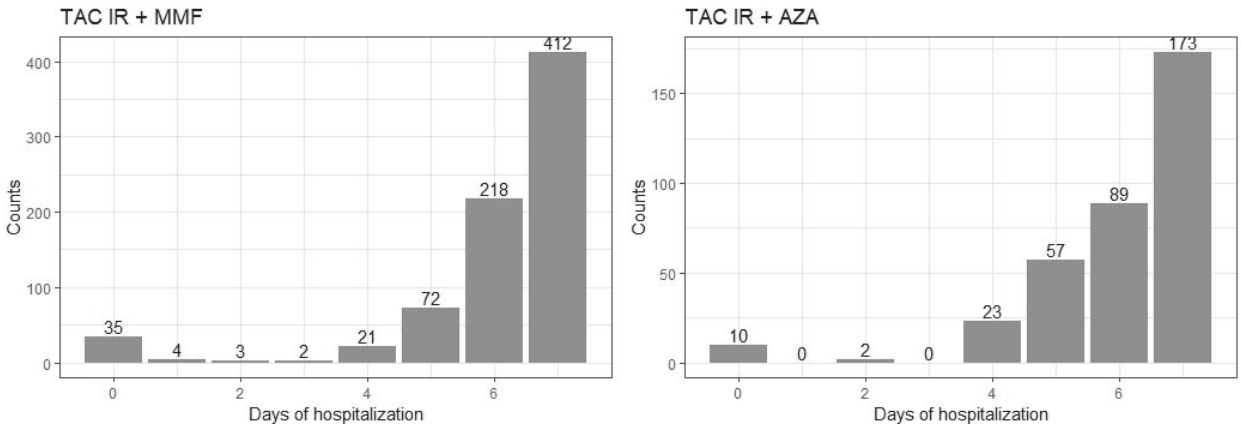
patients receiving tacrolimus- or CsA-based immunosuppressive regimens. Studies in other solid organs, as well as published literature in lung transplant, have frequently described an increased risk of diabetes in tacrolimus as compared to CsA-treated patients. This difference was not evident in the SRTR data.

8.3. Statistical Issues

Data Quality and Integrity

The data on death and graft failure were considered reliable. Particularly, death date was adjudicated by and the Social Security Death Master File. However, clinically implausible hospitalization records raised data quality concern of the SRTR registry data. Median hospitalization days of adult patients were 16 days and 14 days in the TAC IR + MMF and TAC IR + AZA groups, respectively. The database included 35 and 10 adult patients whose length of hospitalization were zero days in the TAC IR + MMF group and TAC IR + AZA group, respectively. Approximately 5% of the adult patients were hospitalized for less than one week (Figure 9). Applicant stated that possible reasons were because of the following: (1) data entry errors where transplantation center staff provided the same date for transplantation and discharge; or (2) patients were transfered from inpatient service to another unit or hospital. The primary cumulative incidence estimates depended on the number of patients who were discharged at the time of the first event (discussed in more detail below). Therefore, not being able to distinguish discharge from the hospital and a transfer after transplant impacted the estimates.

Figure 9. Number of adult patients under 7 days of hospitalization



Source: reviewer's analysis

The primary analysis truncated the data before patients were discharged, meaning even though the time to an event included the time of hospitalization, patients who experienced the event were excluded from the analysis, and patients were included in the risk set only after they were discharged. The risk set soon after transplantation only included the few patients who were discharged by that time. Therefore, with patients being discharged at varying days after transplantation, events that occurred soon after transplantation when the risk set was small,

highly impacted the cumulative incidence and its CI. Four events in the TAC IR + MMF group occurred before Day 10 posttransplant, with the first two events occurring at Day 4. The number of patients included at the risk set at Day 4 (number of patients discharged by Day 4) was 44, which resulted in a higher than expected cumulative incidence rate. Applicant conducted a post-hoc analysis and reassigned the event date of the four events to Day 10. Even though the results of this post-hoc analysis appeared to be clinically reasonable, the analysis was planned after the the primary analysis were conducted and the use of Day 10 was somewhat arbritary. Therefore, we do not recommend including the estimates from the post-hoc analysis in the product labeling.

Because the immunosuppression regimens were defined based on maintenance therapy at discharge, the sensitivity analysis that used the date of discharge as the index date was not affected by the four early events and appears to represent the data adequately. Therefore, we recommend including the estimates from the sensitivity in the product labeling.

8.4. Conclusions and Recommendations

The Applicant has provided substantial evidence of effectiveness for tacrolimus in combination with MMF and CS, or in combination with azathioprine and CS, in the prophylaxis of rejection in lung transplantation. This assessment is based on Study F506-CL-3001 as an adequate and well-controlled study along with other clinical studies serving as confirmatory evidence of effectiveness. The outcomes of Study F506-CL-3001 were compared to historical controls in the absence of an immunosuppressive regimen containing a CNI, where no graft or overall survival was observed at one year and survival was largely limited to several weeks [Veith 1974]. When the treatment group in Study F506-CL-3001 is compared with the historical controls, the study can be considered adequate and well-controlled.

Confirmatory evidence of the effectiveness of tacrolimus is based on adequate and well-controlled randomized trials of adult and pediatric patients receiving liver, kidney, or heart transplantation. The finding that CNIs—including cyclosporine and tacrolimus—contribute to the efficacy of immunosuppressive regimens is supported by mechanistic considerations as well as by clinical trials conducted in kidney transplantation. The specific contribution of tacrolimus compared to cyclosporine is supported by data from clinical trials in kidney transplantation.

The clinical reviewer recommends the approval of this sNDA submission.

9 Advisory Committee Meeting and Other External Consultations

Advisory committee meeting or other external consultations were not needed for this sNDA submission.

10 Pediatrics

Per the Pediatric Research Equity Act (PREA), 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 safety and effectiveness of the product in pediatric patients unless this requirement is waived, deferred or inapplicable. Tacrolimus for the indication of prevention of rejection of lung transplantation has been designated as an Orphan Drug (ODD on September 12, 2019. Based on ODD, the supplemental application for the new indication is exempt from PREA requirements. Nevertheless, the applicant is pursuing an indication in the pediatric patient population for lung transplantation based on limited RWE data from the SRTR.

Per the Applicant's analyses of the SRTR data, a total of 29772 patients were identified as having received a lung transplant between 1999 and 2017. Of these, 26080 (87.6%) patients were eligible for analysis: 25355 patients in the adult group (≥ 18 years old) and 725 patients in the pediatric group (< 18 years old).

Pediatric lung transplant recipients were 90.9% White, 59.3% female and 62.9% between 12 and 17 years old [Table 3]. A greater proportion of patients were diagnosed with cystic fibrosis (45.1%) compared with pulmonary fibrosis (10.1%); however, a substantial number of diagnoses were unknown (37.4%), which should be considered in the interpretation of this result. The number of unknown diagnoses is due in part to the different allocation system used for young children < 12 years, which does not require an LAS and a diagnosis from 1 of the 4 main groups (COPD, pulmonary hypertension, cystic fibrosis or pulmonary fibrosis). Diagnoses for some of these younger children were classified in the database as "other, please specify" without explanatory text and therefore tabulated as unknown for the purpose of this study.

Almost all (> 99%) of pediatric patients received a double-lung transplant. After transplant, patients remained hospitalized for a median of 19 days. During the 2010 - 2017 transplant era, > 90% of pediatric patients (277/302) received tacrolimus IR + MMF at hospital discharge. Similar to adults, most pediatric patientsreceived antibody induction and the most common antibody administered was an IL-2 receptor antagonist.

In the TAC IR + MMF group, the cumulative incidence of death or graft failure at 1-year posttransplant was 7.7% (95% CI: 5.2, 10.1) (Table 14). The sensitivity analysis resulted in a cumulative incidence of 8.3% (95% CI: 5.7, 10.8) at 1-year postdischarge.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
As part of this sNDA approval, sections 1, 2, 6 and 14 of the labeling will be updated by adding the relevant information for the new lung transplantation indication. The final agreed on labeling for these sections is below:

1.1 Prophylaxis of Organ Rejection in Kidney, Liver, Heart, or Lung Transplant

PROGRAF® is indicated for the prophylaxis of organ rejection, in adult and pediatric patients receiving allogeneic kidney transplant [see Clinical Studies (14.1)], liver transplant [see Clinical Studies (14.2)], heart transplant [see Clinical Studies (14.3)], or lung transplant [see Clinical Studies (14.4)] in combination with other immunosuppressants.

2.2 Dosage Recommendations for Adult Kidney, Liver, Heart, or Lung Transplant Patients - Capsules and Injection

Capsules
If patients are able to tolerate oral therapy, the recommended oral starting doses should be initiated. The initial dose of PROGRAF capsules should be administered no sooner than 6 hours after transplantation in the liver, heart, or lung 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, heart, or lung 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 Dosage Recommendations and Whole Blood Trough Concentration Range in Adults

Patient Population	PROGRAF Capsules Initial Oral Dosage	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[2]	0.1 mg/kg/day, divided in two doses, administered every 12 hours	Month 1-12: 4-11 ng/mL
Liver Transplant		
With corticosteroids only	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
Lung Transplant		
With azathioprine or MMF	0.075 mg/kg/day[3], divided in two doses, administered every 12 hours	Month 1-3: 10-15 ng/mL Month 4-12: 8-12 ng/mL

1. African-American patients may require higher doses compared to Caucasians (see Table 2).
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)].
3. Patients with cystic fibrosis may require higher doses due to lower bioavailability [see Clinical Pharmacology (12.3)].

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

2.3 Dosage Recommendations for Pediatric Kidney, Liver, Heart, or Lung 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 dosage 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 Dosage 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[1]	0.3 mg/kg/day capsules or oral suspension, divided in	Month 1-12: 5-20 ng/mL

	two doses, administered every 12 hours	
Pediatric liver transplant patients[2]	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[1]	0.3 mg/kg/day[3]capsules or oral suspension, divided in two doses, administered every 12 hours	Month 1-12: 5-20 ng/mL
Pediatric lung transplant patients	0.3 mg/kg/day[3,4]capsules or oral suspension, divided in two doses, administered every 12 hours	Week 1-2: 10-20 ng/mL Week 2 to Month 12: 10-15 ng/mL

1. See Clinical Pharmacology (12.3), PROGRAF Granules Pharmacokinetics in Pediatric Patients.
2. See Clinical Studies (14.2), Liver Transplantation.
3. Dose at 0.1 mg/kg/day if antibody induction treatment is administered.
4. Patients with cystic fibrosis may require higher doses due to lower bioavailability [see Clinical Pharmacology (12.3)].

In lung transplantation, cystic fibrosis patients may have a reduced bioavailability of orally administered tacrolimus resulting in the need for higher doses to achieve target tacrolimus trough concentrations. Monitor tacrolimus trough concentrations and adjust the dose accordingly.

6.1 Clinical Studies Experience

Lung Transplantation

Adverse reactions in lung transplant patients were similar to those in kidney, liver, or heart transplant patients treated with PROGRAF *[see* Adverse Reactions *(*6.2*)].*

6.2 Postmarketing Experience

Postmarketing Adverse Reactions in Lung Transplantation

Based on U.S. Scientific Registry of Transplant Recipients (SRTR) data, published clinical trials, and postmarketing reports, the safety profile for lung transplant patients treated with PROGRAF is consistent with the safety profile in kidney, liver, and heart transplant patients treated with PROGRAF. The primary adverse reactions described include renal dysfunction, infection, diabetes, gastrointestinal disturbances (e.g., diarrhea), hypertension, and neurological events (e.g., tremor). As expected, lung transplant patients have a higher incidence of pulmonary complications (e.g., pneumonia, bronchiolitis obliterans syndrome) than other solid organ transplant patients, which is in part due to the underlying disease and to the nature of the transplanted organ.

14 CLINICAL STUDIES

14.4 Lung Transplantation

The efficacy and safety of PROGRAF-based immunosuppression in primary lung transplantation were assessed in a non-interventional (observational) study using data from the U.S. Scientific Registry of Transplant Recipients (SRTR). The study analyzed outcomes based on discharge immunosuppression treatment regimen in recipients of a primary lung transplant between 1999 and 2017 who were alive at the time of discharge. In adult patients receiving tacrolimus immediate-release products in combination with MMF (n=15,478) or tacrolimus immediate-release products in combination with AZA (n=4,263), the one-year graft survival estimates from time of discharge were 90.9% and 90.8%, respectively. In pediatric patients receiving tacrolimus immediate-release products in combination with MMF (n= 450) or tacrolimus immediate-release products in combination with AZA (n=72), the one-year graft survival estimates from time of discharge were 91.7% and 84.7%, respectively.

12 Risk Evaluation and Mitigation Strategies (REMS)

Risk Evaluation and Mitigation Strategy (REMS) is not deemed necessary for this new lung transplant indication.

13 Postmarketing Requirements and Commitment

There are no postmarketing requirements and commitments for this sNDA.

14 Division Director (OB) Comments

I concur that there is substantial evidence of effectiveness for the indication based on Study F506-CL-3001 as a adequate and well-controlled study and the confirmatory evidence presented. The contribution of tacrolimus to the treatment regimen has also been established.

15 DRTM Deputy Division Director (designated signatory) Comments

I concur with the team's assessment and recommendations based on the data from Study F506-CL-3001 as an adequate and well-controlled study.

The Applicant has provided substantial evidence of effectiveness for tacrolimus in combination with MMF and CS, or in combination with azathioprine and CS, in the prophylaxis of rejection in lung transplantation.

This approval will constitute a first for an immunosuppressant product to be used in lung transplant recipients.

16 Appendices

16.1. References

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13. Monchaud et al., Population Pharmacokinetic Modelling and Design of a Bayesian Estimator for Therapeutic Drug Monitoring of Tacrolimus in Lung Transplantation. Clin

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16.2. Financial Disclosure

Per the Form 3454, submitted on June 24, 2021, signed by Mary Jo Pritza, Sr. Director Regulatory Affairs, Astellas has not entered into any financial arrangement with the listed clinical investigators (b) (4) (b) (4) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details	Yes ☐	No ☐ (Request details from

of the disclosable financial interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.3. Nonclinical Pharmacology/Toxicology

Not applicable

16.4. OCP Appendices (Technical documents supporting OCP recommendations)

None

16.5. Additional Clinical Outcome Assessment Analyses

None

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/s/

HUSEYIN E VELIDEDEOGLU
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PROGRAF EFFICACY SUPPLEMENT FOR LUNG TRANSPLANTATION - SNDA UNIREVIEW

OZLEM A BELEN
07/16/2021 02:08:14 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50708s053, 50709s045, 210115s005

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA 50-708 / S-053, NDA 50-709 / S-045, and NDA 210115 / S-005**

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original	PAS (Efficacy)	12/16/2020	12/16/2020	12/18/2020	6/15/2021	7/16/2021

3. **Provides For:** the addition of a new indication for the prevention of rejection in lung transplantation.

4. **Review #:** 1

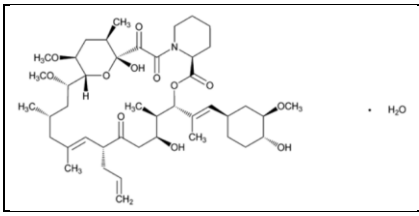
5. **Clinical Review Division:** CDER/OII/DRTM

6. **Name and Address of Applicant**:
   Astellas Pharma US, Inc.
   1 Astellas Way
   Northbrook, Illinois 60062

7. **Drug Product**:

NDA	Drug Name	Dosage Form	Strengths	Route of Administration	Rx or OTC	Special Product
50-708	Prograf® (tacrolimus) Capsules	Capsules	0.5 mg, 1 mg, and 5 mg	Oral	Rx	No
50-709	Prograf® (tacrolimus) Injection	Injection	5 mg/mL	Intravenous	Rx	No
210115	Prograf® (tacrolimus for oral suspension)	Suspension	0.2 mg and 1 mg	Oral	Rx	No

8. **Chemical Name and Structure of Drug Substance**:



USAN: Tacrolimus, USP
CAS Number: 109581-93-3
Chemical name: see full name below[a]
Molecular formula: $C_{44}H_{69}NO_{12}•H_2O$
MW: 822.05 g/mol

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

9. Indication: for the prophylaxis of organ rejection in patients receiving liver transplants.

10. Supporting/Relating Documents: See pages 3-4.

11. Consults: None

12. Executive Summary:

OND Managed: In this supplemental submission, the applicant proposes to add a new indication to the Prograf® (tacrolimus) labeling for the prevention of rejection in lung transplantation.

No changes have been made to the CMC sections of the application and the applicant has provided a categorical exclusion for Environmental Assessment. The applicant claims that "the requested action qualifies for a categorical exclusion from the requirement to prepare an EA, per 21 CFR § 25.31(b), because the estimated concentration of the substance at the point of entry into the aquatic environment is estimated to be below 1 part per billion." Moreover, the applicant states that "no extraordinary circumstances exist that would warrant the preparation of an EA [Environmental Analysis]."

The submitted draft USPI (annotated, tracked-changes) showed no changes to the currently approved CMC-related information included in Section "2 DOSAGE AND ADMINISTRATION". The submitted draft USPI (annotated, tracked-changes) showed no changes at all to Sections "3 DOSAGE FORMS AND STRENGTHS", "11 DESCRIPTION", and "16 HOW SUPPLIED/STORAGE AND HANDLING"; all CMC-related information proposes no changes to the currently approved.

13. Conclusions & Recommendations:

This supplemental submission is recommended for approval from a CMC standpoint.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Richard T. Matsuoka, Ph.D., CMC reviewer, Branch 3, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

Gurpreet Gill-Sangha, Ph.D., Branch Chief, Branch 3, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

CMC ASSESSMENT

I BACKGROUND INFORMATION

Prograf® (tacrolimus) Capsules, approved on 04/08/1994, contain the equivalent of 0.5 mg, 1 mg, or 5 mg of anhydrous tacrolimus and the following inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, and magnesium stearate.
Prograf® (tacrolimus) Injection, approved on 04/08/1994, is a sterile solution containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by intravenous infusion only. Each mL of solution also contains the following inactive ingredients: dehydrated alcohol, 80.0% v/v and polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg." Prograf injection must be diluted with "0.9% Sodium Chloride Injection" or "5% Dextrose Injection" before administration.
PROGRAF Granules (tacrolimus for oral suspension), approved on , contain the equivalent of 0.2 mg or 1 mg of anhydrous tacrolimus and the following inactive ingredients: croscarmellose sodium, hypromellose, and lactose monohydrate.

II PROPOSED CHANGES

The applicant proposes to add a new indication to the Prograf® (tacrolimus) labeling for the prevention of rejection in lung transplantation.

III DATA SUBMITTED TO SUPPORT THE PROPOSED CHANGES

1. OTHER CORRESPONDENCE (1.12)

A. Environmental Analysis (1.12.14)

Comments: The applicant claims that "the requested action qualifies for a categorical exclusion from the requirement to prepare an EA, per 21 CFR § 25.31(b), because the estimated concentration of the substance at the point of entry into the aquatic environment is estimated to be below 1 part per billion." Moreover, the applicant states that "no extraordinary circumstances exist that would warrant the preparation of an EA [Environmental Analysis]."

☑ **Reviewer Evaluation: Acceptable**

2. LABELING (1.14)

A. Draft Labeling (1.14.1)

A(i) Annoted Draft Labeling Text (1.14.1.2)

Comments: The submitted draft "United States Prescribing Information" (USPI) (annotated, tracked-changes) showed no changes to the CMC-related information included in Section "2 DOSAGE AND ADMINISTRATION". The submitted draft USPI (annotated, tracked-changes) showed no changes at all to Sections "3 DOSAGE FORMS AND STRENGTHS", "11 DESCRIPTION", and "16 HOW SUPPLIED/STORAGE AND HANDLING"; all CMC-related information is the same as the currently approved.

☑ **Reviewer Evaluation: Acceptable**

IV RISK ASSOCIATED WITH THE PROPOSED CHANGES AND IMPACT TO PRODUCT QUALITY AND PATIENT SAFETY

Low

Richard Matsuoka

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Gurpreet Gill Sangha

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Date: 7/16/2021 03:33:09PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50708s053, 50709s045, 210115s005

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 10, 2021
To:	Susan Rhee, PharmD Regulatory Project Manager **Division of Rheumatology and Transplant Medicine (DRTM)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Carrie Newcomer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	PROGRAF (tacrolimus)
Dosage Form and Route:	capsules, for oral use/injection for intravenous (IV) use/granules for oral suspension
Application Type/Number/Supplement Number	NDA 050708/S-053 (capsules) NDA 050709/S-045 (IV) NDA 210115/S-005 (oral suspension)
Applicant:	Astellas Pharma US, Inc.

1 INTRODUCTION

On December 15, 2020, Astellas Pharma US, Inc. submitted for the Agency's review efficacy supplements to their New Drug Applications (NDA 050708/S-053) for PROGRAF (tacrolimus) capsules for oral use, (NDA 050709/S-045) PROGRAF (tacrolimus) injection, for intravenous use, and (NDA 210115/S-005) PROGRAF (tacrolimus) granules, for oral suspension. The purpose of the submission is to add a new indication for the prevention of rejection in lung transplantation**,** provide a dosing recommendation for use in the new population and safety information based on Real-World Data (RWD) generated from a retrospective analysis of treatment and outcomes for patients who have received a lung transplant and who were administered tacrolimus collected from the Scientific Registry of Transplant Recipients (SRTR).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Rheumatology and Transplant Medicine (DRTM) on January 12, 2021 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for PROGRAF (tacrolimus) capsules for oral use, injection, for intravenous use, and granules, for oral suspension.

2 MATERIAL REVIEWED

- Draft PROGRAF (tacrolimus) PPI and IFU received on December 15, 2020 and received by DMPP and OPDP on January 12, 2021.
- Draft PROGRAF (tacrolimus) PPI and IFU Prescribing Information (PI) received on December 15, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 28, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

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06/10/2021 09:31:16 AM

MARCIA B WILLIAMS
06/10/2021 09:35:58 AM

LASHAWN M GRIFFITHS
06/10/2021 09:37:22 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 7, 2021

To: Susan Rhee, PharmD
Regulatory Health Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for
PROGRAF (tacrolimus) capsules, for oral use
PROGRAF (tacrolimus) injection, for intravenous use
PROGRAF Granules (tacrolimus for oral suspension)

NDA: 50708/S-053
50709/S-045
210115/S-005

In response to the Division of Rheumatology and Transplant Medicine's (DRTM) consult request dated January 12, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and Instructions for Use (IFU) for PROGRAF (tacrolimus) capsules, for oral use, PROGRAF (tacrolimus) injection, for intravenous use, and PROGRAF Granules (tacrolimus for oral suspension) (Prograf). Astellas Pharma submitted an efficacy supplement for Prograf for the prophylaxis of organ rejection in adult and pediatric patients receiving lung transplants.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRTM on May 28, 2021 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov

55 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

CARRIE A NEWCOMER
06/07/2021 08:35:44 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 13, 2021
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 50708/S-53, 50709/S-45, 210115/S-5
Product Name, Dosage Form, and Strength:	Prograf (tacrolimus) Capsules, 0.5 mg, 1 mg, and 5 mg Prograf (tacrolimus) Injection, 5 mg/mL Prograf (tacrolimus) Granules for Oral Suspension, 0.2 mg and 1 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Astellas
FDA Received Date:	December 15 and 16, 2020 and March 11, 2021
OSE RCM #:	2021-119
DMEPA Safety Evaluator:	Teresa McMillan, Pharm D.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm D.

1 REASON FOR REVIEW

Astellas submitted an efficacy supplement for Prograf (tacrolimus) Capsules, Injection, and Granules for Oral Suspension for the prophylaxis of organ rejection in adult and pediatric patients receiving lung transplants. Subsequently, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed Prograf prescribing information (PI) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Prescribing Information (PI) is acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Prograf received on December 12, 2020 from Astellas.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Prograf</th></tr>
<tr><td>Initial Approval Date</td><td>April 8, 1994</td></tr>
<tr><td>Active Ingredient</td><td>tacrolimus</td></tr>
<tr><td>Indication</td><td>Prograf is a calcineurin-inhibitor immunosuppressant indicated for: Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants
Proposed- Lung cancer transplants</td></tr>
<tr><td>Route of Administration</td><td>Oral and Intravenous</td></tr>
<tr><td>Dosage Form</td><td>Capsules(NDA 050708), Granules for Oral Suspension (NDA 210115), and Injection(NDA 050709</td></tr>
<tr><td>Strength</td><td>Capsules- 0.5 mg, 1 mg, and 5 mg
Granules for Oral Suspension- 0.2 mg and 1 mg
Injection- 5 mg/mL</td></tr>
<tr><td>Dose and Frequency</td><td>
<table>
<tr><th>Patient Population</th><th>Initial Oral Dosage (formulation)</th><th>Whole Blood Trough Concentration Range</th></tr>
<tr><td colspan="3">ADULT</td></tr>
<tr><td colspan="3">Kidney Transplant</td></tr>
<tr><td>With azathioprine</td><td>0.2 mg/kg/day capsules, divided in two doses, every 12 hours</td><td>Month 1-3: 7-20 ng/mL
Month 4-12: 5-15 ng/mL</td></tr>
<tr><td>With MMF/IL-2 receptor antagonist</td><td>0.1 mg/kg/day capsules, divided in two doses, every 12 hours</td><td>Month 1-12: 4-11 ng/mL</td></tr>
<tr><td colspan="3">Liver Transplant</td></tr>
<tr><td>With corticosteroids only</td><td>0.1-0.15 mg/kg/day capsules, divided in two doses, every 12 hours</td><td>Month 1-12: 5-20 ng/mL</td></tr>
<tr><td colspan="3">Heart Transplant</td></tr>
<tr><td>With azathioprine or MMF</td><td>0.075 mg/kg/day capsules, divided in two doses, every 12 hours</td><td>Month 1-3: 10-20 ng/mL
Month ≥ 4: 5-15 ng/mL</td></tr>
<tr><td colspan="3">Lung Transplant</td></tr>
</table>
</td></tr>
</table>

	With azathioprine or MMF	0.075 mg/kg/ [redacted] .capsules, divided in two doses, every 12 hours	Month 1-3: 10-15 ng/mL Month 4-12: 8-12 ng/mL
	PEDIATRIC		
	Kidney Transplant		
		0.3 mg/kg/day capsules or oral suspension, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL
	Liver Transplant		
		0.15-0.2 mg/kg/day capsules or 0.2 mg/kg/day oral suspension, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL
	Heart Transplant		
		0.3 mg/kg/day [redacted] . capsules or oral suspension, divided in two doses, every 12 hours	Month 1-12: 5-20 ng/mL
	Lung Transplant		
		0.3 mg/kg/day [redacted] capsules or oral suspension, divided in two doses, every 12 hours	Weeks 1-2: 10-20 ng/mL Week 2 to Month 12: 10-15 ng/mL
	MMF= Mycophenolate mofetil		
How Supplied	<u>Capsules</u> • Bottle – 100 count • 10 blister cards of 10 capsules <u>Injection</u> • Sterile solution in a 1 mL ampule, in boxes of 10 ampules <u>Granules for Oral Suspension</u> • Carton containing 50 unit-dose packets		
Storage	<u>Capsules and Granules for Oral Suspension</u> • Store at 25°C (77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) <u>Injection</u> Store between 5°C and 25°C (41°F and 77°F).		

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 26, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Prograf. Our search did not identify any relevant previous reviews.

APPENDIX C. HUMAN FACTORS STUDY-N/A

APPENDIX D. ISMP NEWSLETTERS- N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)-N/A

APPENDIX F. N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Prograf labels and labeling submitted by Astellas.

- Prescribing Information (Image not shown) received on March 11, 2021, available from \\CDSESUB1\evsprod\nda050708\0088\m1\us\114-labeling\draft\labeling\tacro-plr4-us-en-indication-for-lung-transplant_25feb2021_cl.doc

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Memorandum

To: Ergun Velidedeoglu, MD, Division of Rheumatology and Transplant Medicine

From: Yan Li, PhD, Epidemiologist, Division of Epidemiology II
Efe Eworuke, PhD, Team Lead, Division of Epidemiology II
Monique Falconer, MD, MS, Deputy Director, Division of Epidemiology II

Date: March 9, 2021

Subject: Review of sponsor's proposed use of real-world evidence report to support the indication expansion of tacrolimus

Background

On January 12, 2021, the Division of Rheumatology and Transplant Medicine (DRTM) consulted the Division of Epidemiology II (DEPI-II) on Astellas's proposed use of real-world evidence (RWE) to support the indication expansion of tacrolimus to adult and pediatric patients receiving allogeneic lung transplant.

Tacrolimus, a calcineurin-inhibitor immunosuppressant, was first approved in 1994 for allogeneic liver transplant. The current product indications include "prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic liver, kidney or heart transplants, in combination with other immunosuppressants."

Regulatory need and gap

FDA's draft guidance "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" suggests in life-threatening and severely debilitating diseases with an unmet medical need, FDA may rely on less rigorous study designs to establish substantial evidence of effectiveness. This is the case for lung transplantation where are no FDA-approved immunosuppressants.

Given the lack of adequate and well-controlled clinical investigations, the sponsor proposes to present data from a retrospective cohort study and other published controlled trials to serve as substantial evidence of effectiveness to support the proposed indication expansion for tacrolimus.

The DRTM clinical reviewer noted that the efficacy supplement will likely be approved based on available RWE and the published literature due to the high unmet medical need, since there are currently no FDA-approved immunosuppressants for lung transplantation, and the fact that tacrolimus is widely used off-label for this indication in clinical practice. Further, DRTM confirmed that a separate epidemiology review will not be necessary; however, DEPI-II's comments on the submitted study and proposed product labels are appreciated.

Overview of study design/methods

The key evidence in support of proposed labeling changes is a retrospective cohort study of treatment and outcomes in the Scientific Registry of Transplant Recipients (SRTR) database. The study included patients who received a primary lung transplant and were discharged alive between January 1, 1999

and December 31, 2017. Eligible patients were followed from the discharge date till the earliest graft failure (GF) or death date. Immunosuppression regimens were defined based on maintenance therapy at discharge. The exposure group included patients receiving tacrolimus immediate release (IR) + mycophenolate mofetil (MMF). Three control groups included patients receiving: tacrolimus + azathioprine; cyclosporin A (CsA) + MMF; CsA + azathioprine. The crude cumulative incidence and 95% CI for death or GF at 1 year was estimated as 100% minus the Kaplan-Meier (KM) survival probability. Hazard ratios for each regimen of interest as compared to tacrolimus IR + MMF and their 95% CIs were estimated using Cox proportional hazards models adjusting for potential confounders. Analyses were conducted using an intention-to-treat approach.

Additional details on the sponsor's study design and methods are presented in Appendices Tables 1 and 2.

High-level assessment of the study report by DEPI-II

In sum, the study is considered well designed. With detailed clinical data from the Organ Procurement and Transplantation Network and supplemental data from Centers for Medicare & Medicaid Services and the National Death Master File. The SRTR database is well-suited to answer the proposed study question. By including almost all lung transplants in the United States, this study is directly generalizable to the U.S. population.

Nevertheless, we identified several threats to study validity, including residual confounding, exposure misclassification, outcome misclassification, and selection bias. While these limitations are considered mitigatable, given the fundamental differences between the current RWE study and a corresponding hypothetical randomized controlled trial, study conclusions should be interpreted with caution.

Additional details on DEPI-II's appraisal of the study's weaknesses and potential mitigation strategies are presented in Appendix Table 3.

Recommendations

DEPI-II has two recommendations regarding the labelling language. (1) Given the potential for residual confounding, labeling language presenting a comparative effectiveness claim between tacrolimus and other regimens should be avoided. (2) Given the potential for exposure misclassification and selection bias, the labeling language used to describe the study population should be clearly worded to avoid ambiguous interpretation. For example, *"The study included all recipients of a primary lung transplant who were alive at discharged between 1999-2017"*, *"Exposure was defined by immunosuppressant treatment received at discharge. At one-year posttransplant, X % of patients maintained on the same regimen"*.

DEPI-II will participate in labeling discussion to assure a balanced presentation of the data is used in the labeling language.

Appendix

Table 1. Study Synopsis

Product, therapeutic area, indication	Tacrolimus: a calcineurin-inhibitor immunosuppressant for the prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic liver, kidney or heart transplants, in combination with other immunosuppressants
Regulatory purpose	To expand the indication to patients receiving allogeneic lung transplant
Existing evidence from other sources	• Tacrolimus was shown to prolong allograft survival in several large animal lung transplant models (dog, monkey, and miniature swine) when administered as monotherapy as well as combination with other immunosuppressants. • FDA approved tacrolimus in liver, kidney or heart transplantations. • At least five small, open-label, randomized controlled trials (RCTs) by academic investigators have evaluated tacrolimus for prevention of organ rejection in lung transplantation. There was no survival benefit observed with tacrolimus as compared to Cyclosporin A (CsA).
Regulatory need and gap	FDA's draft guidance "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" suggests in life-threatening and severely debilitating diseases with an unmet medical need, FDA may rely on less rigorous study designs to establish substantial evidence of effectiveness. This is the case for lung transplantation where are no FDA-approved immunosuppressants. Given the lack of adequate and well-controlled clinical investigations, the sponsor proposes to present data from a retrospective cohort study and other published controlled trials to serve as substantial evidence of effectiveness to support the proposed indication expansion for tacrolimus.
Study objective	Primary objectives • Describe the use of tacrolimus immediate release (IR) and other immunosuppressive agents over time in lung transplanted patients in the US. • Describe the incidence of transplant-related outcomes over time in lung transplanted patients in the US. Secondary objectives • Evaluate the real-world effectiveness of tacrolimus IR + mycophenolate mofetil (MMF) in lung transplantation, as compared to tacrolimus IR + azathioprine, CsA + MMF, or CsA + azathioprine. • Evaluate the safety of tacrolimus IR + MMF in lung transplantation, as compared to tacrolimus IR + azathioprine, CsA + MMF, or CsA + azathioprine. Exploratory objective • Evaluate the contribution of individual agents (specifically tacrolimus IR) over time.

Table 2. Comparison between the real-world evidence (RWE) study and a hypothetical randomized controlled trial (RCT)

Study design	RWE study (Observational study)	Hypothetical RCT (Traditional RCT)
Study period: • Total duration • Date of first enrollment, date of last completed • First date to identify study population, last date of follow-up for RWE	From January 1st, 1999 to December 31st, 2017	From January 2021 until the targeted sample size is accrued
Design	Retrospective cohort study using secondary data	Randomized, double-blinded, active-controlled trial
Data source (including calendar time of data availability, if applicable)	The Scientific Registry of Transplant Recipients (SRTR) is a national transplant registry that contains data on all lung transplant candidates, recipients and donors in the United States from Oct 1987 onward. The primary data source for SRTR is Organ Procurement and Transplantation Network (OPTN), which is supplemented by data from the Centers for Medicare & Medicaid Services (CMS) and the National Technical Information Service's Death Master File.	Primary data collection with pre-specified data collection schedule
Study population inclusion and exclusion criteria	Inclusion and exclusion criteria were assessed retrospectively using information recorded in the SRTR. Inclusion criteria • Patients who had received a primary lung transplant (not re-transplant) in the SRTR registry between 01 Jan 1999 and 31 Dec 2017 Exclusion criteria • Patients with a history of organ transplant prior to and including the date of lung transplant. • Transplant recipients of a multiorgan transplant • Transplant recipients of organ from a living donor • Transplant recipients who had died during the index hospitalization or had graft failure (GF) on or prior to discharge • Transplant recipients with missing discharge date, or discharge date more than 1 year posttransplant	The following exclusion criteria used in the retrospective cohort study would not apply in a trial setting. • Transplant recipients who had died during the index hospitalization or had graft failure (GF) on or prior to discharge • Transplant recipients with missing discharge date, or discharge date more than 1 year posttransplant • Transplant recipients with missing maintenance immunosuppression

Study design	RWE study (Observational study)	Hypothetical RCT (Traditional RCT)
	• Transplant recipients with missing maintenance immunosuppression information at discharge.	information at discharge.
Index time	Date of discharge of the transplant hospitalization	Time of treatment initiation after transplant surgery
Follow-up and censoring	Patients were followed until the earliest of GF date or death date, with follow-up censored at the date of last available follow-up or 1 year posttransplant (for primary endpoint), whichever occurred first. Data for transplant recipients are collected at discharge posttransplant, 6-month posttransplant, 1-year posttransplant, 2-year posttransplant, and 3-year post-transplant.	Patients are followed for at least three years unless they were lost to follow-up
Exposure definition, ascertainment, and validation	Immunosuppression regimens of interest were defined based on maintenance therapy at discharge. The exposure group included patients receiving tacrolimus IR + MMF. Analyses were conducted using an intention-to-treat approach	Patients' treatment will be assigned at random
Comparator definition, ascertainment, and validation	Three control groups included patients receiving: tacrolimus IR + azathioprine; CsA + MMF; CsA + azathioprine	Patients' treatment will be assigned at random
Outcome definition, ascertainment, and validation	Primary endpoint: Graft failure (GF) or death (due to any cause) within 1 year after transplant. Secondary endpoint: GF or death at 2 and 3 years of follow-up Death GF Any rejection Treated rejection Bronchiolitis obliterans syndrome (BOS) Safety endpoints: Causes of death Causes of GF Overall malignancy (excluding nonmelanoma skin cancers) Posttransplant lymphoproliferative disease (PTLD) Hospitalized for infection New onset diabetes after transplant (NODAT) Renal dysfunction†, defined as any of the following: chronic	The outcomes proposed for the retrospective cohort study would also apply to a clinical trial. Patients will be followed according to a standard study protocol and outcomes will be adjudicated by an adjudication committee. Event dates will be collected for all outcomes. Therefore, time to event analysis can be conducted for all outcomes

Study design	RWE study (Observational study)	Hypothetical RCT (Traditional RCT)
	dialysis, renal transplant, eGFR < 15 Study outcomes were determined by individual physicians with varying standards. In the SRTR, exact event dates were only collected for death, GF, cancer, and PTLD, while other outcomes were reported at the interval level. We only know whether these outcomes occurred or not during a given follow-up interval. As a result, no time-to-event analysis was conducted for these interval outcomes.	
Key covariates: measured and unmeasured	There were detailed clinical data collection for a variety of study covariates. Recipient-related covariates: immunosuppressive regimen at discharge, induction agents, Double- vs single-lung transplant, transplant year, transplant eras, primary cause of lung disease, age, sex, BMI, race and ethnicity, cytomegalovirus (CMV) serostatus, urgency at time of transplant, most recent serum creatine, total bilirubin, initiation of dialysis, length of hospital stay Donor-related covariates: age, CMV serostatus, sex, race and ethnicity, donor-recipient human leukocyte antigen mismatches, lung total ischemic time, categorized in approximate quantile, donor-recipient weight ratio	Similar to cohort study
Statistical methods (primary analysis)	The crude cumulative incidence and 95% CI for death or GF at 1 year was estimated as 100% minus the Kaplan-Meier (KM) survival probability. Hazard ratios for each regimen of interest as compared to tacrolimus IR + MMF and their 95% CIs were estimated using Cox proportional hazards models adjusting for potential confounders.	The crude cumulative incidence and 95% CI for death or GF at 1 year was estimated as 100% minus the Kaplan-Meier (KM) survival probability. The HR and the corresponding two-sided 95% CI will be estimated in Cox proportional hazard model using randomized arm as a single covariate.
Sample size (planned or analyzed)	The study included all eligible lung transplant patients in the United States from 1999 to 2017. A formal power or precision analysis has not been conducted.	Followed the planned sample size calculation
Methods to handle confounding, if	To avoid the issue of overfitting, not all listed covariates were	Randomization

Study design	RWE study (Observational study)	Hypothetical RCT (Traditional RCT)
applicable	adjusted in the Cox model. The sponsor used a two-step approach to select covariates for adjustment: (1) A multinomial logistic regression was used to determine a set of covariates that predicted treatment. (2) Covariates retained from the first step were included in univariate Cox models of transplant outcomes to determine covariates that also predicted outcomes. Finally, covariates selected by these two steps were adjusted in the Cox models, along with several pre-determined factors: age group, transplant era, single- vs double-lung transplant, diagnosis group and dialysis since listing.	
Methods to handle missing data, if applicable	For all covariates, an "unknown" level was kept, and the missingness was summarized. In some cases, the missing level were used in models. For outcomes with exact dates of occurrence, patients lost to follow-up were assumed to have the outcome in the sensitivity analyses. For outcomes that were collected at the interval level, a tabulation by endpoint was provided to quantify missingness	Missing data is limited with rigorous study quality control

Table 3. Study Appraisal

Threats to study validity	RWE study (observational study)	Hypothetical RCT (traditional RCT)	Direction of bias and need for quantitative bias assessment (QBA)	Quantitative bias analysis results, if applicable	Impact of limitation (e.g., minor, major)	Approaches to bias mitigation
Residual confounding related to incomplete statistical adjustment	There are strong time trends in the use of different study regimens and the distribution of risk factors for study outcomes. It is not clear whether regression-based adjustment can adequately eliminate the differences between treated and control subjects.	Randomization takes care of confounding	Results could favor tacrolimus IR + MMF. This regimen gained popularity more recently. Meanwhile, transplant outcomes are improving over time.	N/A	Major	(1) Including interaction terms between study eras and covariates. (2) Conducting subgroup analyses by study eras, in which potential confounders were adjusted within subgroups. (3) Use propensity score based methods to address confounding and examining the balance in baseline covariates between groups.
Residual confounding related to retrospective patient selection	Patient eligibility was determined by using the secondary information in the SRTR. Not all clinical details were recorded in this secondary data source, which could potentially confound the study results. For example, patients may	Patient eligibility will be determined by investigators based on detailed clinical examinations	Unknown	N/A	Minor/Major	Linking a small subset of patients in the SRTR to other external data sources to examine additional patient

Threats to study validity	RWE study (observational study)	Hypothetical RCT (traditional RCT)	Direction of bias and need for quantitative bias assessment (QBA)	Quantitative bias analysis results, if applicable	Impact of limitation (e.g., minor, major)	Approaches to bias mitigation
	have needs for immunosuppressive regimens other than study medications or have other disorders that affect the function of immune system. These patients would not be eligible for an RCT.					characteristics
Exposure misclassification	Exposure was defined based on the index regimen reported at discharge Patients may have switched or discontinued treatment(s) temporarily or permanently. No dosing information was recorded. Two- and three-year follow-up data were unavailable for over half of the cohort. The planned analysis used an intention-to-treat approach to define exposure group.	Patients' adherence to the assigned regimen is usually high. There are standard dosing protocols. Patients are closely monitored for treatment discontinuation.	The benefits of tacrolimus IR + MMF relative to other regimens could be underestimated. At the 1-year follow up, the tacrolimus IR + MMF group had the highest continuation rate. Patients in other groups were more likely to switch to the tacrolimus IR + MMF group. Under the ITT framework, this would put the comparator group in advantage.	N/A	Minor	Conducting a sensitivity analysis using an "as-treated" approach in which only patients who stayed on the same regimen at 1-year is included.
Outcome misclassification	Outcomes were determined by individual reporting physicians with varying standards.	Outcomes will be defined following standard criteria.	In general, we would not expect differential reporting between different regimens. However, there were strong time	N/A	Minor, the primary outcome death or GF should be reported with limited variation between	Providing more information on the quality of outcome reporting in the SRTR.

Threats to study validity	RWE study (observational study)	Hypothetical RCT (traditional RCT)	Direction of bias and need for quantitative bias assessment (QBA)	Quantitative bias analysis results, if applicable	Impact of limitation (e.g., minor, major)	Approaches to bias mitigation
			trends in the use of different regimens. The changing practice of outcome reporting over time may render differential reporting between regimens.		transplant centers.	
Selection bias	Only patients who were discharged alive were included. All endpoints were conditional on survival to discharge.	Patients who develop outcome events before the discharge will be included	Unknown	N/A	Minor	Collecting data on patients who develop outcome events during the transplant hospitalizations

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50708s053, 50709s045, 210115s005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 50708 SUPPL # 053, 50709/S-045, 210115/S-005 HFD #

Trade Name Prograf

Generic Name tacrolimus

Applicant Name Astellas

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)2

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 50708 Prograf

NDA#	50709	Prograf
NDA#	210115	Prograf
	206406	Envarsus
	50777	Protopic
	204096	Astagraf XL
	There are also ANDAs for the tablet, ointment and injectable	

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Ergun Velidedeoglu, MD
Title: Clinical Reviewer
Date: July 16, 2021

Name of Division Director signing form: Ozlem Belen, MD, PhD on behalf of Nikolay Nikolov, MD
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSAN RHEE
07/16/2021 12:32:11 PM

OZLEM A BELEN
07/16/2021 02:04:12 PM

NDA 50708

MEETING MINUTES

Astellas Pharma US, Inc.
1 Astellas Way
Northbrook, IL 60062

Attention: Mary Jo Pritza, MPH, PharmD
Senior Director, Regulatory Affairs

Dear Dr. Pritza:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prograf (tacrolimus) capsules.

We also refer to the teleconference between representatives of your firm and the FDA on August 21, 2020. The purpose of the meeting was to discuss the adequacy of the plan and content of the submission which utilizes Real World Evidence (RWE) to support the filing and review of the supplemental NDA for the addition of a new indication to the Prograf label, prophylaxis of organ rejection in lung transplantation.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-2402.

Sincerely,

{See appended electronic signature page}

Susan Rhee, PharmD
LCDR, US Public Health Service
Regulatory Project Manager
Rheumatology and Transplant Medicine
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-sNDA

Meeting Date and Time: August 21, 2020 10:30 AM – 11:30 AM EDT
Meeting Location: teleconference

Application Number: 50708
Product Name: Prograf (tacrolimus)
Indication: Prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic lung transplant in combination with other immunosuppressants
Sponsor Name: Astellas Pharma US, Inc.
Regulatory Pathway: 505(b)(1) of the Food, Drug, and Cosmetics Act

Meeting Chair: Ozlem Belen, MD, MPH
Meeting Recorder: Susan Rhee, PharmD

FDA ATTENDEES

Ozlem Belen, MD, MPH, (Acting) Deputy Division Director, DRTM
Jane Filie, MD, Associate Director for Labeling, DRTM
Ergun Velidedeoglu, MD, Clinical Reviewer, DRTM
Jianmeng Chen, PhD, Team Leader, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Tao Liu, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Clara Kim, PhD, Biostatistics Team Leader, Division of Biometrics VII (DBVII), Office of Biostatistics (OB)
Tae Hyun (Ryan) Jung, PhD, Biostatistics Reviewer, DBVII, OB
John Concato, MD, MPH, Deputy Director, Office of Medical Policy Initiatives, Office of Medical Policy
Susan Rhee, PharmD, Regulatory Project Manager, DRTM

SPONSOR ATTENDEES

Richard Croy, Director, Biostatistics
Jay Erdman, MS, Senior Director, Global Development Project Leader
Salim Mujais, MD, Senior Vice President and Head, Medical Specialties
David Nimke, Sr. Director, Real World Evidence-US, Advanced Informatics and Analytics
David Aschermann, MBA, Director, Development Project Management, Medical Specialties
Mary Jo Pritza, MPH, PharmD, Sr. Director, Regulatory Affairs
David Smethurst, Executive Director, Regulatory Affairs

Xuegong Wang, MD, PhD, Senior Medical Director, Medical Specialties, Transplant and Immunology/Inflammation
Josephine Wolfram, MA, MSc, Director, Development Applications Lead, Real World Data & Evidence, Advanced Informatics and Analytics

Consultants

(b) (4)

Melissa Skeans, Manager of Biostatistics, Chronic Disease Research Group (CDRG)
Jon Snyder, Director of Transplant Epidemiology, CDRG

1.0 BACKGROUND

In a submission received on June 22, 2020, Astellas Pharma Inc. (Astellas) requested a meeting to discuss and obtain advice from the Agency on the adequacy of the plan and content to support the filing and review of a supplemental NDA submission which utilizes Real World Evidence (RWE). Astellas references the FDA Written Responses and Meeting Minutes dated October 3, 2019, and March 13, 2020, respectively, which support their plans to add a new indication to the labeling for Prograf based on RWE. The evidence in support of labeling changes will be based on RWE generated using a retrospective analysis of data—collected from the Scientific Registry of Transplant Recipients (SRTR)—pertaining to treatment and outcomes among patients who had received a lung transplant and were administered tacrolimus. Additional support for the application will come from available journal publications, which report the results from studies conducted in lung transplant recipients. Astellas' specific questions from the briefing document received on July 17, 2020, are listed below in *italics* and the FDA responses are provided in normal font.

In an email correspondence received on August 20, 2020 from Mary Jo Pritza, Astellas requested further discussion on FDA Response to question 3d and comment 2 under Additional Statistical Comments.

2.0 DISCUSSION

2.1. CLINICAL AND STATISTICAL

Question 1:
Astellas refers to the outcomes from the Type C teleconference meeting held 26 Feb 2020 and to the Agency's comments addressing our use of comparative analyses in the planned supplement. The Agency stated that these analyses would be considered supplemental and not serve as the primary basis for establishing efficacy. The primary consideration will be the rate of death or graft failure in the

tacrolimus IR and MMF treatment group. Astellas included preliminary results from this analysis in this briefing document [Table 2].

Does the Agency agree that the rate of death or graft failure in the tacrolimus IR and MMF treatment arm appears sufficient to support the filing and review of the application?

FDA Response to Question 1:

In principle, we agree that the rates of death or graft failure at one year and at three years post-transplantation as the primary efficacy outcome assessments in lung transplant recipients treated with the tacrolimus IR and MMF regimen are sufficient to support the filing and review of the application. We also request that you submit the subgroup analyses specified in your meeting package, including outcome analyses based on single versus double lung transplantations.

Discussion to Question 1:
No discussion

Question 2a:
Does the Agency agree that the number of pediatric lung transplant recipients exposed to tacrolimus would be sufficient to support the filing and review of the application?

FDA Response to Question 2a:

Based on the information provided, the number of pediatric lung transplant recipients exposed to tacrolimus appears to be sufficient to support the filing and review of the application. However, the final decision will be a review issue.

Discussion to Question 2a:
No discussion

Question 2b:
Would the recommendations from ISHLT for pediatric lung transplant that are also consistent with the pediatric heart labeling be adequate to support a review of the proposed dosing and trough levels intended for inclusion in the draft product labeling?

FDA Response to Question 2b:

Along with other submitted evidence from the published literature, the ISHLT recommendations for pediatric lung transplant recipients will be taken into consideration during the review of the proposed starting dose and the target trough range for pediatric patients to be included in the product labeling. Final decision will be a review issue.

Discussion to Question 2b:
No discussion

Question 3a:
Does the Agency concur with the intended plan for submission of the SAF metadata and data collection forms as described in these documents?

FDA Response to Question 3a:

We agree with your intended plan for submission of SAF metadata and data collection forms.

Discussion to Question 3a:
No discussion

Question 3b:
Does the Agency concur with the intended plan for submission of the analysis-ready data?

FDA Response to Question 3b:

We concur with your plan, but we might request additional data if we decide to conduct sensitivity analyses not included in your study report.

Discussion to 3b:
The sponsor confirmed that the analysis-ready data will be less than 5 gigabytes.

Question 3c:
Does the Agency concur that the programs submitted in .Rmd and html formats will be acceptable for review of the application?

FDA Response to Question 3c:

We agree with the program submission using R markdown. However, generate the final format into both html and pdf formats, given that the html output will not have page breaks and is difficult to annotate. Also, if your programs use R packages, specify alternative packages if applicable.

Discussion to 3c:
No discussion.

Question 3d:
Does the Agency have any feedback regarding Astellas' intended approach, as described, for submitting the patient level datasets?

FDA Response to Question 3d:

See FDA response to Question 3b.

Discussion to 3d:

Astellas' proposal to submit the datasets in xpt version 8 or 9:
Astellas requested clarification on the acceptability of submitting datasets in xpt version 8 or 9 because their datasets contain variables and labels of length greater than 8 and 40, respectively. FDA stated that these file formats do not represent the FDA policy, and version 8's limitations include increased file size, no native mechanism for support of audit trails and referencing data sources. Additionally, FDA stated that the only benefit of version 8 is that it allows longer character lengths compared to version 5. All electronic submissions for NDA should use version 5 and follow the maximum permissible number of characters (8 characters for variable names; 40 characters for variable descriptive labels; and 40 characters for dataset labels) based on the *Study Data Technical Conformance Guide* (July 2020, version 4.5.1). Astellas stated that they will map the current variable names and labels to shorter ones if version 8 is not acceptable.

The Agency stated that internal discussion would be needed before we provide a definitive answer. Action items based on the post-meeting discussion are described in section 2.5.

Astellas' proposal to submit the datasets outside the Gateway:
Regarding the Astellas' proposal that patient-level datasets will be provided directly to the FDA by CDRG, [*the Chronic Disease Research Group, a division of the Hennepin Healthcare Research Institute responsible for operating the Scientific Registry of Transplant Recipients (SRTR)*] via CDRG's secure File Transfer Protocol (FTP), the FDA clarified that (1) Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA, and (2) Astellas' proposal to submit data by a third party outside the ESG needs further discussion within the FDA before a definitive response can be provided. The FDA will include their response on this request as part of the meeting minutes as a Post-Meeting Comment (see section 2.6).

2.2. REGULATORY

Question 4:
Does the Agency agree with the format and planned submission content of the supplement application?

FDA Response to Question 4:

We reviewed the Electronic Common Technical Document (eCTD) Table of Contents in your meeting package. For clarification, we request that you submit the study protocol and the final study report in detailed narrative format (*supplemented by tables and figures to the extent of data available in the SRTR*) for your main study F506-CL-3001, titled "*Retrospective Study of Treatment and Outcomes for Lung*

Transplant Patients in the United States using the Scientific Registry of Transplant Recipients (SRTR)" in Module 5, and the relevant summaries (Summary of Clinical Efficacy and Safety) in Module 2. We expect the study report to contain a detailed discussion of the study findings.

Discussion to Question 4:
No discussion.

Question 5a:
Does the Agency have any comment on the locations selected in the draft labeling to present the data?

FDA Response to Question 5a:

The locations selected in the draft labeling to present the data seem acceptable. We can comment further following the review of the sNDA.

Discussion to Question 5a:
No discussion.

Question 5b:
Subject to the review of the application, does the Agency have other recommendations that pertain to the draft labeling?

FDA Response to Question 5b:

We do not have any additional recommendations that pertain to the draft labeling at this time.

Discussion to Question 5b:
No discussion.

2.3. ADDITIONAL STATISTICAL COMMENTS

1. Submit an updated statistical analysis plan (SAP) for FDA's review before submitting the sNDA. The SAP should describe the non-comparative primary analysis and also include all analyses the sponsor plans to submit to the sNDA

Discussion to 1:
No discussion.

2. It appears that patient and graft survival (primary efficacy endpoint) can reliably be ascertained. However, the secondary efficacy and safety endpoints might not be reliably ascertained. Discuss the availability of these endpoints and how you will ascertain them in the SAP.

Discussion to 2:
As long as the primary efficacy endpoint is well established, given the clinical evidence, we consider the secondary and safety endpoints as supportive. Astellas stated that the SAP will describe methods to assess the extent of missing data and missing follow up forms. We agree with Astellas' approach.

3. In the SAP, include plans to describe the amount of missing data and how you will handle it in the analysis.

Discussion to 3:
No discussion.

4. In Table 2 (p.16) of the Type-B meeting briefing document, you calculated the cumulative incidence percentage using 100% minus the K-M survival percentage. This is correct for the primary composite endpoint. However, each component of the primary endpoint, graft failure and death, are competing events. Therefore, one minus the K-M survival percentage will overestimate the cumulative incidence. Provide the 95% confidence intervals of the cumulative incidence and K-M plots.

Discussion to 4:
No discussion.

2.4. ADDITIONAL SUMMARY DISCUSSIONS:

1. FDA requested clarification that the analysis of the primary endpoint would take place both at 1 year and 3 years, as the recent submission puts less emphasis on the 3-year time point. Astellas confirmed that both time points, 1 year and 3 years, would be assessed and submitted.

2. FDA requested that a subgroup analysis be conducted for single vs. double lung transplant in addition to the sponsor's proposed subgroup analyses. Astellas confirmed that this would be completed.

3. FDA requested that an updated study protocol also be submitted at the time of the sNDA submission in addition to the SAP, which Astellas agreed to.

4. FDA requested that a full study report with a narrative including the sponsor's discussion of the efficacy and safety data be submitted; Astellas agreed that they will work to provide a written narrative as part of the study report.

5. Astellas advised their plans to submit the supplemental NDA by December 2020.

2.5 Post Meeting Comments regarding data submission using XPORT version 8 instead of version 5.

To evaluate the SRTR data structure and compatibility, we request the sponsor to submit sample datasets in both version 5 (.xpt) and version 8 (.v8xpt, .xpt8, or .2xpt). Submit data of all variables that will be included in the sNDA submission for 50 subjects. Provide R codes to import the data. In a separate document, identify the variables and labels that are greater than 8 and 40 characters, respectively, of length.
Also, clarify whether the data dictionary you plan to submit is the same as the data dictionary available publicly. If not, please submit the private data dictionary when submitting the sample data.

2.6. Post Meeting Comments regarding data submission of real-world data outside of FDA's Electronic Submission Gateway (ESG), from Chronic Disease Research Group (CDRG), a third-party consultant to Astellas.

FDA does not accept regulatory submissions with File Transfer Protocol (FTP). For the submission of files larger than 10 Gigabyte, sponsors can submit data on a physical drive and send to the FDA. FDA website provides more detail about submissions at (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd). For further details, please contact esub@fda.hhs.gov for further assistance on this.

eSUB recommendation is for the sponsor/applicant to obtain the RWD and then submit under their application in eCTD so that the information is all in one place.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

[Identify any issues that remain open at the end of the meeting and require further discussion at a later date. If none exist, please indicate that there were no issues requiring further discussion]

5.0 ACTION ITEMS

[Insert any action items that were identify during the meeting. Include who is responsible to complete the action item and the due date. Responsible party should not be an individual, but either sponsor or FDA. Consider the use of a table to present the information]

Action Item/Description	Owner	Due Date
[Insert action item with a brief description, if applicable]	FDA	[Insert date]
[Insert action item with a brief description, if applicable]	Sponsor	[Insert date]

6.0 ATTACHMENTS AND HANDOUTS

[Identify any attachments or handouts used during the discussion at the meeting. Generally, a copy of presented slides should be attached. If there are no attachments, insert a comment that there were no attachments or handouts for the meeting summary.]

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSAN RHEE
09/11/2020 12:31:26 PM