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APPLICATION NUMBER:

210115Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	210115
Link to EDR	EDR Link
Submission Date	07/26/2017
Submission Type	Standard
Brand Name	PROGRAF Granules
Generic Name	Tacrolimus
Dosage Form and Strength	Granules for oral suspension; 0.2 mg and 1.0 mg packets
Route of Administration	Oral
Proposed Indication	For the prophylaxis of organ rejection in pediatric liver transplant patients.
Applicant	Astellas Pharma US, Inc.
Associated IND	IND 034654
OCP Review Team	Abhay Joshi, Ph.D. *DCP IV Clinical Pharmacology Reviewer;* Philip Colangelo Pharm. D., Ph.D. *DCP IV Clinical Pharmacology Team Leader*

1. Table of Contents

1. EXECUTIVE SUMMARY

This submission is a 505(b)(1) NDA for PROGRAF granules for oral suspension[1], which is a new tacrolimus formulation. Tacrolimus is a calcineurin inhibitor immunosuppressant approved in the US for the prophylaxis of organ rejection in patients receiving allogeneic heart, kidney, or liver transplants. The currently approved United States Product Insert (USPI) for tacrolimus formulations, i.e., capsules and IV injection, includes dosing recommendations for adult kidney and heart transplant patients as well as for adult and pediatric liver transplant patients.

This submission was in accordance to a Post Marketing Requirement (PMR) under the Pediatric Research Equity Act (PREA) for NDA 204096 (Astagraf XL®, tacrolimus extended-release capsules). The PMR was to develop an age-appropriate formulation to allow dosing for ages 1 to <5 years. PROGRAF granules are packaged as packets (b) (4) containing 0.2 mg and 1 mg of tacrolimus and the same granule formulation is currently marketed as Modigraf in other countries.

The safety and efficacy of PROGRAF granules has been evaluated in pediatric liver transplantation via an adequate and well-controlled clinical study provided in this current NDA submission. Pharmacokinetic data was also collected in pediatric liver transplant patients. The efficacy and safety of PROGRAF granules has not been evaluated via adequate and well-controlled clinical studies in pediatric kidney and heart transplantation. The clinical experience with PROGRAF granules in pediatric kidney and heart transplantation is limited to pharmacokinetic trials. From a Clinical Pharmacology perspective, the following two proposals from the Applicant are the key review issues:

(1) The proposed starting dose of PROGRAF granules for pediatric liver transplant patients.
(2) The proposed revisions to the Section 12.3 of the currently approved USPI to include PK information from studies that evaluated PROGRAF granules in pediatric patients undergoing *de novo* kidney, heart, and liver transplantation including the starting doses that was assessed and observed whole blood trough concentrations of tacrolimus.

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information provided by the Applicant in NDA 210115 and recommends approval of this NDA for PROGRAF Granules.

The Reviewer's proposed label changes to the Applicant proposed labeling, as outlined in **Section 2.4** of this review, will be forwarded to the sponsor.

[1] For the purpose of this review, PROGRAF granules is also referred as Modigraf Granules, tacrolimus granules, tacrolimus granules for oral suspension, or the tacrolimus granule formulation. Tacrolimus is also referred as FK506.

Table 1: Summary of OCP's Recommendations & Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal evidence of effectiveness for PROGRAF granules in the pediatric liver transplant prophylaxis indication is derived from Study FG-506-01-08 (Phase 2) and Study FG-506-01-13 (Phase 3). The supportive evidence for pediatric heart, kidney, and liver transplantation is derived from the following three studies: Study F506-CL-0403 (OPTION) (Phase 4) Study F506-CL-0404A (a follow-up study to the OPTION study) Study 95-0-001 (Phase 1)
General dosing instructions	The Applicant's proposed starting oral dose of PROGRAF granules for pediatric liver transplant patients is same as the currently approved dose for PROGRAF capsules, i.e., 0.15 - 0.20 mg/kg/day to be administered in two divided doses, every 12 hours. However, the starting dose evaluated in the pivotal Phase 2 and Phase 3 studies listed above was approximately 0.3 mg/kg/day. An information request (IR) was sent to the Applicant requesting the rationale for the proposed lower starting dose than the starting dose evaluated in the supportive clinical studies. Based on the information in original submission and the Applicant's response to the abovementioned IR, the Clinical Pharmacology review team recommends that the starting dosing for tacrolimus granules for pediatric liver transplantation be changed in the USPI to *0.20 mg/kg/day to be administered in two divided doses, every 12 hours*. Please see **Section 3.3.2** for further details.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No new information is provided in this submission with respect to the effect of intrinsic or extrinsic factors on the pharmacokinetics of tacrolimus.
Labeling	The Applicant is proposing to include the tacrolimus PK related information from the OPTION study, which enrolled pediatric liver, heart, and kidney transplant patients, in Section 12.3 of the currently approved USPI. The safety and efficacy of PROGRAF granules has not been established in pediatric kidney or heart transplant patients. The experience in pediatric kidney and heart transplantation patients with PROGRAF granules is limited to pharmacokinetic trials. Following discussion with the FDA Pediatrics and Maternal Health (PMH) team regarding inclusion of PK data for all three pediatric organ transplant indications, PMH indicated that such inclusion of PK data and extrapolation of efficacy and safety from adult to pediatric heart and kidney transplant patients is acceptable for PROGRAF Granules. Thus, the Applicant proposed inclusion of the PK data from pediatric kidney and heart transplant patients, who were administered PROGRAF granules, in **Section 12.3** of the currently approved USPI is acceptable to the Clinical Pharmacology Review team.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable. To-be-marketed formulation is the clinical trial formulation.
Bioavailability and dose conversion between formulations	Pharmacokinetic findings from a single dose healthy volunteer adult study indicated that the systemic exposure (AUC) to tacrolimus from PROGRAF granules was approximately 16% higher than that from PROGRAF capsules. The mean Cmax for PROGRAF granules was approximately 23% higher than PROGRAF capsules. The Applicant is proposing (b) (4)

	dosing conversion between formulations along with therapeutic drug monitoring following a conversion to ensure that systemic exposure to tacrolimus is maintained. The Applicant's proposals listed above are acceptable to the Clinical Pharmacology Review team.

1.1. Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1. Clinical Pharmacokinetics

The relative bioavailability (BA) of tacrolimus was assessed in healthy subjects by comparing the mean AUC estimate following administration of PROGRAF granules and was 16 % higher compared to that following administration of PROGRAF capsules; this difference in BA is not considered to be clinically significant by the Clinical Pharmacology review team. Regarding conversion from one oral PROGRAF formulation to another in pediatric liver transplant patients, i.e., patients who initiated oral tacrolimus therapy with the granule formulation and get converted to the capsule formulation or vice versa, the Applicant proposes to keep the same total daily dose following conversion. In addition, the Applicant also proposes therapeutic drug monitoring (TDM) of trough tacrolimus whole blood concentrations following conversion. From a Clinical Pharmacology perspective, the Applicant's proposals are acceptable.

The proposed starting oral dose of the granule formulation for pediatric liver transplant patients in the Applicant proposed labeling is same as the currently approved starting dose for PROGRAF capsules, i.e., 0.15 - 0.20 mg/kg/day to be administered in two divided doses, every 12 hours. The key safety and efficacy studies, i.e., Study FG-506-01-08 (Phase 2) and Study FG-506-01-13 (Phase 3), that evaluated the granule formulation in the pediatric liver transplant patients used a starting dose that approximated 0.3 mg/kg/day. Therefore, an information request (IR) was sent by the FDA to the Applicant on 11/29/2017, which requested the rationale for the proposed lower starting dose for the granule formulation than the dose that was evaluated in Study FG-506-01-13. The Applicant's response to the IR dated 01/24/2018 was reviewed by the Clinical Pharmacology review team and we recommend the starting dose for PROGRAF granules be revised in the labeling to *0.20 mg/kg/day to be administered in two divided doses, every 12 hours* in the USPI. See **Section 3.3.2** for additional details.

For tacrolimus based immunosuppressive therapy, monitoring of whole blood tacrolimus trough concentrations is recommended. The currently approved USPI of tacrolimus capsules lists the range of 5-20 ng/mL for Month 1-12 for pediatric liver transplant patients as the observed whole blood concentrations. The Applicant is not proposing any revisions to this whole blood trough concentration range, which is acceptable from a Clinical Pharmacology perspective.

The Applicant also proposes to include the PK related information including the starting doses that was assessed and the whole blood trough concentration ranges of tacrolimus in *de novo* pediatric liver, heart, and kidney transplant patients from the OPTION study in Section 12.3 of the currently approved USPI. The safety and efficacy of PROGRAF granules has not been established in pediatric kidney or heart transplant patients. The experience in pediatric kidney and heart transplantation patients with PROGRAF granules is limited to pharmacokinetic trials.

Following discussion with the FDA Pediatrics and Maternal Health (PMH) team regarding inclusion of PK data for all three pediatric organ transplant indications, PMH indicated that such inclusion of PK data and extrapolation of efficacy and safety from adult to pediatric heart and kidney transplant patients is acceptable for PROGRAF Granules. Thus, the proposed inclusion of the PK data from pediatric kidney and heart transplant patients in Section 12.3 of the currently approved USPI is acceptable to the Clinical Pharmacology Review team. Please refer to **Section 4.4** for additional details.

2.2.Dosing and Therapeutic Individualization

2.2.1. General dosing

The Applicant's proposed oral starting dose of the granule formulation for pediatric liver transplant patients is 0.15 - 0.20 mg/kg/day to be administered in two divided doses, every 12 hours, which is same as the initial dosing listed for PROGRAF capsules in the currently approved USPI. However, based on the doses and whole blood tacrolimus trough concentrations reported from Studies FG-506-01-08 and FG-506-01-13 in pediatric *de novo* liver transplant patients, the Clinical Pharmacology review team recommends that the starting dose for the granule formulation should be revised to 0.20 mg/kg/day. Please see **Section 3.3.2** for further details.

2.2.2. Therapeutic individualization

The relative risks of toxicity and efficacy failure are known to be partially related with tacrolimus whole blood trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended for the tacrolimus therapy. For the granule formulation, the Applicant is proposing to list the whole blood trough concentration ranges in USPI that are same as the values listed for PROGRAF capsules in the currently approved USPI.

2.3.Outstanding Issues

From a Clinical Pharmacology perspective, there are no outstanding issues with this application.

2.4.Summary of Labeling Recommendations

The Reviewer proposed specific additions to the Applicant proposed labeling are in *blue underlined* text and proposed deletions are marked as ~~*red strike out*~~ text. The summary of the Reviewer proposed labeling recommendations/revisions is provided below in *orange italics* text.

Section: HIGHLIGHTS OF PRESCRIBING INFORMATION - DOSAGE AND ADMINISTRATION

For the pediatric liver transplantation patients, the starting dose for the granule formulation was revised from 0.15-0.20 mg/kg/day to 0.20 mg/kg/day.

Section 2.4: PROGRAF Capsule or Granules Dosage in Pediatric Liver Transplant Patients

For the pediatric liver transplantation patients, the starting dose for granules was revised from 0.15-0.20 mg/kg/day to 0.20 mg/kg/day.

Section 2.4: PROGRAF Capsule or Granules Dosage in Pediatric Liver Transplant Patients

"In pediatric liver transplant patients, initiate oral therapy with PROGRAF capsules or granules. For conversion of pediatric patients from PROGRAF (b) (4) granules to capsules or capsules to granules, the total daily (b) (4) dose should remain the same. (b) (4) Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained."

Section 2.9: Preparation of PROGRAF Granules for Oral Suspension

"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."

Section 12.3: Pharmacokinetics -> Specific Populations -> PROGRAF granules

"Two pharmacokinetic (PK) profiles, AUC, Cmax, Tmax and Ctrough, 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 (b) (4) the observed whole-blood trough levels, (b) (4) and/or occurrence of adverse events."

In Table 17, along with the number of patients from each transplant group, inclusion of a group specific age range was recommended to the Applicant. Additional minor revisions were also included.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1. Overview of the Product and Regulatory Background

Tacrolimus capsule and intravenous injection formulations, i.e., PROGRAF capsules and injection, are currently approved for:

- Prophylaxis of organ rejection in patients receiving an allogeneic liver, kidney, or heart transplant
- Use concomitantly with adrenal corticosteroids; in kidney and heart transplant, use in conjunction with azathioprine or mycophenolate mofetil (MMF)

In support of the proposed PROGRAF granule formulation, the Applicant has provided clinical study reports from one pharmacokinetic study (PK) in adult healthy volunteers (Study 95-0-001), and 2 safety and efficacy studies in pediatric liver transplant patients (Study FG-506-01-08 and Study FG-506-01-13).

The Applicant has also provided a study report for a Phase 4 open-label study (Study F506-CL-0403, OPTION) that characterized the pharmacokinetics of tacrolimus following administration of PROGRAF granules after the first oral dose and at steady state in pediatric patients undergoing de novo allograft transplantation (heart, liver and kidney). The Applicant has also submitted findings from a follow-up study to the OPTION study (Study F506-CL-0404A), which evaluated the safety and efficacy in patients enrolled in the OPTION study and who's treatment was converted from the granule formulations to PROGRAF capsules[2].

3.2.General Pharmacology and Pharmacokinetic Characteristics

This submission is a 505(b)(1) NDA for the PROGRAF granules for oral suspension, which is a new formulation of tacrolimus for use in the US. Tacrolimus is a calcineurin inhibitor immunosuppressant approved for the prophylaxis of organ rejection in patients receiving allogeneic heart, kidney, or liver transplants. The summary of pharmacokinetic information for pediatric patients provided by the Applicant is summarized in **Table 2** below. No new information on general pharmacology or pharmacokinetic characteristics was provided in this submission.

Table 2: Summary of Pediatric Pharmacokinetic Information Following Oral Administration of the Granule Formulation for Suspension: Mean (± SD) Pharmacokinetic Parameter Estimates (Source: Adapted from2.7.2 Summary of Clinical Pharmacology Studies: Appendix Table 2.7.2.1)

Study	Study Objective	Study Design Subjects	Treatments		Average Pharmacokinetic Parameter Estimates (SD)					
FG-506-01-08	To assess the safety and efficacy of tacrolimus in children undergoing liver allograft transplantation, to refine the current dosing schedule in children and to compare dosing based on weight with dosing based on body surface area. A PK assessment was undertaken to help to evaluate the dosing regimen for the fine granule formulation.	Open-label, pilot, 2-center study in liver transplant recipients. Initiation with intravenous tacrolimus then tacrolimus fine granules. 28 pediatric patients enrolled and 16 had evaluable PK profiles (aged 0.5 to 11 years) Range: < 1 - 13 < 5: n = 18	Mean dose was 0.045 mg/kg as a continuous 24 h intravenous tacrolimus infusion		C_{max} (ng/mL)	t_{max} (h)	AUC_{inf} (ng·h/mL)	$t_{½}$ (h)	V_d (L/kg)	CL (L/h)
					21.3 (14.8)	23.9 (8.9)	577 (357)	10.4 (5.3)	NC	1.9‡ (1.5)
			0.15 mg/kg orally twice-daily tacrolimus fine granules suspension	First dose	38.3 (40.9)	2.0 (2.0)	413 (295)	11.6 (6.2)		
				SS	19.6 (11.1)	2.8 (2.1)	NC	8.3 (4.2)	NC	NC
F506-CL-0403 (OPTION)	To determine the PK of tacrolimus following oral administration of tacrolimus granules, after the first oral dose and at steady state in pediatric patients 12 years of age or younger undergoing de novo allograft transplantation and to determine safety and efficacy of tacrolimus granules.	Phase 4, multicenter, open-label, single-arm, PK study with tacrolimus granules. 52 pediatric patients enrolled with liver, kidney and heart transplant 38 patients had 2 evaluable PK profiles Range: < 1 - 12 Liver < 5: n = 17 Kidney < 5: n = 10 Heart < 5: n = 9	tacrolimus granules: 0.3 mg/kg/day orally in 2 divided doses		AUC_{tau} (ng·h/mL)		C_{max} (ng/mL)	t_{max} (h)		C_{trough} (ng/mL)
					Day 1					
					179.11 (99.81)		29.35 (17.55)	2.498 (2.691)		10.04 (9.59)
					Week 1					
					189.81 (72.97)		33.14 (14.99)	1.241 (0.866)		8.78 (3.36)

NC: not calculated; PK: pharmacokinetics; SS: steady state. ‡ mL/min/kg

[2] From the follow-up study, the Applicant has provided very limited information related to the dosing and the observed trough concentration data that were collected pre- and post-conversion from the granules formulation to the capsule formulation. Therefore, no further review of the follow-up study was conducted.

3.3.Clinical Pharmacology Review Questions

3.3.1. To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The Clinical Pharmacology information submitted by the Applicant in support of the proposed granule formulation provides supportive evidence of efficacy for the following aspects:

- The relative bioavailability between the capsule and granule formulations
- The granule formulation was evaluated in one Phase 2 pharmacokinetic study as well as one Phase 3 efficacy and safety study

The relative bioavailability between the capsule and granule formulations was evaluated in a single-dose, randomized, open-label, 4-period, 4-sequence, crossover study in healthy subjects, i.e., Study 95-0-001. The selected information on the study conduct and pharmacokinetic findings are summarized in **Table 3** below. The $AUC_{0\text{-}inf}$ values from the treatment arm receiving the granule formulation was 16.4% higher on average compared to the values from the treatment arm receiving PROGRAF capsules and the associated 90% confidence interval ranged from 7 to 26%. The mean Cmax for the granule formulation was approximately 23% higher than that of the capsule formulation. Based on these findings, the Applicant concluded that the differences between the formulations are not clinically significant, and the Clinical Pharmacology review team is in agreement with the Applicant's conclusion. Please refer to **Section 4.1** for additional details from Study 95-0-001.

Table 3: Summary of Bioavailability Information for Tacrolimus Granules and Capsules *(Source*: Adapted from 2.7.1 Summary of Biopharmaceutic Studies and Analytical Methods: Appendix Table 2.7.1.1*)*

Study Reference [Report Number]	Study Objective	Study Design Subjects	Treatments [Lot number]		Mean Tacrolimus Pharmacokinetic Parameters in Whole Blood				
					C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{½}$ (h)	BA/BE (90% CI)
95-0-001 [R96-0007-506-C4B-E]	To determine the bioequivalence of tacrolimus granular and capsule formulations when administered to healthy adult subjects	Single-dose, open-label, 4-period, 4-sequence, randomized, crossover study 32 healthy subjects were enrolled and 30 completed (aged 19 to 50 years)	5 x 1 mg tacrolimus capsules [3007D]	A1	29.2 (8.7)	1.6 (0.7)	267 (90)	30.5 (6.3)	NC
				A2	28.5 (9.1)	1.5 (0.6)	265 (110)	34.1 (9.9)	
			5 x 1 mg tacrolimus granule packets [702153K]	B1	35.7 (11.2)	1.2 (0.5)	334 (174)	33.3 (6.1)	BE†: 116.4% (107.4 to 126.2%) BE††: 122.9% (115.2 to 131.1%)
				B2	35.5 (9.9)	1.3 (0.5)	305 (125)	31.0 (5.8)	

BA: bioavailability; BE: bioequivalence; CI: confidence interval; NC: not calculated. Parameters are presented as mean (SD). † $AUC_{0\text{-}t}$ †† C_{max}

The currently approved tacrolimus therapy is initiated with a starting dose, which is administered in two divided doses every 12 hours. The subsequent daily doses are titrated based on monitoring of whole blood tacrolimus trough concentrations, clinical assessment of rejection, and tolerability. See the response to the next question for additional details on the clinical pharmacology information that was submitted by the Applicant in support of the proposed starting dose for the granule formulation.

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

No, the Applicant proposed starting oral dose for PROGRAF granules for pediatric liver transplant patients is 0.15 - 0.20 mg/kg/day, which is same as the currently approved starting dose for PROGRAF capsules.

- *However, the Clinical Pharmacology review team recommends that the starting dose for tacrolimus granules should be revised to 0.20 mg/kg/day to be administered in two divided doses, every 12 hours.*

To support the granule formulation, the Applicant is relying on two clinical studies, i.e., Study FG-506-01-08 (Phase 2) and Study FG-506-01-13 (Phase 3), for the evidence of effectiveness for the liver transplant indication in pediatric patients, from which Study FG-506-01-13 is the pivotal study. The starting dose of the granule formulation evaluated in Study FG-506-01-13 was approximately 0.3 mg/kg/day and the subsequent doses of study drug were adjusted based on the clinical evidence and whole blood tacrolimus trough concentrations. The following are the protocol specified, or reference, whole blood tacrolimus trough concentration ranges that were used during the study:

- First 2 weeks post-transplant: 10-20 ng/mL
- Weeks 3 and 4 post-transplant: 10-15 ng/mL
- Months 2 and 3 post-transplant: 5-15 ng/mL
- Thereafter: 5-10 ng/mL

The Applicant proposed starting dose for PROGRAF granules is 0.15 – 0.20 mg/kg/day to be administered in two divided doses 12 hours apart, which is lower than the starting dose used in Study FG-506-01-03, i.e., 0.3 mg/kg/day. Therefore, an information request (IR) was sent to the Applicant which requested the rationale for the proposed lower starting dose than the dose that was evaluated in Study FG-506-01-13. The Applicant's rationale primarily focused on the following two aspects:

Aspect 1: Study FG-506-01-13 evaluated the starting dose of approximately 0.3 mg/kg/day using the granules formulation and the observed median tacrolimus trough concentrations were towards the high end of the reference range that was used in the study for at least 50% of patients (P50 ≥ 18.2 ng/mL) and above the upper limit for at least 40% of patients (P60 ≥ 20.8 ng/mL) during the first 2 days post-transplant (Days 0 and 1). However, by Day 2 and Day 3 post-transplant, the median dose was adjusted down to 0.17 and 0.14 mg/kg/day, which resulted in median trough concentrations of 16.8 ng/mL and 14.4 ng/mL on Day 3 and Day 4, respectively.

Aspect 2: The reason for selecting the higher starting dose, i.e., approximately 0.3 mg/kg/day, was that a dual therapy regimen was used in this study and there was a concern of under dosing in the early post-transplant period. Over the time since study had been designed/conducted, treatment paradigms have evolved in management of solid organ transplantation and the current clinical practice utilizes tacrolimus combined with mycophenolate mofetil (MMF) with/without corticosteroids, as dual or triple drug regimen, which is postulated to allow a lower initial dose of tacrolimus without compromising efficacy. Additionally, in the US, the use of antibody induction in conjunction with a tacrolimus-based regimen is more prevalent.

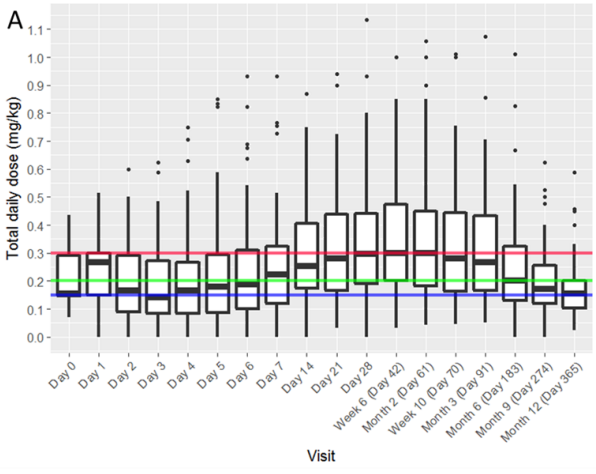
The use of antibody induction provides immunosuppressive coverage in the immediate post-transplant period and is postulated to support a lower initial dose therapy for the first 4 to 5 days of treatment.

Aspect 1 above relates to PK, i.e., the observed whole blood trough concentrations were higher than the protocol specified target range in most patients following the starting dose of 0.3 mg/kg/day. Based on the originally submitted information and the Applicant's response to the abovementioned IR, the Applicant's conclusion appears reasonable that the starting dosing of 0.3 mg/kg/day resulted in the tacrolimus trough concentrations that were near or above 20 ng/mL, which is the highest limit of observed whole blood tacrolimus concentration listed in the currently approved USPI. Therefore, the Applicant's proposal to use a starting dosing of less than 0.3 mg/kg/day appears reasonable. Although the Applicant is proposing the initial dose in the range from 0.15 mg/kg/day to 0.2 mg/kg/day, the median daily doses administered in the first week of treatment in Study FG-506-01-13 and Study FG-506-01-08 were closer to 0.2 mg/kg/day on most days (**Figures 1** and **2**). The total daily dose was below 0.15 mg/kg, i.e., 0.14 mg/kg only on one occasion, i.e., Day 3, in study FG-506-01-13 (**Figure 1B**). If the starting dose for PROGRAF granules is listed as proposed, i.e., 0.15 – 0.20 mg/kg/day, there is a potential for under dosing for most patients if the initial dose is closer to 0.15 mg/kg/day (**Figure 1B**, P50 Days 1 - 7).

- *Therefore, the Clinical Pharmacology review team recommends that the starting dose for tacrolimus granules should be revised to 0.20 mg/kg/day in the USPI.*

Figure 1: Box Plots (A) and Summary Table (B) for the Total Daily Oral Dose of Tacrolimus Over Time in Study FG-506-01-13

A



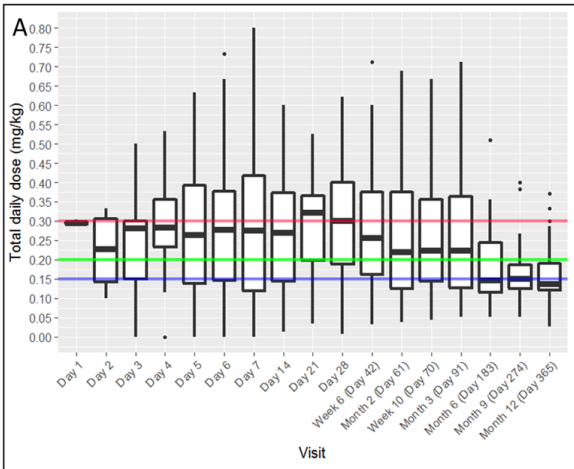
Red line represents the starting oral dose (0.3 mg/kg/day) used in the clinical trial. Blue and green lines represent the lower limit (0.15 mg/kg/day) and upper limit (0.2 mg/kg/day) of the proposed starting oral dose. Green line represents the FDA proposed (0.2 mg/kg/day) starting oral dose.

B

	Total daily dose (mg/kg)							
Percentile	LL	UL	P10	P25	***P50***	P75	P90	N
Visit								
Day 0	0.07	0.44	0.13	0.15	***0.15***	0.29	0.32	82
Day 1	0	0.51	0.12	0.15	***0.27***	0.3	0.33	91
Day 2	0	0.6	0	0.09	***0.17***	0.29	0.34	91
Day 3	0	0.62	0	0.08	***0.14***	0.27	0.35	90
Day 4	0	0.75	0	0.08	***0.17***	0.27	0.4	90
Day 5	0	0.85	0	0.09	***0.18***	0.29	0.46	90
Day 6	0	0.93	0.04	0.1	***0.19***	0.31	0.47	89
Day 7	0	0.93	0.05	0.12	***0.22***	0.32	0.48	89
Day 14	0	0.87	0.09	0.17	***0.25***	0.41	0.58	88
Day 21	0.03	0.94	0.12	0.17	***0.28***	0.44	0.59	84
Day 28	0	1.13	0.12	0.19	***0.3***	0.44	0.59	81
Week 6 (Day 42)	0.03	1	0.12	0.2	***0.3***	0.47	0.59	79
Month 2 (Day 61)	0.04	1.06	0.12	0.18	***0.3***	0.45	0.55	78
Week 10 (Day 70)	0.05	1.01	0.13	0.16	***0.28***	0.44	0.56	77
Month 3 (Day 91)	0.05	1.07	0.12	0.17	***0.27***	0.43	0.56	77
Month 6 (Day 183)	0	1.01	0.07	0.13	***0.2***	0.32	0.48	71
Month 9 (Day 274)	0	0.62	0.05	0.12	***0.17***	0.26	0.31	68
Month 12 (Day 365)	0.02	0.59	0.07	0.1	***0.16***	0.2	0.3	58

Figure 2: Box Plots (A) and Summary Table (B) for the Total Daily Oral Dose of Tacrolimus Over Time in Study FG-506-01-08

A



Red line represents the starting oral dose (0.3 mg/kg/day) used in the clinical trial. Blue and green lines represent the lower limit (0.15 mg/kg/day) and upper limit (0.2 mg/kg/day) of the proposed starting oral dose. Green line represents the FDA proposed (0.2 mg/kg/day) starting oral dose.

B

	Total daily dose (mg/kg)							
Percentile	LL	UL	P10	P25	***P50***	P75	P90	N
Visit								
Day 1	0.29	0.3	0.29	0.29	***0.29***	0.3	0.3	3
Day 2	0.1	0.33	0.12	0.14	***0.23***	0.31	0.32	21
Day 3	0	0.5	0.12	0.15	***0.28***	0.3	0.34	25
Day 4	0	0.53	0.12	0.23	***0.28***	0.36	0.43	25
Day 5	0	0.63	0.05	0.14	***0.26***	0.39	0.51	26
Day 6	0	0.73	0.05	0.15	***0.28***	0.38	0.52	26
Day 7	0	0.8	0.06	0.12	***0.28***	0.42	0.53	26
Day 14	0.01	0.6	0.07	0.14	***0.27***	0.37	0.53	26
Day 21	0.03	0.52	0.09	0.2	***0.32***	0.37	0.48	26
Day 28	0.01	0.62	0.11	0.19	***0.3***	0.4	0.53	25
Week 6 (Day 42)	0.03	0.71	0.12	0.16	***0.26***	0.38	0.55	24
Month 2 (Day 61)	0.04	0.69	0.08	0.12	***0.22***	0.38	0.49	24
Week 10 (Day 70)	0.04	0.67	0.11	0.14	***0.22***	0.36	0.42	23
Month 3 (Day 91)	0.05	0.71	0.11	0.13	***0.22***	0.36	0.41	23
Month 6 (Day 183)	0.05	0.51	0.1	0.11	***0.15***	0.24	0.35	22
Month 9 (Day 274)	0.05	0.4	0.1	0.12	***0.15***	0.19	0.27	22
Month 12 (Day 365)	0.03	0.37	0.1	0.12	***0.14***	0.19	0.3	21

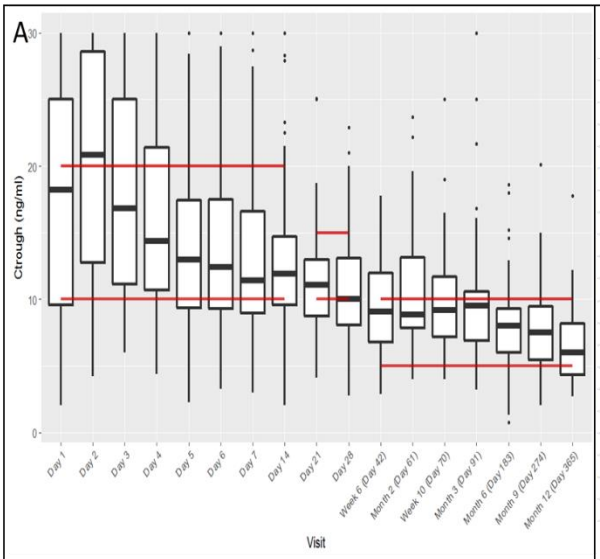
Regarding Aspect 2 listed above, it relates to the current clinical practice aspects, and was deferred to the Clinical Review team; thus, please see the Medical Officer's review (Dr. Ergun Velidedeoglu) for additional details.

Regarding the whole blood trough concentration ranges of tacrolimus listed in the current USPI, the Applicant is not proposing any revisions, which is acceptable from a Clinical Pharmacology perspective.

The whole blood trough concentrations of tacrolimus that were observed from Study FG-506-01-13 and Study FG-506-01-08 are presented in **Figures 3** & **4**, respectively. The 10th percentile of the observed

Figure 3: Box Plots (A) and Summary Table (B) for the Observed Trough Concentrations of Tacrolimus in Study FG-506-01-13

A



Red lines represent the protocol specified whole blood concentration range used to inform dose adjustments.

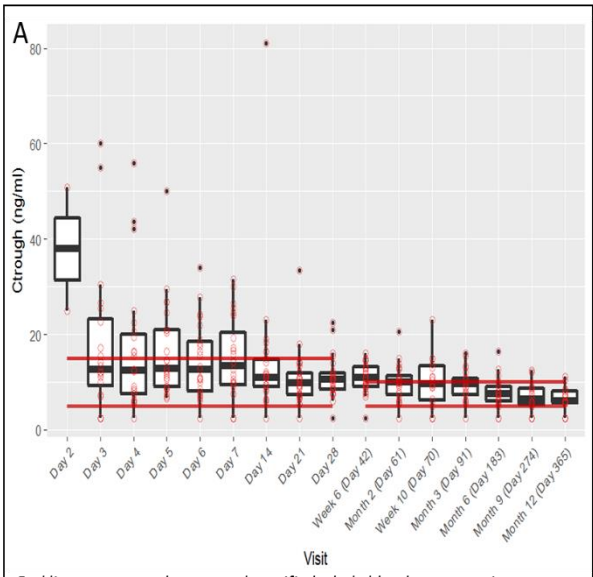
B

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

whole blood trough concentrations on Day 7 and Day 365 were 6.54 ng/mL and 3.5 ng/mL, respectively, in Study FG-506-01-13 and 4 ng/mL and 2.5 ng/mL, respectively, in Study FG-506-01-08. The 90th percentile on Day 7 and Day 365 were 22.21 ng/mL and 10 ng/mL, respectively, in Study FG-506-01-13 and 26.2 ng/mL and 9.26 ng/mL, respectively, in Study FG-506-01-08. The range of these observed trough concentartions were generally within the protcol specified targets.

Figure 4: Box Plots (A) and Summary Table (B) for the Observed Trough Concentrations of Tacrolimus in Study FG-506-01-08

A



Red lines represent the protocol specified whole blood concentration range used to inform dose adjustments.

B

	Trough Con. (mg/mL)									
Percentile	LL	UL	P10	P25	***P50***	P75	P90	N	TargetTc_LL	TargetTc_UL
Visit										
Day 2	25	50.8	27.58	31.45	***37.9***	44.35	48.22	2	5	15
Day 3	2.5	60	2.5	9.35	***12.8***	23.33	32.95	20	5	15
Day 4	2.5	56	5.94	7.5	***12.5***	20	38.68	23	5	15
Day 5	6.7	50	7.8	9.07	***12.8***	21	26.87	24	5	15
Day 6	2.5	34	6.72	8.2	***12.7***	18.45	24.04	23	5	15
Day 7	2.5	31.5	4	9.52	***13.4***	20.38	26.2	24	5	15
Day 14	2.5	81	6.35	9.12	***11.1***	14.78	18.65	26	5	15
Day 21	2.5	33.5	6	7.32	***9.75***	11.97	14.2	26	5	15
Day 28	2.5	22.5	7.36	8.5	***10.5***	11.98	15.85	24	5	15
Week 6 (Day 42)	2.5	16	7.65	9.15	***11***	13.2	14.5	24	5	10
Month 2 (Day 61)	2.5	20.5	5.66	7.45	***9.95***	11.4	13.56	24	5	10
Week 10 (Day 70)	2.5	23	2.5	6.2	***9.7***	13.35	15	19	5	10
Month 3 (Day 91)	2.5	16	5.8	7.4	***9.6***	10.8	13.5	21	5	10
Month 6 (Day 183)	2.5	16.5	5	6	***7.5***	9	11.4	21	5	10
Month 9 (Day 274)	2.5	12.5	2.5	5.22	***6.35***	8.72	10.5	16	5	10
Month 12 (Day 365)	2.5	11.2	2.5	5.6	***6.1***	8.2	9.26	17	5	10

3.3.3. Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

This submission does not contain any new information that can further inform alternative dosing regimen and/or management strategy for subpopulations based on intrinsic factors.

3.3.4. Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The presence and composition of food is known to decrease the bioavailability of tacrolimus from PROGRAF capsules. Therefore, PROGRAF capsules are recommended to be taken consistently every day either with or without food. The Applicant has not conducted any food-drug interaction pharmacokinetic study with PROGRAF granules. However, a dedicated food-drug interaction pharmacokinetic study is not needed given the following:

1. The Labeling recommendation, "Prograf Granules should be taken consistently every day either with or without food", will be included.
2. Tacrolimus dosing is individualized using whole blood trough concentration monitoring.

4. APPENDICES[3]

4.1. Study 95-0-001

Title:

Bioequivalence Study of Tacrolimus Granular and Capsule Formulations in Healthy Volunteers

Trial Information:

Study center:	**Bio-analytical Laboratory**
Harris Laboratories, Inc. Clinical Research Lincoln, NE 68502 Study dates: ~ June 1995 – July 1995	(b) (4)

Primary Objective:

To determine the bioequivalence of the tacrolimus granular formulation relative to the capsule formulation in healthy volunteers. The absolute bioavailability of each oral formulation was also determined.

Study Design:

This was a single-dose, randomized, open-label, 4-period, 4-sequence, crossover study. The study evaluated the bioavailability of tacrolimus granule formulation that was administered on two different occasions (Treatments B1 and B2) relative to capsule formulation that was administered on two different occasions (Treatments A1 and A2), when administered as single 5 mg oral doses. Comparison of Treatment A1 to Treatment A2 and Treatment B1 to Treatment B2 evaluated intrasubject/intraoccasion variability and the crossover design was used to account for the variance. Each period consisted the administration of single tacrolimus dose followed by a six-day washout. At least two weeks after the conclusion of four-period crossover, a single tacrolimus intravenous infusion (Treatment C) was administered to a subset of subjects in a randomized fifth period.

[3] For the purpose of this review, PROGRAF granules is also referred as Modigraf Granules, tacrolimus granules, tacrolimus granules for oral suspension, or the tacrolimus granule formulation. Tacrolimus is also referred as FK506.

Treatments and Test Preparations:

Treatment Arms	Treatment	Description
A1, A2	A single oral dose of five tacrolimus 1 mg capsules followed by 100 mL of room temperature water.	Tacrolimus 1 mg capsule Prograf® Fujisawa Ireland, LTD for Fujisawa USA Lot No. 3007D Expiration date: February 29, 1996
B1, B2	A single oral dose of five tacrolimus 1 mg granules mixed into 50 mL room temperature water followed by one 50 mL rinse of container with water.	FK 506 Granules 1 mg (1 mg FK506/500 mg granules) Fujisawa Pharmaceutical Co. LTD (Japan) for Fujisawa USA Lot No. 702153K Expiration date: April 30, 1996
C	A single intravenous infusion of FK 506 0.005 mg/mL in dextrose 5% solution at a dose of 0.025 mg/kg over a four-hour period.	FK 506 5 mg, 1 mL ampules for injection (5 mg/mL) Fujisawa Ireland, LTD for Fujisawa USA Lot No. A Y3007 A Expiration date: January 31, 1996

Demographic Information:

Thirty-two subjects (18 males, 14 females) were enrolled and 30 subjects completed all treatment periods. The selected demographic information of enrolled subjects is summarized in **Table 1**.

Table 1: Demographic Information Summary

Parameter	Value
Average Age (±SD)	30 (±9) Years
Average Height (±SD)	174 (±7) cm
Average Weight (±SD)	75 (±12) kg

Sample Collection and Bioanalysis:

For pharmacokinetic assessments, 18 blood samples were collected at pre-dose through 72 hours post-dose following administering oral doses and 20 blood samples were collected at pre-dose through 116 hours post-dose following administering IV doses. Samples were frozen and stored at -20°C until assayed. Review summary of the bio-analytical validation and performance reports is provided in **Table 2.**

Table 2: Review Summary of the Bio-Analytical Method

Validation Report	Validation report provided	☒ Yes ☐ No
	Validation report acceptable	☒ Yes ☐ No
Performance Report	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	N/A
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Overall performance acceptable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected?	☐ Yes ☒ No

Pharmacokinetic Measures

Reported estimates: C_{max}, T_{max}, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, and $t_{1/2}$

Pharmacokinetic Results:

The observed mean whole blood tacrolimus concentrations-time profiles from all treatment groups are presented in **Figure 1.** The mean (±SD) pharmacokinetic parameter estimates for the subjects receiving oral tacrolimus formulations are summarized in **Table 3**. The summary of mean absolute bioavailability values for the capsule and granule formulations can be found in **Table 4** and the relative bioavailability related information is summarized in **Table 5**.

Figure 1: Whole Blood Tacrolimus Concentrations-Time Profiles Following Oral Administration of the Capsule and Granule formulations: Mean (± SD) Concentrations on Linear and Mean Concentrations on Semi-Logarithmic Scales *(Source: Tacrolimus Protocol 95-0-001, Figure 1 and 2)*

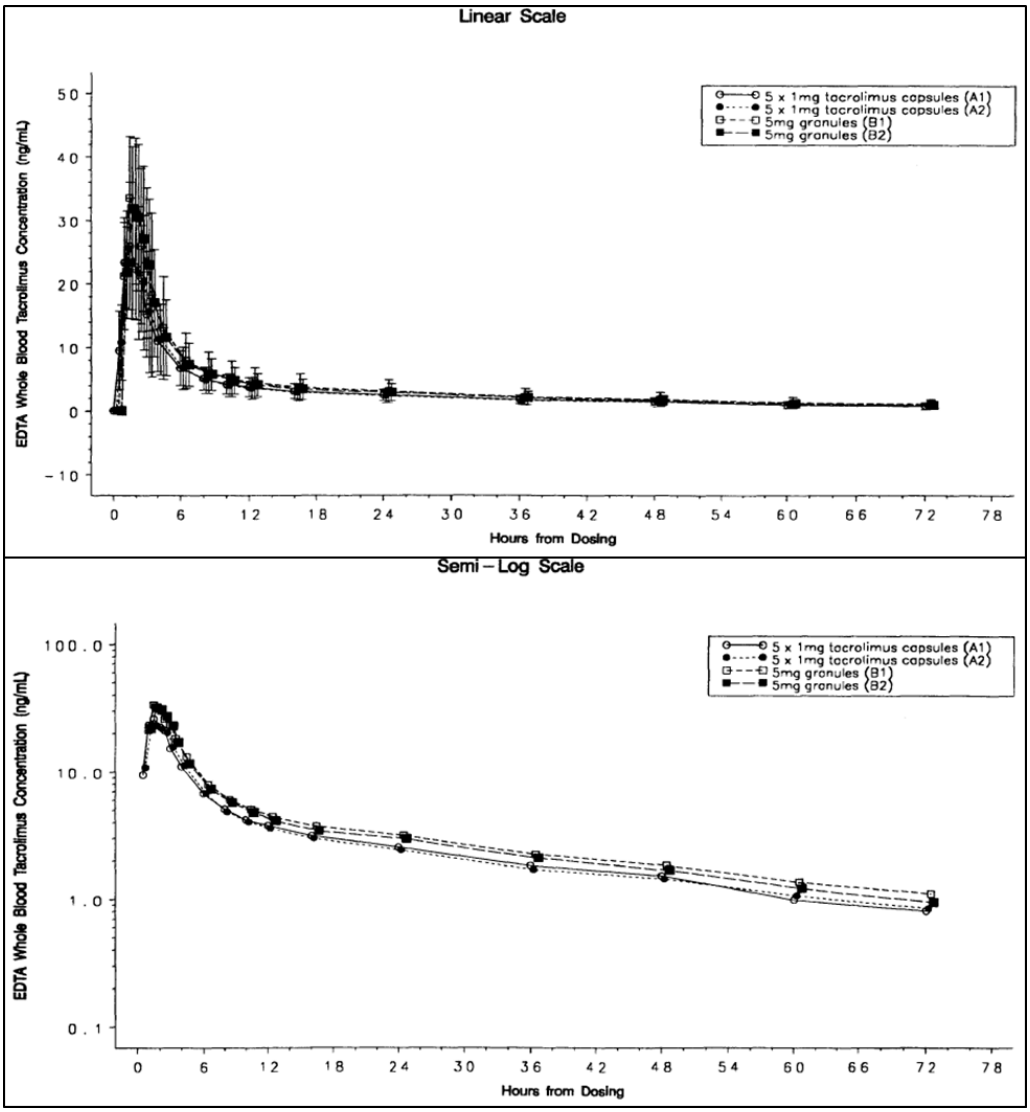


Table 3: Mean (± SD) Pharmacokinetic Parameter Estimates Following Oral Administration of the Capsule and Granule formulations *(Source: Tacrolimus Protocol 95-0-001, Table on Page 3)*

Parameter	A1	A2	B1	B2
Cmax(ng/mL)	29.1±8.7	28.5±9.1	35.7±11.2	35.5±9.9
Tmax(hr)	1.6±0.7	1.5±0.6	1.2±0.5	1.3±0.5
AUC(0-t) ng•hr/mL	224±73	218±90	279±142	261±104
AUC(0-inf) ng•hr/mL	267±90	265±110	334±174	305±125
$t_{1/2}$(hr)	30.5±6.3	34.1±9.9	33.3±6.1	31.0±5.8

Treatments A1, A2 = 5 x 1 mg tacrolimus capsules
Treatments B1, B2 = 1 x 5 mg tacrolimus granules

Table 4: Summary of Absolute Bioavailability of The Oral Tacrolimus Formulations *(Source: Adapted from Tacrolimus Protocol 95-0-001, Table 79)*

Treatment	F*	F**
A1	16.8%	18.4%
A2	15.1%	17.2%
B1	20.4%	23.2%
B2	22.5%	24.5%

A1: 5 x 1mg tacrolimus capsules (A1)
A2: 5 x 1mg tacrolimus capsules (A2)
B1: 5mg granules (B1)
B2: 5mg granules (B2)

Percentages are comparing parameter for oral dosage form versus intravenous dosage form.

* Bioavailability calculated using AUC(0-t) values.
**Bioavailability calculated using AUC(0-inf) values.

Table 5: Summary of Relative Bioavailability of The Oral Tacrolimus Formulations *(Source: Tacrolimus Protocol 95-0-001, Table 24)*

	Treatment Means					Confidence Intervals		
Parameter	X	W	Pct Difference	PR>|T|	Power (%)	(90% Confidence)	(95% Confidence)	Mean Ratio
Cmax	35.586	28.772	23.68	0.0001*	99.66	116.7 - 130.7	115.3 - 132.0	.
Tmax	1.258	1.517	-17.03	0.0098*	86.57	72.2 - 93.7	70.1 - 95.8	.
AUC(0-t)	269.632	220.668	22.19	0.0006*	89.12	111.9 - 132.5	109.9 - 134.5	.
AUC(0-inf)	319.551	265.846	20.20	0.0015*	89.50	110.0 - 130.4	108.0 - 132.4	.
Kel	0.022	0.023	-1.58	0.6392	99.99	92.8 - 104.0	91.8 - 105.1	.
T 1/2el	32.138	32.280	-0.44	0.9072	99.93	93.3 - 105.8	92.1 - 107.0	.
LN(Cmax)	3.519	3.313	6.23	0.0001*	99.89	115.2 - 131.1	113.8 - 132.8	122.9
LN[AUC(0-t)]	5.486	5.324	3.04	0.0017*	97.62	108.2 - 127.8	106.4 - 129.9	117.6
LN[AUC(0-inf)]	5.664	5.512	2.76	0.0023*	98.27	107.4 - 126.2	105.7 - 128.2	116.4

Treatment X = 5mg granules (B1 & B2): test
Treatment W = 5 x 1mg tacrolimus capsules (A1 & A2): reference

Values for Treatments X and W are the least-square means (LSMEANS) from the ANOVA

Pct Difference = difference between treatments (X - W) expressed as a percentage of Treatment W

PR>|T| = ANOVA test for significant differences between treatments
(* difference is statistically significant; p<0.05)

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*exp(test-reference) for log-transformed parameters

Applicant's Conclusions:

- The observed differences in the tacrolimus bioavailability from the granule formulation and the capsule formulation may not be clinically significant.
- Comparison of the bioavailability data following IV administration showed that the capsule formulations were, on average, 17-18% bioavailable and the granules formulations were, on average, 23-25% bioavailable.

Reviewer's Assessment:

- *The mean relative BA estimates for the granule formulation was approximately 16% higher when compared to the capsule formulation, based on $AUC_{(0\text{-}inf)}$.*
- *The mean C_{max} for the granule formulation was approximately 23% higher than that of the capsule formulation.*
- *The Applicant's conclusion that the 16% higher relative BA, based on $AUC_{(0\text{-}inf)}$, for the granule formulation is not clinically relevant is acceptable.*

4.2. Study FG-506-01-08

The Applicant has submitted a separate pharmacokinetic (PK) report for the PK assessments that were performed as a part of Study FG-506-01-08. Study FG-506-01-08 evaluated safety and efficacy of tacrolimus granules in children undergoing liver allograft transplantation. PK assessments were performed in this study to help evaluate the dosing regimen for the tacrolimus granule formulation.

Title:

An open label, two center clinical pilot study in children with tacrolimus granule formulation as immunosuppressive therapy in liver allograft transplantation

Trial Information:

Study center:	**Bio-analytical Laboratory**
This 2-center study was conducted at 2 contracted sites, 1 site each in France and Belgium. Study dates: March 1996 – April 1998 Specific information on the timeline for PK sampling was not identified.	(b) (4)

Primary Objective:

To obtain information on the pharmacokinetics of tacrolimus administered as a granule formulation in pediatric liver transplant patients.

Study Design:

This was a 3-month study that was followed by a 9-month extension phase. During the study, blood samples were collected for pharmacokinetic evaluations from the following three periods:

Period 1: During intravenous dosing

Period 2: After the first oral dose

Period 3: On the last day of hospitalization during oral steady state dosing.

Treatment:

The intravenous infusion of tacrolimus was initiated within 6 hours of transplantation at a mean infusion rate of 0.0025 mg/kg/h, for at least 12 hours but no longer than 2-4 days. Thereafter, the first oral dose of 0.3 mg/kg/day was administered as two equally divided doses using the granule formulation. Subsequent oral doses were adjusted based on clinical evidence of efficacy, occurrence of adverse events, and to maintain tacrolimus trough whole blood concentrations in the range 5 - 15 ng/mL for the first month post-transplantation and 5 – 10 ng/mL thereafter. The maximum dose allowed was 0.5 mg/kg/day.

Demographic Information:

Twenty eight patients were enrolled and 16 (9 males, 7 females) were deemed evaluable patients at the end of the study. The selected demographic information is summarized in **Table 1**.

Table 1: Demographic Information Summary

Parameter	Value
Average Age (±SD)	3.2 (±3.2) Years
Average Height (±SD)	NA
Average Weight (±SD)	13 (±7) kg

Sample Collection and Bioanalysis:

For pharmacokinetic assessments, blood samples were collected over three different periods: during and following the intravenous infusion, following first oral dose, and at steady state dosing. During the intravenous infusion period, five blood samples were collected over the period of 24 hours after start of infusion and then every 24 hours thereafter that when the patient remained on intravenous infusion. After the stop of infusion, during the wash-out phase, additional four samples were collected. Following to the first oral dose of tacrolimus, eight samples were collected over the period of 12 hours after oral administration. During steady state dosing, eight samples were collected over the period of 12 hours immediately after oral administration.

The concentration of tacrolimus and three of its known metabolites (M-I [13-O-demethylated tacrolimus], M-II [31-O-demethylated tacrolimus] and M-III [15-O-demethylatedtacrolimus]) in whole blood samples were determined using a validated HPLC-MS/MS method.

Review summary of the bio-analytical validation and performance reports is provided in **Table 2.**

Table 2: Review Summary of the Bio-Analytical Method

Validation Report	Validation report provided	☒ Yes ☐ No
	Validation report acceptable	☒ Yes ☐ No
Performance Report	Samples analyzed within the established stability period[4]	☒ Yes ☐ No
	Quality control samples range acceptable	☒ Yes ☐ No
	Sample chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Overall performance acceptable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected?	☐ Yes ☒ No

Pharmacokinetic Measures

Pharmacokinetic parameters were estimated using non-compartmental analysis and the reported parameters included: C_{max}, T_{max}, $AUC_{(0\text{-}12)}$, $AUC_{(0\text{-}inf)}$, and $t_{1/2}$. $AUC_{(0\text{-}inf)}$ was determined as $AUC_{(0\text{-}t)} + C_T/\lambda_z$ (Period 1) and as $AUC_{(0\text{-}tau)} + C_{12}//\lambda_z$ (Period 2), where C_T is the last measurable concentration-time point, C_{12} is the 12 hour concentration and λ_z is the calculated elimination rate constant.

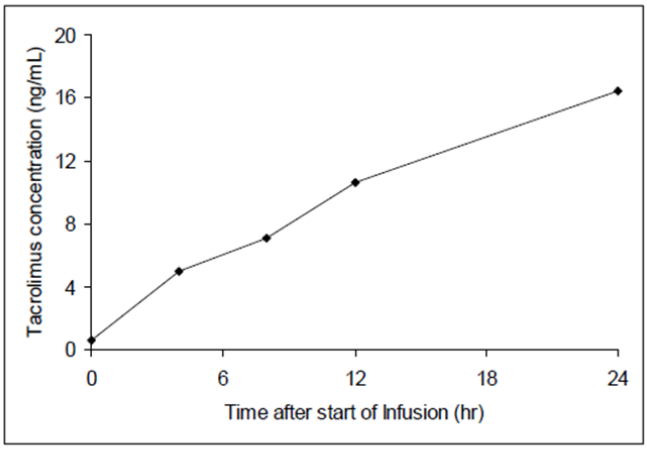
Pharmacokinetic Results:

The mean whole blood concentrations-time profiles for tacrolimus and M-I from all three treatment periods are presented in **Figure 1.** The M-II and M-III concentrations were reported below the limit of quantification for all samples. The pharmacokinetic parameter estimates from Period 2 and Period 3 are summarized in **Table 3** below. The mean (± s.d.) absolute bioavailability after first oral dose was calculated to be 23 % (± 21 %) with a range of 4 to 80 % (n=12). For three patients, $t_{1/2}$ was not calculable for one of the profiles. A correlation analysis was performed between minimum concentration (the value 12 hours after oral dosing) and $AUC_{(0\text{-}tau)}$ using the data from both oral profiles and the correlation coefficient estimates was found to be 0.881 (**Figure 2**).

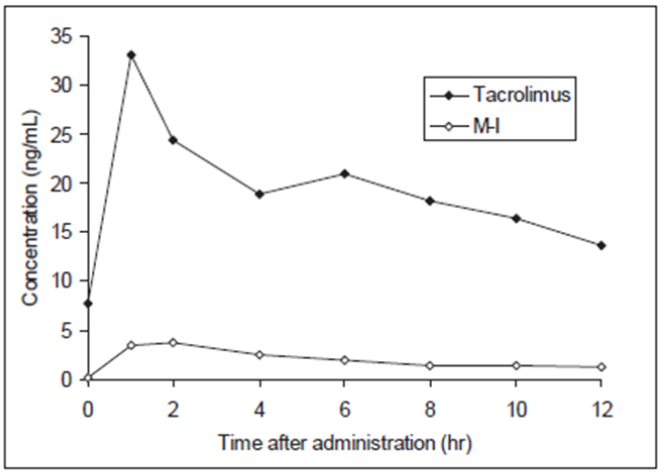
[4] Specific information on the timeline for PK sampling was not identified. However, based on the extrapolation of stability related information from the report of [redacted] (b) (4) and the treatment starting date, it appears that the pharmacokinetic samples were analyzed within the indicated stability for 775 days at -20°C.

Figure 1: Mean Whole Blood Concentration-Time Profiles: Tacrolimus and M-I *(Source: Adapted from FG-506-01-08-R-PK-1, Figure 2 and 3)*

Period 1 (Following IV dosing)



Period 2 (FIRST ORAL DOSE)



Period 3 (STEADY STATE)

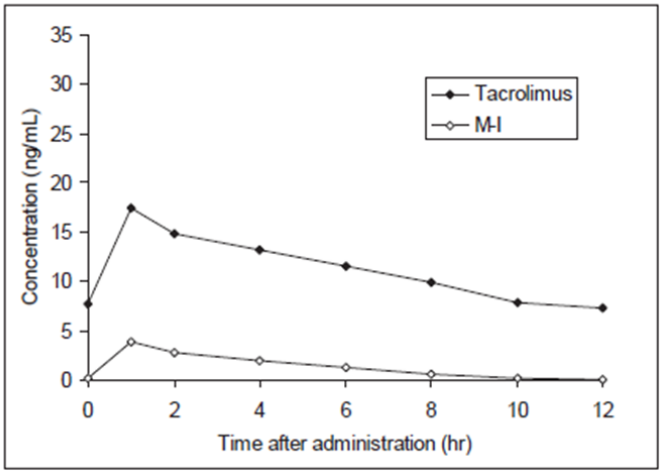
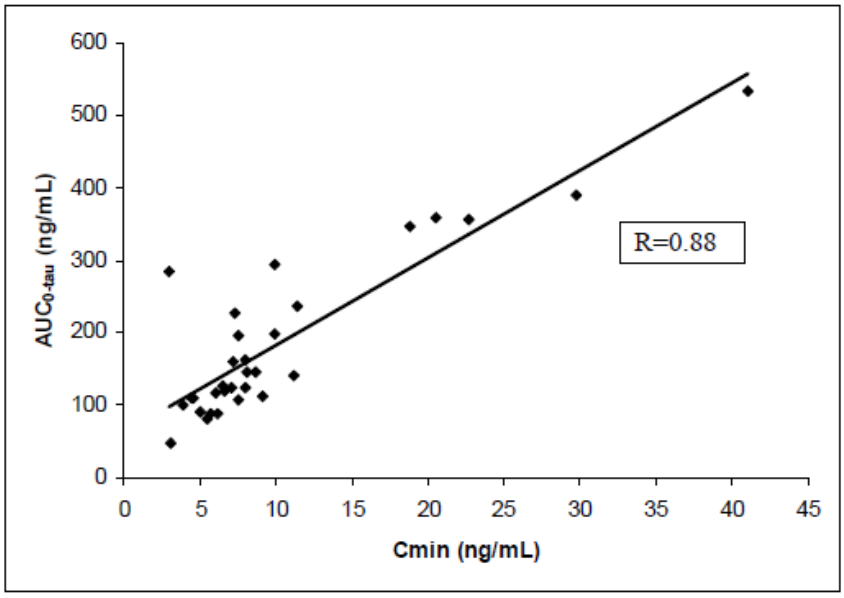


Table 3: Pharmacokinetic Parameters Estimates Following Administration of the Tacrolimus Granule Formulation *(Source: Adapted from FG-506-01-08-R-PK-1, Table 3)*

	$t_{1/2}$	t_{max}	C_{max}	AUC_{0-12}	AUC_{0-inf}
	hr	hr	ng/mL	ng/hr/mL	ng/hr/mL
Period 2 (First Oral Dose)					
n	14	16	16	16	14
Mean	11.58	1.95	38.34	232.36	413.01
s.d.	6.16	2.00	40.87	139.18	295.08
Min	5.64	0.00	6.84	54.37	89.13
Median	9.70	1.10	32.45	217.90	342.28
Maximum	29.48	8.62	180.20	532.15	1166.15
Period 3 (At Steady State)					
n	15	16	16	15	NC
Mean	8.34	2.79	19.62	134.61	
s.d.	4.22	2.07	11.08	37.60	
Min	3.82	0.00	8.97	88.94	
Median	7.01	2.09	15.58	124.90	
Maximum	18.01	6.08	47.80	227.99	

NC Not calculated

Figure 2: Correlation between the Observed Minimum Concentrations and AUC Values of Tacrolimus Following Administration of The Tacrolimus Granule Formulation *(Source: Adapted from FG-506-01-08-R-PK-1, Figure 4)*



Sponsor's Conclusions:

- The mean (± s.d.) concentration over the 24 hours after start of infusion was 16.46 (± 14.84) ng/mL and clearance was calculated to be 1.89 (± 1.49) mL/min/kg.

- Following first oral dose, the mean C_{max} (± s.d.) was 38.34 (± 40.87) ng/mL. The Mean AUC_{0-12} (± s.d.) estimate was 231.17 ng*h/mL and mean AUC_{0-inf} (± s.d.) estimate was 411.99 (± 295.38) ng*h/mL.
- The median time to maximum concentration was 1.1 hours.
- At steady state, the mean C_{max} was 19.62 (± 11.08) ng/mL, which was decreased compared to that observed in Period 2, as was the mean AUC_{0-12} of 134.61 (± 37.60) ng*h/mL. The time to maximum concentration was extended as compared to Period 2 with a median value of 2.1 hours.
- The mean absolute bioavailability of 23 % observed for the granule formulation in this study, which is similar to that observed with PROGRAF capsules in adult liver transplant patients (22%) (Lee 1993) and slightly higher than that in pediatric renal transplant patients (19%) (Webb 2002).

Reviewer's Assessment:

Based on the provided findings, the Sponsor's conclusions are reasonable.

4.3. Study FG-506-01-13

This was a Phase 3 study that investigated the efficacy and safety of tacrolimus granules in comparison to a cyclosporin-microemulsion (ME) based standard regimen in children receiving a primary liver transplant. The study did not perform any formal pharmacokinetic assessments; therefore, the detailed review of this study was not performed from a Clinical Pharmacology perspective. However, the information on the median daily doses administered and the observed whole blood trough concentrations are summarized in **Section 3.3.2** above.

4.4.Study FG-506-01-403

Title:

A Multicenter, Open-label, Pharmacokinetic Study of Modigraf® (Tacrolimus Granules) in *de Novo* Pediatric Allograft Recipients

Trial Information:

Study center:	**Bio-analytical Laboratory**
This multicenter study was conducted at 10 contracted sites in a total of 6 countries including UK (1 site), Spain (3 sites), Germany (2 sites), Belgium (1 site), Poland (1 site) and France (2 sites). Study dates: June 2011 – February 2015	(b) (4)

Primary Objective:

- To determine the pharmacokinetics of tacrolimus following oral administration of Modigraf, after the first oral dose and at steady state in pediatric patients undergoing de novo allograft transplantation.
- To determine safety and efficacy of Modigraf.

Study Design:

This was a multicenter, open-label, single arm study conducted in pediatric patients undergoing liver, kidney, or heart transplantation. Patients were treated with a tacrolimus granule (Modigraf) based immunosuppressive regimen. During the study, for pharmacokinetic evaluations whole blood samples were collected from the following two periods:

Period 1: First dose of tacrolimus after reperfusion

Period 2: Day 7 (+ 7 days) after a minimum of 4 days without a dose change (due to the higher clearance in very young children this may have been possible after 3 days).

Treatment:

Patients were treated with the tacrolimus granule formulation (Modigraf) based immunosuppressive regimen and the initial daily dose was 0.3 mg/kg per day orally given in 2 doses (equals 0.15 mg/kg twice daily) postoperatively. The first dose of 0.15 mg/kg of tacrolimus was to be administered within 24 h after reperfusion. Subsequent oral tacrolimus doses were adjusted based on clinical evidence of efficacy and occurrence of adverse events (AEs), and to maintain tacrolimus trough whole blood concentrations in the range of 5 to 20 ng/mL.

Demographic Information:

Fifty-three patients were screened and 52 patients were transplanted and received treatment. Out of 52 treated patients, 46 (88.5%) patients completed the study (17 [100.0%] patients in the heart transplant group, 17 [85.0%] patients in the liver transplant group and 12 [80.0%] in the kidney transplant group).

Regarding the pharmacokinetic dataset, 38 (73.1%) patients were included in the pharmacokinetic dataset (PKAS) (12 [70.6%] patients in the heart transplant group, 14 [70.0%] patients in the liver transplant group, and 12 [80.0%] patients in the kidney transplant group). Overall, 25 (69.4%) patients under 5 years of age and 13 (81.3%) patients 5 years of age or older were included in the PKAS. The selected demographic information from the patients in PKAS is summarized in **Table 1**.

Table 1: Reported Demographic Information for the Patients in PKAS Dataset (Source: From Study: F506-CL-0403, Table 7)

Parameter Category/Statistics	Heart Transplant (n = 12)	Liver Transplant (n = 14)	Kidney Transplant (n = 12)	Total (n = 38)
Sex, n (%) (Recipient)				
Male	10 (83.3%)	9 (64.3%)	10 (83.3%)	29 (76.3%)
Female	2 (16.7%)	5 (37.5%)	2 (16.7%)	9 (23.7%)
Sex, n (%) (Donor)				
Male	5 (41.7%)	7 (50.0%)	9 (75.0%)	21 (55.3%)
Female	6 (50.0%)	7 (50.0%)	3 (25.0%)	16 (42.1%)
Missing	1 (8.3%)	0	0	1 (2.6%)
Race, n (%) (Recipient)				
White	12 (100.0%)	12 (85.7%)	11 (91.7%)	35 (92.1%)
Black or African American	0	0	0	0
Asian	0	0	1 (8.3%)	1 (2.6%)
Other	0	2 (14.3%)	0	2 (5.3%)
Recipient Age (Years)				
n	12	14	12	38
Mean (SD)	6.2 (4.4)	2.5 (3.2)	5.6 (3.3)	4.6 (3.9)
Recipient Age Subgroup (Years)				
< 5 Years	5 (41.7%)	12 (85.7%)	8 (66.7%)	25 (65.8%)
≥ 5 Years	7 (58.3%)	2 (14.3%)	4 (33.3%)	13 (34.2%)
Recipient Age Subgroup 2				
0 ≤ Days≤ 27 Days(Newborn)	0	0	0	0
≥ 28 Days to ≤ 23 Months (Infants and Toddlers)	3 (25.0%)	9 (64.3%)	0	12 (31.6%)
≥ 2 Years to ≤ 11 Years (Children)	8 (66.7%)	5 (35.7%)	12 (100.0%)	25 (65.8%)
≥ 12 Years to ≤ 17 Years (Adolescents)	1 (8.3%)	0	0	1 (2.6%)
Donor Age (Years)				
n	8	3	2	13
Mean (SD)	7.9 (4.6)	34.7 (5.9)	23.5 (27.6)	16.5 (14.9)
Recipient Weight (kg)				
n	12	14	12	38
Mean (SD)	18.87 (9.41)	11.54 (7.29)	16.73 (5.76)	15.49 (8.06)
Recipient Height (cm)				
n	12	13	12	37
Mean (SD)	107.58 (28.54)	81.71 (21.02)	99.72 (15.07)	95.94 (24.26)

Sample Collection and Bioanalysis:

For pharmacokinetic assessments, blood samples were collected over two different periods: On Day 1 following the first dose of Modigraf and on Day 7. For both the periods, seven blood samples were over the period of 12 hours post-dose. The concentration of tacrolimus in whole blood samples were determined using a validated HPLC-MS/MS method. Review summary of the information from the submitted bio-analytical validation and performance reports is provided in **Table 2.**

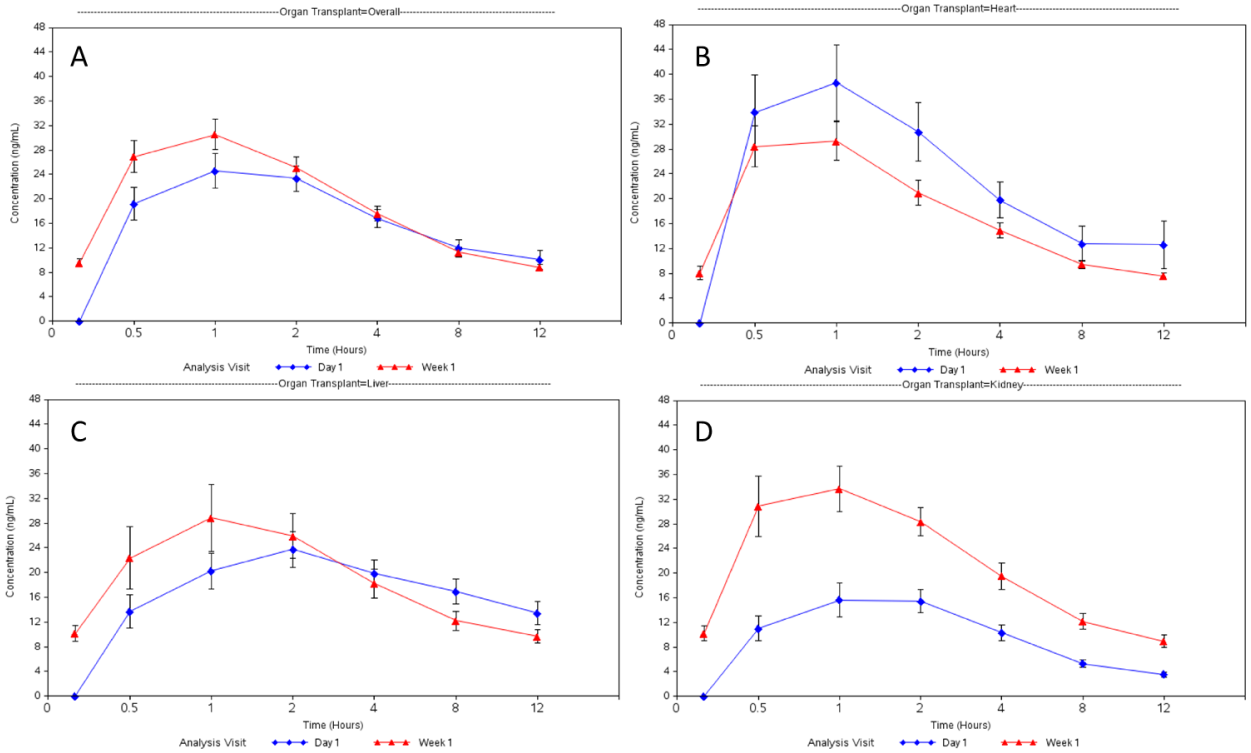
Table 2: Review Summary of the Bio-Analytical Method

Validation Report	Validation report provided	☒ Yes ☐ No
	Validation report acceptable	☒ Yes ☐ No
Performance Report	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control samples range acceptable	☒ Yes ☐ No
	Sample chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Overall performance acceptable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected? Inspection findings: As per the memorandum from the Office of Study Integrity and Surveillance (OSIS) dated 03/26/2018, an inspection of study F506-CL-0403 (b) (4) was conducted and no objectionable conditions were observed. In addition, the memorandum document recommends that the data from studies F506-CL-0403 be accepted for further Agency's review.	☒ Yes ☐ No

Pharmacokinetic Results:

From the PKAS dataset, the mean whole blood tacrolimus concentrations time-curves from Day 1 and Day 7 (Week 1) are presented in **Figure 1.** The pharmacokinetic parameter estimates from Day 1 and Day 7 (Week 1) are summarized in **Table 3** and **Table 4,** respectively. Scatter plot of C_{trough} vs AUC_{tau} including all patients with a regression line and equation for PKAS are presented in **Figure 2**.

Figure 1: Mean Whole Blood Concentrations of Tacrolimus After the Administration of the Tacrolimus Granule Formulation (PKAS) *(Source: Adapted from Study: F506-CL-0403, Figure 12.4.1.3)*



A: All organ transplants, B: Heart transplants, C: Liver transplants, D: Kidney transplants

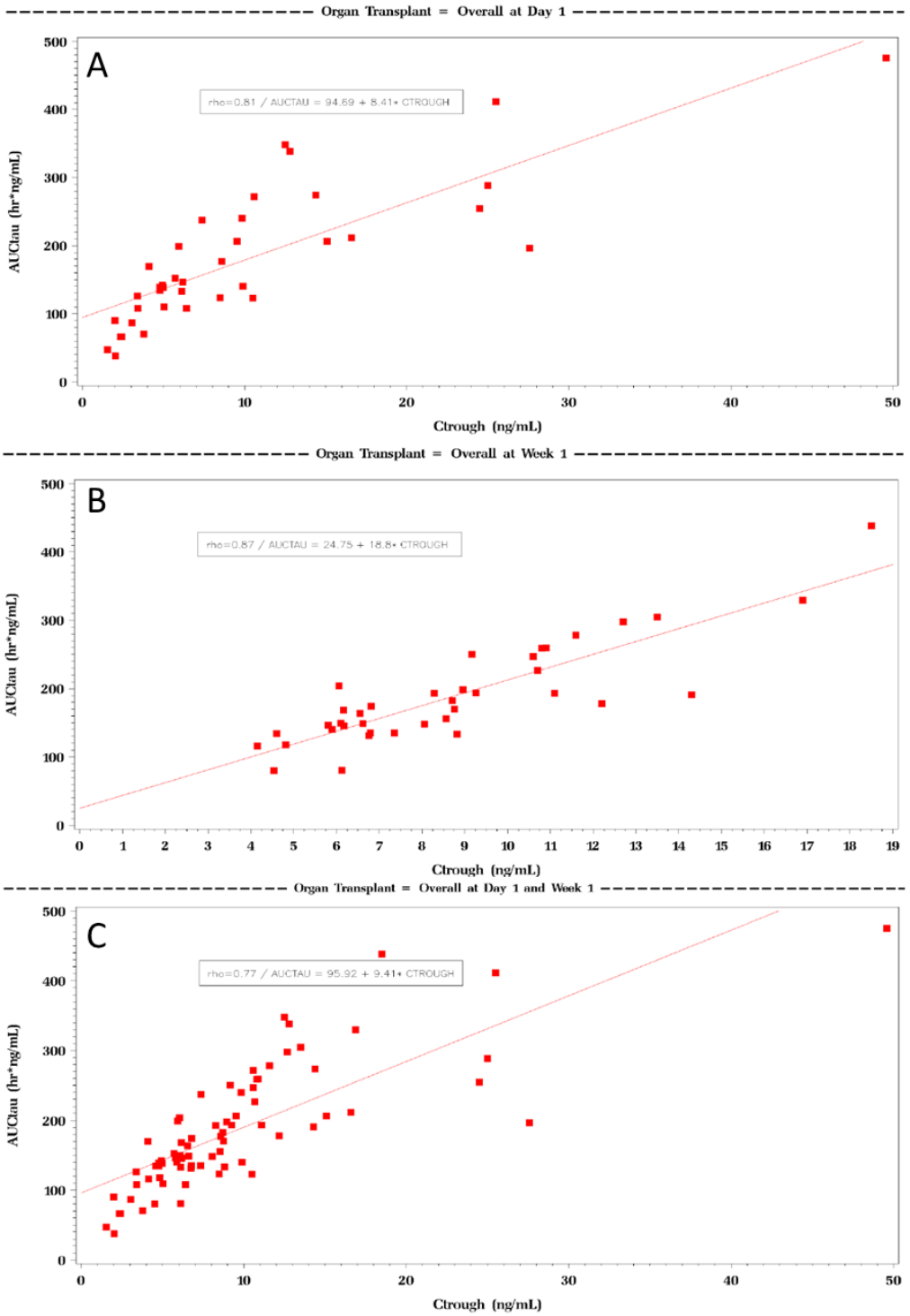
Table 3: Summary of Whole Blood Tacrolimus Pharmacokinetic Parameter Estimates Following an Initial Dose of 0.3 mg/kg/day of Granules on Day 1 (PKAS) *(Source: Adapted from F506-CL-0403, Table 27)*

Statistical Parameter	AUC_{tau} (h*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	C_{trough} (ng/mL)
Heart Transplant				
n	12	12	12	12
Mean (SD)	224.13 (114.30)	45.61 (19.55)	2.953 (4.328)	12.60 (13.40)
Median	198.03	47.50	1.000	7.93
Min – Max	66.6 - 475.6	15.0 - 71.2	0.50 - 12.00	2.4 - 49.6
GM	199.00	41.20	1.300	8.80
Liver Transplant				
n	14	14	14	14
Mean (SD)	210.56 (84.01)	25.11 (10.78)	2.727 (1.837)	13.41 (7.11)
Median	206.61	23.10	2.017	10.55
Min – Max	108.0 - 411.8	11.8 - 47.5	0.98 - 8.10	5.0 - 25.5
GM	196.00	23.20	2.300	11.80
Kidney Transplant				
n	12	12	12	12
Mean (SD)	97.40 (36.77)	18.04 (8.10)	1.776 (0.880)	3.54 (1.45)
Median	99.15	18.75	1.992	3.41
Min – Max	38.1 - 146.8	6.9 - 30.1	0.97 - 4.03	1.6 - 6.2
GM	90.00	16.10	1.600	3.30
Total				
n	38	38	38	38
Mean (SD)	179.11 (99.81)	29.35 (17.55)	2.498 (2.691)	10.04 (9.59)
Median	144.76	24.55	2.000	6.30
Min – Max	38.1 - 475.6	6.9 - 71.2	0.50 - 12.00	1.6 - 49.6
GM	154.00	24.80	1.700	7.20

Table 4: Summary of Whole Blood Tacrolimus Pharmacokinetic Parameter Estimates on Day 7 (Week 1) (PKAS) *(Source: Adapted from F506-CL-0403, Table 27)*

Statistical Parameter	AUC_{tau} (h*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	C_{trough} (ng/mL)
Heart Transplant				
n	12	12	12	12
Mean (SD)	165.17 (39.12)	32.69 (9.78)	0.838 (0.438)	7.57 (1.80)
Median	147.07	31.95	0.775	7.43
Min – Max	131.8 - 259.9	19.2 - 50.3	0.50 - 2.00	4.6 - 10.9
GM	161.00	31.40	0.800	7.40
Liver Transplant				
n	14	14	14	14
Mean (SD)	195.08 (94.63)	30.52 (19.35)	1.714 (1.117)	9.71 (4.03)
Median	184.77	23.15	1.500	9.63
Min – Max	80.5 - 438.8	9.0 - 83.0	0.50 - 4.00	4.5 - 18.5
GM	176.00	25.90	1.400	8.90
Kidney Transplant				
n	12	12	12	12
Mean (SD)	208.32 (68.75)	36.63 (13.97)	1.093 (0.608)	8.92 (3.59)
Median	186.55	32.85	1.000	8.16
Min – Max	116.5 - 329.8	17.7 - 59.4	0.48 - 2.08	4.2 - 16.9
GM	198.00	34.20	0.900	8.30
Total				
n	38	38	38	38
Mean (SD)	189.81 (72.97)	33.14 (14.99)	1.241 (0.866)	8.78 (3.36)
Median	172.59	31.25	1.000	8.43
Min – Max	80.5 - 438.8	9.0 - 83.0	0.48 - 4.00	4.2 - 18.5
GM	178.00	30.00	1.000	8.20

Figure 2: Correlation Between Tacrolimus Minimum Concentration and AUC on Day 1 (A), Day 7 (B), and Days 1&7 combined (C) After the Administration of Granule Formulation in Patients Receiving Liver, Kidney, or Heart Transplants (PKAS) *(Source: Adapted from FG-506-01-08-R-PK-1, Figure 4)*



Sponsor's Conclusion:

- Overall, the mean AUC_{tau} for the first pharmacokinetic profile (Day 1) was 224.13 h*ng/mL in patients with heart transplant, 210.56 h*ng/mL in patients with liver transplant and 97.40 h*ng/mL in patients with kidney transplant. The mean AUC_{tau} for the second PK profile (Day 7 or Week 1) was 165.17 h*ng/mL in patients with heart transplant, 195.08 h*ng/mL in patients with liver transplant and 208.32 h*ng/mL in patients with kidney transplant.
- Overall, C_{trough} and AUC_{tau} were positively correlated both at Day 1 and Day 7 (Week 1) (Pearson's coefficients were 0.81 and 0.87, respectively).

Reviewer's Assessment:

Based on the provided findings, the Sponsor's conclusions are reasonable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABHAY JOSHI
05/22/2018

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05/22/2018