CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210115Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 210115
Supplement #:	0000
Drug Name:	Prograf ® (tacrolimus) granules
Indication(s):	Oral suspension for prevention of rejection in heart, kidney, or liver transplant in pediatric patients
Applicant:	Astellas Pharma US, Inc
Date(s):	Receipt Date: July 26, 2017
	PDUFA Due Date: May 26, 2018
Review Priority:	Standard
Biometrics Division:	IV
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Keywords: NDA review, clinical studies, liver transplant, pediatric study

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1. EXECUTIVE SUMMARY

This NDA submission for immediate-release tacrolimus granules 0.2 mg and 1 mg packets for oral suspension is in response to a Post Marketing Requirement included in the approval letter of Astagraf XL® (tacrolimus extended-release capsules) to develop an age-appropriate formulation to allow for dosing for ages 1 to <5 years. The applicant proposes to revise the product labeling for PROGRAF® (tacrolimus) to incorporate the efficacy and safety data from Study FG-506-01-13. The study was a pediatric phase 3 study in primary liver allograft transplantation comparing a tacrolimus based (tacrolimus granules) dual drug immunosuppressive regimen (i.e., tacrolimus with low-dose corticosteroids) with a cyclosporin-ME based triple drug immunosuppressive regimen (i.e., cyclosporin-ME with low-dose corticosteroids and azathioprine). The study was designed as a superiority study, conducted outside of the United States, and completed in 2000. The patients enrolled in this study had an average age of 3.5 years. The protocol-defined primary endpoints were the incidence and time to first acute rejection (AR) at 12 months. However, the statistical review focuses primarily on the efficacy results of the composite endpoint of BPAR/GL/D (biopsy proven acute rejection/graft loss/death) as this endpoint is recommended by the FDA for current clinical trials.

The efficacy analysis population (the ITT population) consisted of all randomized patients who received at least one dose of study drug, including 91 patients in the tacrolimus granules group and 90 patients in the cyclosporin-ME group. At 12 months, the incidence rate for composite endpoint of BPAR/GL/D was lower for the tacrolimus granules group (50.5%) than the incidence rate for the cyclosporin-ME group (61.1%), with a difference between the two groups (test – control) of -10.6% and 95% confidence interval (CI) of (-24.9%, 3.8%). The Kaplan-Meier estimates for BPAR/GL/D at 12 months were 51.2% for tacrolimus granules, and 64.2% for cyclosporin-ME group respectively. The difference of the K-M estimates for BPAR/GL/D between the two groups (test-control) at 12 month was -13.0% with a 95% CI of (-27.6%, 1.6%). There was no statistically significant difference on BPAR/GL/D between the two treatment groups based on either incidence rate or K-M estimate.

The incidence rate of AR at 12 months was lower in the tacrolimus granules group (42.9%) compared with the cyclosporin group (54.4%), with a treatment difference of -11.6% and 95% CI of (-26.1%, 2.9%). The incidence rate of BPAR was also lower in the tacrolimus granules group (44.0%) compared with the cyclosporin-ME group (54.4%), with a difference between the two groups (test – control) of -10.5% and 95% CI of (-25.0%, 4.0%). One more death occurred in the cyclosporin-ME group than in the tacrolimus granules group (7 vs 6) by 12 months, with one-year patient survival 93.4% for tacrolimus granules group and 92.2% for cyclosporine-ME group. The incidence rate of graft loss at 12 months was also higher for the cyclosporin-ME group compared with the tacrolimus granules group (13 or 14.4% vs 7 or 7.7%). The corresponding one-year graft survival was 92.3% for the tacrolimus granules group and 85.6% for the cyclosporine-ME group.

In conclusion, the efficacy results of Study FG-506-01-13 are numerically in favor of tacrolimus granules group compared with the cyclosporin-ME group for both the FDA recommended composite endpoint of BPAR/GL/D and the protocol-defined primary endpoint of AR. For both endpoints, the upper limit of the 95% CI for the treatment difference in the incidence rates is less than 4%. In the assessment of this reviewer, this study will provide useful information for healthcare professionals and patients regarding the efficacy and safety of tacrolimus treatment for pediatric liver patients, in addition to the two liver transplant studies (>12 years old) currently in the Prograf label. This reviewer recommends the addition of the safety and efficacy data of Study FG-506-01-13 in the PROGRAF® labeling (see Section 5.3 for the detailed recommendation).

2. INTRODUCTION

Tacrolimus, a calcineurin inhibitor marketed as Prograf® given twice daily, was first approved in 1994 in the United States for the prophylaxis of organ rejection in patients receiving liver transplants and was approved 3 years later for use in patients receiving kidney transplants. The indication for the prophylaxis of organ rejection in patients receiving allogeneic heart transplants was approved in 2006. On July 19, 2013, the Division of Transplant and Ophthalmology Products (DTOP) approved NDA 204096 Astagraf XL® (tacrolimus extended-release capsules) for the indication of prophylaxis of organ rejection in adult patients receiving kidney transplants. For details, see statistical reviews in DARRTS dated 6/12/2013 and 7/17/2013.

The current NDA for immediate-release tacrolimus granules 0.2 mg and 1 mg packets for oral suspension is in response to a Postmarketing Requirement under the Pediatric Research Equity Act (PREA) included in the approval letter of Astagraf XL® to develop an age-appropriate formulation to allow for dosing for ages 1 to <5 years. Immediate-release tacrolimus granules for oral suspension (marketed as Modigraf® in Europe and Prograf Granules® in Japan) is currently approved outside of the US in 32 countries, initially approved in Japan in 2001, followed by Europe in 2009. In the US, tacrolimus for oral use is commercially manufactured as a 0.5, 1 and 5 mg capsule formulation.

This NDA is supported by two clinical studies, FG-506-01-08 and FG-506-01-13; two pharmacokinetic studies, F506-CL-0403 (OPTION) and F506-CL-0404A (PROGRESSION); and a healthy subject bioequivalence study 95-0-001. This statistical review will focus on the only controlled study, Study FG-506-01-13. The study was conducted outside of the United States and the protocol was not submitted to the FDA prior to the NDA submission. The study report stated that the first patient enrolled in the study on 06/02/1997 and the last patient completed the study on 12/23/2000.

The NDA submission can be found at \\CDSESUB1\evsprod\N DA210115\0000.

3. Evaluation of Efficacy

This section presents and discusses the details of the Study FG-506-01-13 titled “An Open, Randomized, Comparative, Multicenter Pediatric Clinical Trial Comparing the Efficacy and Safety of a Dual Regimen with Oral Tacrolimus (FK506) Versus a Triple Regimen with Oral Cyclosporin-Microemulsion in Primary Liver Allograft Transplantation”.

3.1 Study Design and Endpoints

The study objective was to investigate the safety and efficacy of a tacrolimus based regimen using a new formulation (fine granules) in comparison to a cyclosporin-microemulsion (ME)

based standard regimen in children receiving a primary liver transplant. This was an open-label, randomized, multicenter, pediatric phase 3 study in primary liver allograft transplantation comparing a tacrolimus based dual drug immunosuppressive regimen (i.e., tacrolimus with low-dose corticosteroids) with a cyclosporin-ME based triple drug immunosuppressive regimen (i.e., cyclosporin-ME with low-dose corticosteroids and azathioprine).

Male and female children 16 years of age or younger undergoing a primary liver allograft transplantation were enrolled into the study. Randomization was performed directly before the first administration of study drug, usually within 6 hours posttransplantation. In case of postoperative renal impairment, the randomization could be delayed up to 24 hours posttransplantation. Patients were randomly assigned in 1:1 ratio to receive either tacrolimus granules with low-dose corticosteroids or cyclosporin-ME with low-dose corticosteroids and azathioprine as immunosuppressive therapy.

Tacrolimus therapy was to commence as soon as possible after surgery but no longer than 6 hr (24 hr in case of postoperative renal impairment) after closure of the skin. The planned initial daily dose for tacrolimus was 0.3 mg/kg per day administered via nasogastric or nasojejunal tube at 12-hr intervals. After the initial period of nasogastric or nasojejunal therapy, tacrolimus was to be administered orally at a starting dose of 0.3mg/kg/day, given in 2 doses (equals 0.15 mg/kg twice daily). Cyclosporin-ME therapy was to commence as soon as possible after surgery but no longer than 6 hr (24 hr in case of postoperative renal impairment) after closure of the skin. The planned initial daily dose for cyclosporin-ME was 10 mg/kg per day orally, given in 2 doses (equals 5 mg/kg twice daily). Intravenous administration was to be conducted in addition to oral therapy when needed.

After the initial screening on day 0 (date of skin closure), patients were observed for efficacy and safety variables over a period of 12 months. Study visits were scheduled at days 1, 5, 9, 14, 21 and 28; weeks 6, 8, 10 and 12; and months 6, 9 and 12. Time windows of ± 2 days were acceptable for study visits 1 to 10 prior to 6 months posttransplant, and the time window of ± 7 were acceptable for study visits 11 to 13 at Month 6, 9, and 12.

The primary efficacy endpoint specified in the protocol was the incidence and time to first acute rejection (AR). The definition appears to be for two co-primary endpoints. According to the Applicant's analysis plan, the incidence of rejections was to be assessed using chi-square test based method. The time to first acute rejection was to be analyzed using Kaplan-Meier survival procedures with treatments compared using the Wilcoxon test. Patient survival and graft survival were also to be analyzed using Kaplan-Meier survival procedures. The applicant proposed (b) (4) (b) (4) (b) (4). See details in Section 3.3.

The sample size calculation assumed an acute rejection rate of 50% for pediatric patients in the control arm, and the 200 patients (100 per arm) would give the study a power of 80% to detect a difference of 20% in the acute rejection rate with a two-sided significance level of 0.05. As seen in Table 4, the difference of the acute rejection rate between the two groups was < 20%. The study was not sufficiently powered.

The intent-to-treat (ITT) population consisted of all randomized patients who received at least 1 dose of study drug and was used for efficacy analysis for this study.

3.2 Patient Disposition, Demographic and Baseline Characteristics

Study FG-506-01-13 was initiated (first enrollment) on June 2, 1997 and was completed (last evaluation) on December 23, 2000. The study was conducted at 10 contracted sites in 6 countries including Belgium, France, Germany, Italy, Spain and the UK. The study enrolled male and female children 16 years of age or younger undergoing a primary liver allograft transplantation. Note that the current NDA is in response to a Postmarketing Requirement under the Pediatric Research Equity Act (PREA) to develop an age-appropriate formulation to allow for dosing for ages 1 to <5 years, the results for age group of younger than 5 years will be presented separately throughout this review.

A total of 185 patients were randomized to tacrolimus granules (93) and cyclosporin-ME groups (92). Of the 185 randomized patients, 91 patients received tacrolimus and 90 patients received cyclosporin-ME, which are defined as the ITT population. Table 1 displays the patient disposition in ITT population through 12 months. Of the patients who received study treatment, 23 patients discontinued study drug in the tacrolimus granules group and 46 patients discontinued study drug in the cyclosporin-ME group. A higher proportion of subjects in the cyclosporine-ME group (51.1%) discontinued study medication compared with the tacrolimus granules group (25.3%). The proportion of subjects who discontinued due to AEs was higher in the cyclosporin-ME group (38.9%) compared with that in the tacrolimus granules group (12.1%). The two treatment groups each had 3 patients who discontinued due to re-transplantation.

Of the 23 patients who discontinued study drug in the tacrolimus granules group, 17 patients were < 5 years of age and 6 patients were ≥ 5 years of age. Of the 46 patients who discontinued study drug in the cyclosporin-ME group, 38 patients were < 5 years of age and 8 patients were ≥ 5 years of age. The <5 years of age group had slightly lower discontinuation rate than the ≥5 years of age group in the tacrolimus granules group (24.3% vs 28.6%). In the Cyclosporin ME group, the <5 years of age group had higher rate of discontinuation compared with the ≥5 years of age group (54.3% vs 40%).

Table 1 Patient Disposition (ITT population)

	Tacrolimus Granules			Cyclosporin ME		
	Total N=91	<5 Y N=70	≥5 Y N=21	Total N=90	<5 Y N=70	≥5 Y N=20
Completed study/treatment	**68 (74.7)**	**53(75.7)**	**15(71.4)**	**44 (48.9)**	**32(45.7)**	**12(60)**
Discontinued study treatment	**23 (25.3)**	**17(24.3)**	**6(28.6)**	**46 (51.1)**	**38(54.3)**	**8(40)**
Adverse Event	11 (12.1)	7(10)	4(19.0)	35 (38.9)	31(44.3)	4(20)
Retransplantation	3(3.3)	3(4.3)	0	3(3.3)	2(2.9)	1(5)
Protocol prohibited medication required	4 (4.4)	2(2.9)	2(9.5)	1 (1.1)	0	1(5)
Suspension of study drug	3(3.3)	3(4.3)	0	3(3.3)	2(2.9)	1(5)
Death	2 (2.2)	2(2.9)	0	3 (3.3)	3(4.3)	0
Other	0	0	0	1 (1.1)	0	1(5)

Source: Table 12.1.1.3.1 of the Clinical Study Report and reviewer analysis

Table 2 presents reasons for study discontinuation for subjects who died or experienced graft loss during the study. All patients who died or experienced graft loss during the study discontinued the study prior to 12 months. Of the 6 patients (5 were <5 years old and 1 was≥5 years) who died by 12 months in the tacrolimus granules group, 2 patients (<5 years) discontinued study due to death, 3 patients (<5 years) died after discontinuation from the study due to re-transplantation, and 1 patient (≥5 years) died after discontinuation from the study due to AE. Of the 7 patients (all <5 years old) who died by 12 months in the cyclosporin-ME group, 3 patients discontinued study due to death, and 4 patients died after discontinuation from the study due to AE.

Of the 7 patients (6 were <5 years old and 1 was≥5 years) who experienced graft loss by 12 months in the tacrolimus granules group, 2 patients (<5 years) discontinued study due to death, 3 patients (<5 years) discontinued due to re-transplantation, and 2 patients (1 was <5 years and 1 was ≥5 years) experienced graft loss after discontinuation from the study due to AE. Of the 13 patients (12 were <5 years old and 1 was≥5 years) who experienced graft loss by 12 months in the cyclosporin-ME group, 3 patients (<5 years) discontinued study due to death, 3 patients (2 were <5 years and 1 was ≥5 years) discontinued from the study due to re-transplantation, and 7 patients (<5 years) experienced graft loss after discontinuation from the study due to AE.

Table 2 Reasons for Study Discontinuation for Patients who died or experienced graft Loss

	Prograf Granules		Cyclosporin ME	
	<5 years	≥5 years	<5 years	≥5 years
Total number of Death	**5**	**1**	**7**	**0**
death	2	0	3	0
AE	0	1	4	0
retransplantation	3	0	0	0
Total number of graft loss	**6**	**1**	**12**	**1**
retransplantation	3	0	2	1
death	2	0	3	0
AE	1	1	7	0

Source: Reviewer analysis

General demographic and background information for patients in the ITT population is listed in Table 3. The treatment groups were balanced with respect to demographic and background characteristics. In both the tacrolimus granules and cyclosporin-ME groups, approximately half of patients were male (50.5% and 53.5%, respectively). The majority of patients was Caucasian (82.4% and 88.9%, respectively). The proportion of patients who had living related donors and the proportion of patients who had identical ABO blood type match were comparable for the two treatment groups.

Table 3 demographic and baseline characteristics by treatment group and age group for the ITT population

	Tacrolimus Granules			Cyclosporin ME		
	Total N=91	<5 years N=70	≥5 years N=21	Total N=90	<5 years N=70	≥5 years N=20
Age						
Mean(s.d.)	3.5 (3.9)	1.6 (1.2)	9.9 (3.2)	3.5 (4.2)	1.5 (1.3)	10.3(3.6)
range	0.3-15.0	0.3-4.8	5.0-15.0	0.1-16.0	0.1-4.9	5.0-16.0
Sex						
Male	46 (50.5)	35 (50)	11 (52.4)	48 (53.3)	33 (47.1)	15(75)
Female	45 (49.5)	35 (50)	10 (47.6)	42 (46.7)	37 (52.9)	5(25)
Race						
Caucasian	75 (82.4)	59(85.5)	16(76.2)	80 (88.9)	62(88.6)	18(90)
Black	6 (6.6)	6(8.7)	0	3(3.3)	2(2.9)	0
Asian	6 (6.6)	2(2.9)	3(14.3)	4(4.4)	3(4.3)	0
Other	3 (3.3)	2(2.9)	2(9.5)	3(3.3)	3(4.3)	2(10)
Unknown	1(1.1)	1(1.4)	0	0	0	0
Weight (kg)						
Mean(s.d.)	14.6(10.3)	10.0(3.9)	29.9(10.2)	13.9 (10.7)	9.2 (3.5)	30.0(11.8)
range	5.0-51.3	5.0-23.0	14.0-51.3	3.0-60.0	3.0-21.0	14.0-60.0
Living related donor						
Yes	10 (11.0)	9 (12.9)	1(4.8)	11 (12.2)	11 (15.7)	0
No	81 (89.0)	61(87.1)	20 (95.2)	79 (87.8)	59 (84.3)	20 (100)
ABO match						
Identical	75 (82.4)	59(84.3)	16(76.2)	75 (83.3)	57 (81.4)	18 (90)
compatible	16 (17.6)	11(15.7)	5(23.8)	15 (16.7)	13 (18.6)	2 (10)

Source: Table 3 of the Clinical Study Report and reviewer analysis

The tacrolimus granules and cyclosporin-ME groups each included 70 patients <5 years of age. Among patients < 5 years of age, male patients made up roughly half of patients (50% in the tacrolimus granules group and 47.1% in the cyclosporin-ME group). The tacrolimus granules and cyclosporin-ME groups included 21 and 20 patients ≥ 5 years of age, respectively. Among patients ≥ 5 years of age, male patients made up approximately half of patients (52.4%) in the tacrolimus granules group and the majority of patients (75.0%) in the cyclosporin-ME group. The majority of patients ≥ 5 years of age was Caucasian (76.2% in the tacrolimus granules group

and 90.0% in the cyclosporin-ME group). For patients younger than 5 years old, the demographic and baseline characteristics were also fairly balanced between the two treatment groups.

3.3 Results and Conclusions

Comparisons between treatment groups on endpoints of AR, BPAR, death, graft loss and the composite endpoint of BPAR/GL/D at 12 months are summarized in Table 4. The incidence rate of AR was lower in the tacrolimus granules group (39 or 42.9%) compared with the cyclosporin group (49 or 54.4%). The incidence rate of BPAR was also lower in the tacrolimus granules group (40 or 44.0%) compared with the cyclosporin group (49 or 54.4%). The 95% confidence interval for the difference of BPAR incidence rate between the two groups was (-25.0%, 4.0%). One more death occurred in the cyclosporin-ME group than in the tacrolimus granules group (7 vs 6). The incidence rate of graft loss was also higher for the cyclosporin-ME group compared with the tacrolimus granules group (13 or 14.4% vs 7 or 7.7%).

The applicant did not present the result of the efficacy failure endpoint (a composite of biopsy proven acute rejection (BPAR), graft loss, death or loss to follow-up) in the study report. The incidence rate for the composite endpoint of BPAR, graft loss or death (BPAR/GL/D) was lower for the tacrolimus granules (50.5%) than the incidence rate for the cyclosporin-ME group (61.1%), with a difference between the two groups (test – control) of -10.6% and 95% confidence interval of (-24.9%, 3.8%). If the patients marked as having “unknown status” in the efficacy dataset ADEFF.xpt were considered as lost to follow-up, the incidence rate for BPAR/GL/D/LTFU was still lower for the tacrolimus granules (52.7%) than the incidence rate for the cyclosporin-ME group (61.1%), with a difference between the two groups (test – control) of -8.4% and 95% confidence interval of (-22.7%, 6.0%). The confidence intervals were constructed using a normal approximation.

Table 4 Efficacy Results by Treatment Group at 12 Month

Endpoints	Tacrolimus Granules	Cyclosporin ME	Risk Difference (95% CI) (tacrolimus granules – Cyclosporin ME)
ITT Population			
	N=91	N=90	
AR	39* (42.9%)	49 (54.4%)	-11.6% (-26.1%, 2.9%)
BPAR	40* (44.0%)	49 (54.4%)	-10.5% (-25.0%,4.0%)
Death	6 (6.6%)	7 (7.8%)	-1.2% (-8.7%, 6.3%)
Graft loss	7 (7.7%)	13 (14.4%)	-6.8% (-15.8%, 2.3%)
Graft loss excluding death	1 (1.1%)	6 (6.7%)	-5.6% (-13.0%, 0.2%)
BPAR/GL/D	46 (50.5)	55 (61.1%)	-10.6% (-24.9%, 3.8%)
Unknown status	2 (2.2%)	0	2.2% (-2.1%, 8.3%)
BPAR/GL/D/LTFU	48 (52.7%)	55(61.1%)	-8.4% (-22.7%, 6.0%)
< 5 years of age			
	N=70	N=70	
AR	31*(44.3%)	40 (57.1%)	-12.9% (-29.3%, 3.6%)
BPAR	32* (45.7%)	40 (57.1%)	-11.4% (27.9%, 5.0%)
Death	5 (7.1%)	7 (10%)	-2.9% (-12.1%, 6.4%)
Graft loss	6(8.6%)	12(17.1%)	-8.6% (-19.6%, 2.4%)
Graft loss excluding death	1 (1.4%)	5 (7.1%)	-5.7% (-14.5%, 1.6%)
BPAR/GL/D	37 (52.9%)	45 (64.3%)	-11.4% (-27.6%, 4.8%)
Unknown status	2 (2.2%)	0	2.2% (-2.1%, 8.3%)
BPAR/GL/D/LTFU	39 (55.7%)	45 (64.3%)	-8.6% (-24.7%, 7.6%)
≥ 5 years of age			
	N=21	N=20	
AR	8 (38.1%)	9 (45%)	-6.9% (-37.0%, 23.2%)
BPAR	8 (38.1%)	9 (45%)	-6.9% (-37.0%, 23.2%)
Death	1 (4.8%)	0	4.8% (-12.4%,24.3%)
Graft loss	1 (4.8%)	1 (5%)	-0.2% (-20.6%, 19.9%)
Graft loss excluding death	0	1(5%)	-5% (-24.9%, 11.6%)
BPAR/GL/D	9 (42.9%)	10 (50%)	-7.1% (-37.6%, 23.3%)
Unknown status	0	0	0% (-16.8%, 16.2%)

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

(b) (4)

(b) (4) Additionally in the study report, the applicant stated on

page 44 that the corresponding rate at 12 months was also lower in the tacrolimus granules group compared to the cyclosporin-ME group (44.5% and 59.8%, respectively), with a statistically significant difference of -15.3 (95% CI: -30.5, -0.2; P = 0.047, normal approximation).

(b) (4)

Table 5 presents the reviewer's results on K-M estimates for AR, death, graft loss and the composite endpoint of BPAR/GL/D. For K-M estimate on AR, the events of death and graft losses were not treated as failures but censored at the time of death or graft loss, or at the time of study discontinuation if it occurred earlier than death or graft loss. The Kaplan-Meier survival curve for patients in the treatment groups on AR over the 12 month period is shown in Figure 1.

Table 5 Kaplan-Meier Estimates of efficacy Endpoints at 12 Months

	Tacrolimus granules (n = 91)	**Cyclosporine-ME (n = 90)**	**95% CI of difference of K-M estimates**	**P-value (normal approximatio**
First Acute	45.5%	59.9%	-14.3% (-29.4%, 0.8%)	0.0638
BPAR	46.9%	60.0%	-13.1% (-28.3%, 2.0%)	0.0899
Death	7.2%	11.2%	-4.1% (-13.9%, 5.7%)	0.4164
Graft Loss	7.8%	18.4%	-10.5% (-21.4%, 0.4%)	0.0586
BPAR/GL/Death	51.2%	64.2%	-13.0% (-27.6%, 1.6%)	0.0816
BPAR/GL/D/LTF	53.6%	64.2%	-10.6% (-25.2%, 4.1%)	0.1573
Patient Survival*	92.8%	88.8%	4.1% (-5.7%, 13.9%)	0.4164
Graft Survival*	92.2%	81.7%	10.5% (-0.4%, 21.4%)	0.0586

*Patient and graft survival are included for comparison with sponsor's proposal.
Source: Reviewer analysis

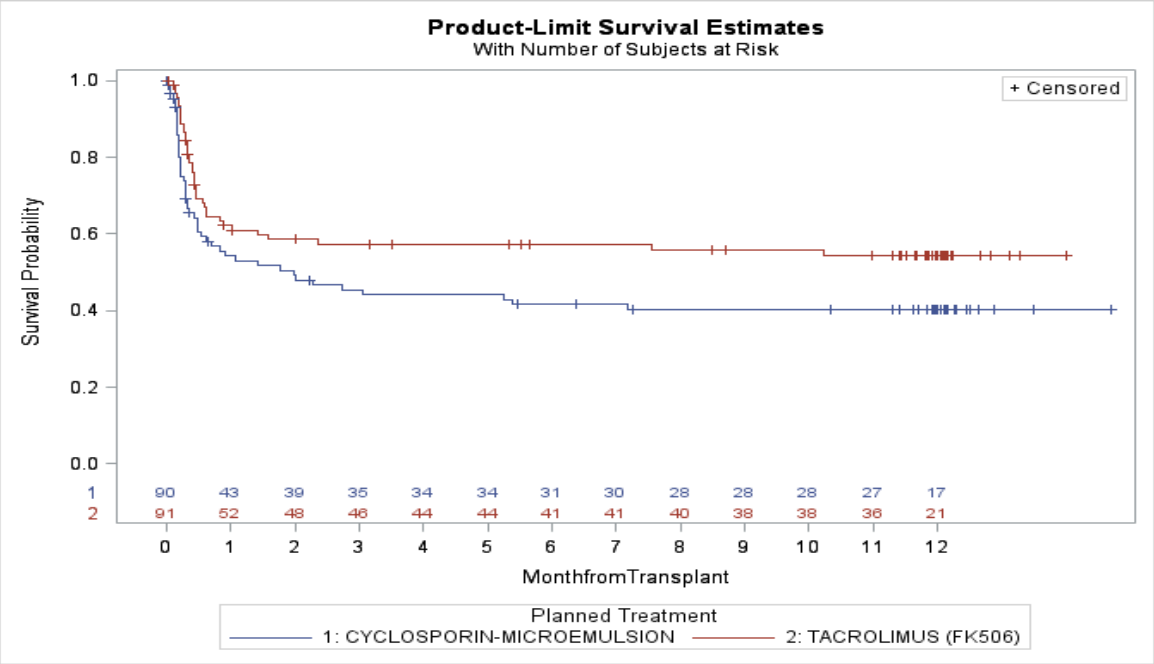
The K-M estimates for AR in Table 5 were 45.5% and 59.9% respectively for tacrolimus granules group and cyclosporin-ME group. The difference of the K-M estimates for AR between the two groups at 12 month was -14.3% with a 95% CI of (-29.4%, 0.8%). There is no statistically significant difference of Kaplan-Meier estimates between the two treatment groups as shown with the endpoints in Table 5.

The results in Table 5 are different from the applicant's results. The discrepancy between the reviewer's and applicant's results is the K-M estimate for AR in the tacrolimus granules group. The reviewer's result was 45.5% whereas the applicant had 44.5%. The reviewer found that Table 12.3.4.1 of the study report listed Kaplan-Meier estimates over time for AR. The column for number of cumulative events showed 38 AR events at Day 365 for tacrolimus granules. As shown in Table 5 above and also in Table 12.3.1.1, there was a total of 39 AR events occurred by 12 months in the tacrolimus granules group. The applicant's analysis for crude incidence of first

acute rejection at 12 months in Table 12.3.1.1 of the study report also showed that the number of AR events by 12 months is 39. Hence the applicant's K-M estimate of 44.5% for AR originated from 38 AR events in the tacrolimus granules group was not correct.

The applicant was asked to reconcile the discrepancy between Table 12.3.4.1 and Table 12.3.1.1 in an Information Request dated April 3, 2018. The applicant responded that Patient (b) (6) received study drug on day 0 only and was formally discontinued from the study on day 10. Following discontinuation, the patient experienced a rejection on day 27. This patient was censored on the day of treatment discontinuation (day 10) for the Kaplan-Meier analyses (Table 12.3.4.1), therefore accounting for the discrepancy and reported estimate of acute rejection.

Figure 1 Kaplan-Meier Survival Curve of Time to First Acute Rejection (ITT Population)



Source: Reviewer analysis

For completeness, Table 6 lists the p-values for Wilcoxon test and Log-rank test. Both tests are used to test homogeneity of Kaplan-Meier survival curves between the two treatment groups.

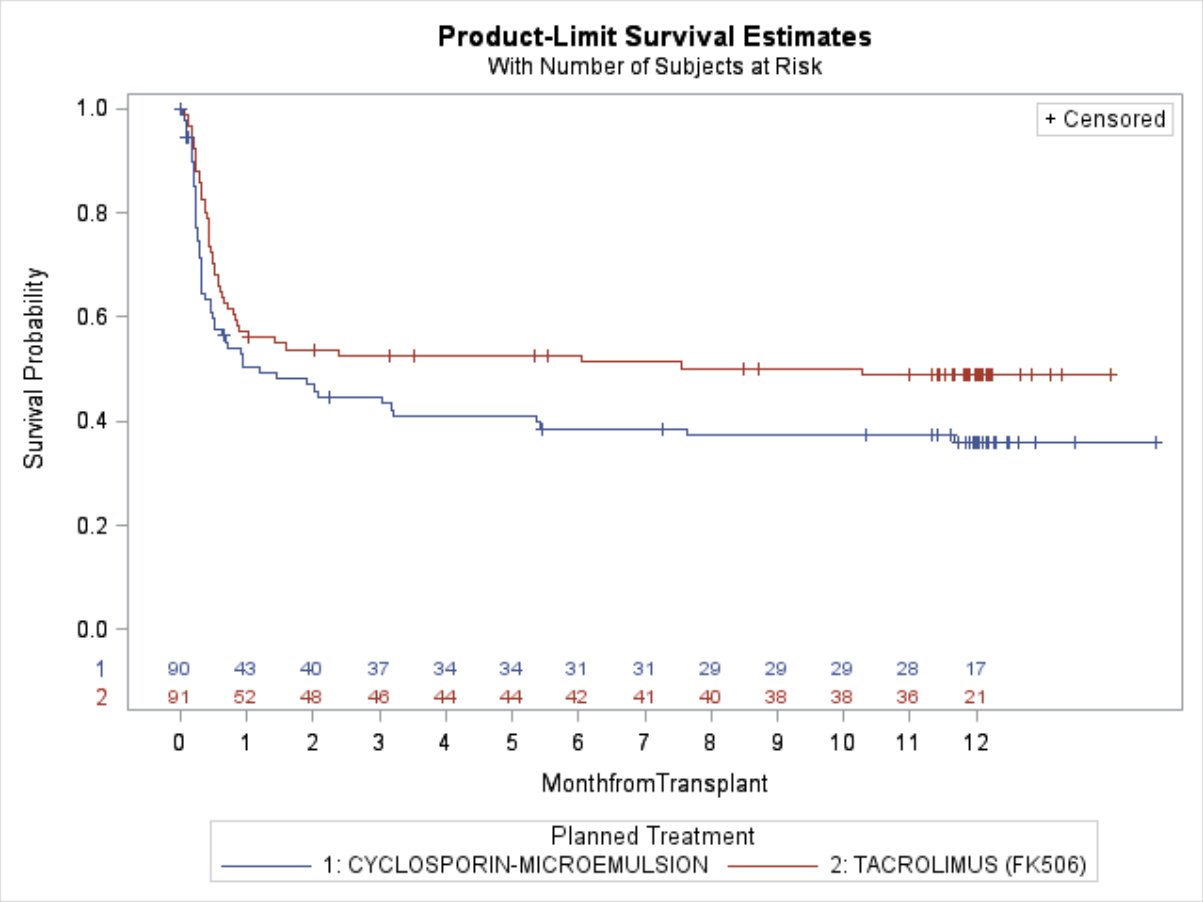
Table 6 Testing Homogeneity of Survival Curves over Time between Treatment Groups

	P-value (Log-rank test)	**P-value (Wilcoxon test)**
First Acute Rejection	0.0489	0.0373
BPAR	0.0708	0.0568
Death	0.4619	0.5155
Graft Loss	0.0871	0.1355
BPAR/GL/Death	0.0715	0.0573
BPAR/GL/D/LTFU	0.1063	0.0706

Source: Reviewer analysis

Figure 2 displays the Kaplan-Meier survival curve for patients in the treatment groups on BPAR/Graft Loss/Death over the 12 months period. The tacrolimus granules group appears to have better responses compared to the Cyclosporin ME group through 12 months. The K-M estimates at 12 months were 51.2 % for tacrolimus granules, and 64.2% for cyclosporin-ME group respectively. The difference of the K-M estimates for BPAR/GL/D between the two groups at 12 month was -13.0% with a 95% CI of (-27.6%, 1.6%).

Figure 2 Kaplan-Meier Survival Curve of Time to BPAR/GL/D in ITT Population



Source: Reviewer analysis

3.4 Evaluation of Safety

The number and percentage of patients (≥10% of patients in either treatment group) who experienced adverse reactions including infections are summarized by primary system organ class is listed in Table 7 (from Table 24 of the Clinical Study Report). The overall adverse event rates were similar between treatment groups for the ITT population as well as for the <5 years and ≥5 years age groups.

For overview of the safety results, please see details in the clinical review by the medical officer.

Table 7 Summary of Common (≥ 10% of Patients in Any Subgroup) AEs (COSTART *) by Age Group (ITT Population)

COSTART System Organ Class Preferred Term	**Number of Patients**					
	Tacrolimus Granules			**Cyclosporin-ME**		
	Total N=91	**<5 years N=70**	**>5 years N=21**	**Total N=90**	**<5 years N=70**	**≥5 years N=20**
Any AE	89 (97.8)	69 (98.6)	20 (95.2)	88 (97.8)	70 (100)	18(90)
Body as a whole	78 (85.7)	63 (90)	15 (71.4)	77 (85.6)	62 (88.6)	15 (75)
Cardiovascular System	50 (54.9)	40 (57.1)	10 (47.6)	53 (58.9)	44 (62.9)	9 (45.0)
Digestive System	73 (80.2)	58 (82.9)	15 (71.4)	63 (70)	51 (72.9)	12 (60.0)
Endocrine System	6 (6.6)	2 (2.9)	4 (19.0)	3(3.3)	0	3 (15)
Hemic and Lymphatic System	45 (49.5)	37 (52.9)	8 (38.1)	31 (34.4)	25 (35.7)	6 (30.0)
Metabolic and Nutritional Disorders	55 (60.4)	41 (58.6)	14 (66.7)	44 (48.9)	34 (48.6)	10 (50.0)
Nervous System	18 (19.8)	11 (15.7)	7 (33.3)	16 (17.8)	10 (14.3)	5 (25.0)
Respiratory System	46 (50.5)	35 (50.0)	11 (52.4)	37 (41.1)	32 (45.7)	5 (25.0)
Skin and Appendages	16 (17.6)	13 (18.6)	3 (14.3)	30 (33.3)	24 (34.3)	6 (30.0)
Urogenital System	27 (29.7)	19 (27.1)	8 (38.1)	22 (24.4)	16 (22.9)	6 (30.0)

* Coding Symbols for a Thesaurus of Adverse Reaction Terms
Source: Table 24 of the Clinical Study Report

The clinical reviewer noted that the numbers for the tacrolimus group patients who discontinued due to AEs match (n=11) between Figure 1, Table 12.1.1.3.1 and Table 15 in Section 9.1.2.3 in the study report, but the numbers for the cyclosporine group discontinuations due to AEs do not match between the tables and Figure 1 (n=35 in Figure 1 and Table 12.1.1.3.1 but n=13 in Table 15 of Section 9.1.2.3.). The applicant was asked to reconcile this discrepancy in an Information Request dated April 3, 2018. The applicant responded(\\CDSESUB1\evsprod\NDA210115\0013) that the n = 35 from Figure 1 represents all patients who were discontinued due to adverse event (AE), including graft rejections leading to withdrawal of study drug and AEs with a fatal outcome. Table 15 identified all AEs from the AE CRF where the action taken was “drug withdrawn” but it specifically excluded graft rejections (preferred term, “graft rejection”) and AEs with fatal outcome (outcome, “fatal”). The applicant further noted that they have now

identified 12 cyclosporin-ME patients instead of 13 in Table 15. The discrepancy resulted from a single patient (b) (6) who was inadvertently listed in 2 separate rows (liver function tests abnormal on day 69 and hirsutism on day 55), leading to a miscount in the text and Table 15. Table 15 was presented in the response with patient ID added. The response also included Narratives of Cyclosporin Patients who discontinued due to AE. However, there were two patient IDs (b) (6) in Table 15 were not found in the Narratives. The patient IDs in the Narratives matched with the information from dataset ADSL.xpt. Both Patient (b) (6) and Patient (b) (6) discontinued study due to suspension of study drug, not due to AE based on dataset ADSL.xpt. In addition, Patients (b) (6) in the Narratives were not in Table 15. Based on the applicant's explanation above, this indicated that they discontinued the study due to graft rejection or AE with a fatal outcome. But these 3 patients did not experience rejections nor died.

Clinical reviewer believes that it may not be necessary to ask the sponsor clarify these discrepancies any further for two reasons:

1) These discrepancies pertain to the CsA arm and not the investigational (tacrolimus granules) arm.
2) These discrepancies will not affect the safety assessment of the tacrolimus granules arm.

Table 15 with patient ID added and Narratives of Cyclosporin Patients who discontinued due to AE shown below are taken from the applicant's Response to 03 Apr 2018 FDA Information Request submitted on 4/16/2018 (\\CDSESUB1\evsprod\NDA210115\0013).

Table 15 AEs Resulting in Discontinuation (All Randomized Subjects)

Patient ID	AEs Resulting in Discontinuation† COSTART Preferred Term	Last Dose Day	Onset/ Stop Day	Outcome	Relationship to Study Drug
Tacrolimus granules					
≥ 5 Years					
(b) (6)	Anemia	61	53/Ongoing	Not recovered/not resolved	Possible
	Lung edema	162	151/Ongoing	Not recovered/not resolved	Probable
	Drug level increased	3	3/5	Recovered/resolved	Definitely not
< 5 Years					
(b) (6)	EBV infection	172	163/Ongoing	Not recovered/not resolved	Possible
	Allergic reaction	265	265/269	Recovered/resolved	Possible
	Hepatic failure	115	110/Ongoing	Not recovered/not resolved	Possible
	Hepatic failure	9	15/17	Recovered/resolved	Unlikely
	Liver function tests abnormal	27	22/27	Recovered/resolved	Possible
	Bilirubinemia				
	Lymphoma like reaction	168	143/Ongoing	Not recovered/not resolved	Highly probable
	Lymphoma like reaction	367	224/248	Recovered/resolved	Highly probable
	Diarrhea	96	94/104	Recovered/resolved	Possible
	Lymphoma like reaction		94/Ongoing	Not recovered/not resolved	Probable
	Intestinal obstruction		128/128	Recovered/resolved	Unlikely

Table continued on next page

Patient ID	AEs Resulting in Discontinuation† COSTART Preferred Term	Last Dose Day	Onset/ Stop Day	Outcome	Relationship to Study Drug
Cyclosporin-ME					
≥ 5 Years					
(b) (6)	Fever	18	5/7	Recovered/resolved	Probable
	Hyperglycemia	21	5/Ongoing	Not recovered/not resolved	Possible
	Ascites	202	13/38	Recovered/resolved	Unlikely
	Drug level decreased	71	25/71	Recovered/resolved	Highly probable
	Drug level decreased	35	14/Ongoing	Not recovered/not resolved	Not assessable
	Drug level decreased	10	6/Ongoing	Not recovered/not resolved	Not assessable
	Drug level decreased	11	4/Ongoing	Not recovered/not resolved	Not assessable
	Liver function tests abnormal	166	157/Ongoing	Not recovered/not resolved	Definitely not
	EBV infection		166/Ongoing		Possible
	Diarrhea	314	298/315	Recovered/resolved	Unlikely
	Liver function tests abnormal	**85**	**69/111**	**Recovered/resolved**	**Highly probable**
	Convulsion	68	49/Ongoing	Not recovered/not resolved	Possible
	Hirsutism	**85**	**55/Ongoing**	**Not recovered/not resolved**	**Highly probable**
	Fever	39	0/Ongoing	Not recovered/not resolved	Highly probable
	Diarrhea		2/Ongoing	Not recovered/not resolved	Highly probable
	Vomiting		2/Ongoing	Not recovered/not resolved	Highly probable

AE: adverse event; COSTART: Coding Symbols for a Thesaurus of Adverse Reaction Terms; CRF: case report form; EBV: Epstein-Barr virus; ME: microemulsion.

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

3 ATTACHMENT 1 NARRATIVES OF CYCLOSPORIN PATIENTS WHO DISCONTINUED

All requested narratives were previously submitted at the time of the NDA.

		Reason(s) for Narrative								
				AEs of Interest						
Patient Number	Treatment Group	Death	Retransplant	[1]	[2]	[3]	[4]	Other SAE Not (1–4)	Non-SAE Leading to Disc.	Other Reason for Disc.
(b) (6)	CYCLOSPORIN-MICROEMULSION	X	X			X	X	X		
	CYCLOSPORIN-MICROEMULSION	X	X					X		
	CYCLOSPORIN-MICROEMULSION	X			X	X		X		
	CYCLOSPORIN-MICROEMULSION	X					X	X	X	
	CYCLOSPORIN-MICROEMULSION	X						X		
	CYCLOSPORIN-MICROEMULSION		X		X		X	X		
	CYCLOSPORIN-MICROEMULSION		X				X	X		
	CYCLOSPORIN-MICROEMULSION		X				X			
	CYCLOSPORIN-MICROEMULSION		X					X		
	CYCLOSPORIN-MICROEMULSION				X	X	X	X		
	CYCLOSPORIN-MICROEMULSION				X	X		X		
	CYCLOSPORIN-MICROEMULSION				X	X		X		
	CYCLOSPORIN-MICROEMULSION				X		X	X	X	
	CYCLOSPORIN-MICROEMULSION				X		X	X		
	CYCLOSPORIN-MICROEMULSION				X		X	X		

Table continued on next page

		Reason(s) for Narrative								
				AEs of Interest						
Patient Number	Treatment Group	Death	Retransplant	[1]	[2]	[3]	[4]	Other SAE Not (1-4)	Non-SAE Leading to Disc.	Other Reason for Disc.
(b) (6)	CYCLOSPORIN-MICROEMULSION				X		X	X		
	CYCLOSPORIN-MICROEMULSION				X			X	X	
	CYCLOSPORIN-MICROEMULSION				X			X		
	CYCLOSPORIN-MICROEMULSION				X			X		
	CYCLOSPORIN-MICROEMULSION				X					
	CYCLOSPORIN-MICROEMULSION				X					
	CYCLOSPORIN-MICROEMULSION						X	X		
	CYCLOSPORIN-MICROEMULSION						X	X		
	CYCLOSPORIN-MICROEMULSION						X	X		
	CYCLOSPORIN-MICROEMULSION						X	X		
	CYCLOSPORIN-MICROEMULSION						X		X	
	CYCLOSPORIN-MICROEMULSION						X		X	
	CYCLOSPORIN-MICROEMULSION							X	X	
	CYCLOSPORIN-MICROEMULSION							X		
	CYCLOSPORIN-MICROEMULSION							X		
	CYCLOSPORIN-MICROEMULSION								X	
	CYCLOSPORIN-MICROEMULSION								X	
	CYCLOSPORIN-MICROEMULSION								X	
	CYCLOSPORIN-MICROEMULSION								X	
	CYCLOSPORIN-MICROEMULSION								X	

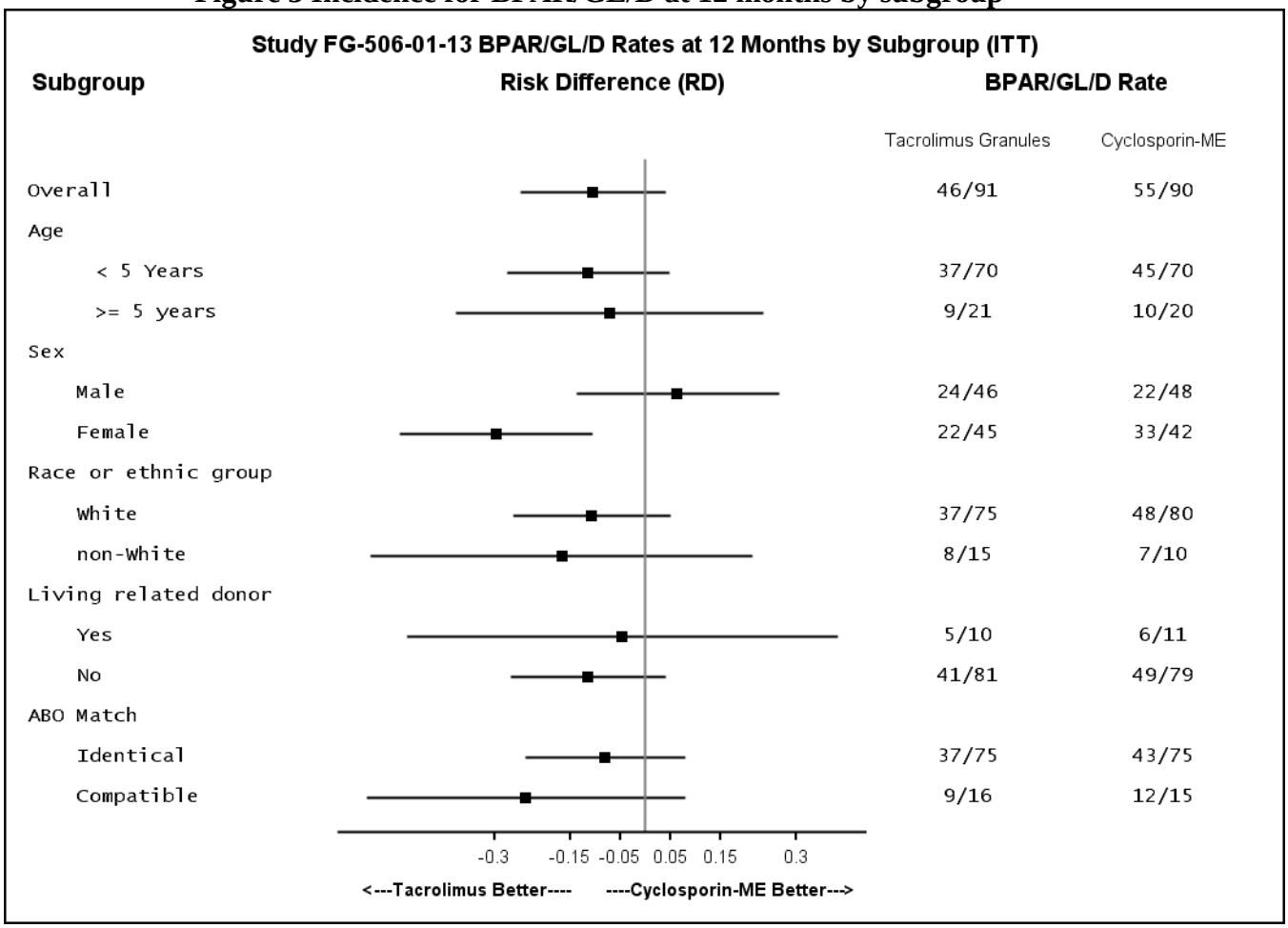
[1] Malignancy, [2] SAE Infection, [3] SAE Cardiovascular, [4] CMV, EBV and/or BK virus Infection.

AE: adverse event; CMV: cytomegalovirus; Disc.: discontinuation; EBV: Epstein-Barr virus; SAE: serious adverse event.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Figure 3 shows summary and comparison of composite endpoint of BPAR, graft loss, or death (BPAR/GL/D) at 12 months by subgroup. In addition to the common demographic factors such as gender, race and age, subgroup analyses by ABO match status and whether or not the recipient had a living related donor were also included in the forest plot for comparison. The incidence rate among males was higher (52.2%) in tacrolimus granules group than the rate (45.8%) in cyclosporin-ME group. Among females, the incidence rate in tacrolimus granules group (48.9%) was lower than the incidence rate in cyclosporin-ME group (78.6%). The 95% CI of the difference of the incidence rates of BPAR/GL/D between the tacrolimus granules group and cyclosporin-ME group among female patients [(-48.9%, -10.5%)] was below 0, which is in favor of tacrolimus granules group with respect to this composite endpoint in female subgroup. Note that the subgroup analyses results presented in this section are considered descriptive and no definitive conclusions can be drawn based on observed treatment differences between the subgroups.

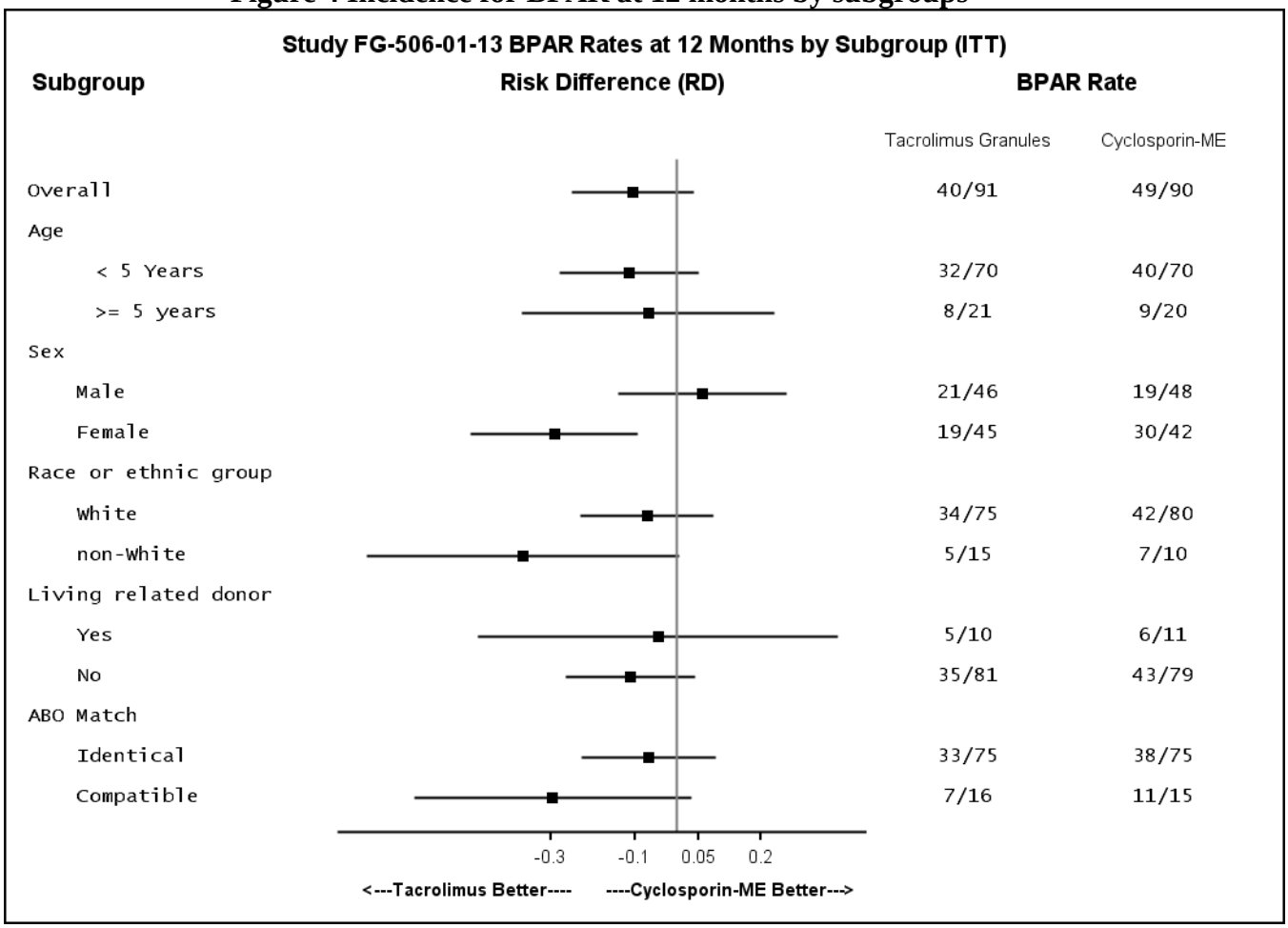
Figure 3 Incidence for BPAR/GL/D at 12 months by subgroup



Note: One patient in tacrolimus granules group had missing race information and was not included in the subgroup analysis for race.
Source: Reviewer analysis

Figure 4 shows subgroup analyses for BPAR endpoint by gender, race, age, ABO match status and whether or not the recipient had a living related donor. The BPAR rate among males was higher (45.7%) in tacrolimus granules group than the rate (39.6%) in cyclosporin-ME group. Among females, the rate of BPAR in tacrolimus granules group (42.2%) was lower than the rate in cyclosporin-ME group (71.4%). The 95% of the difference of the BPAR rates between the tacrolimus granules group and cyclosporin-ME group among female patients [(-49.1%, -9.3%)] was below 0. The female subgroup showed results in favor of the tacrolimus granules group with respect to BPAR endpoint.

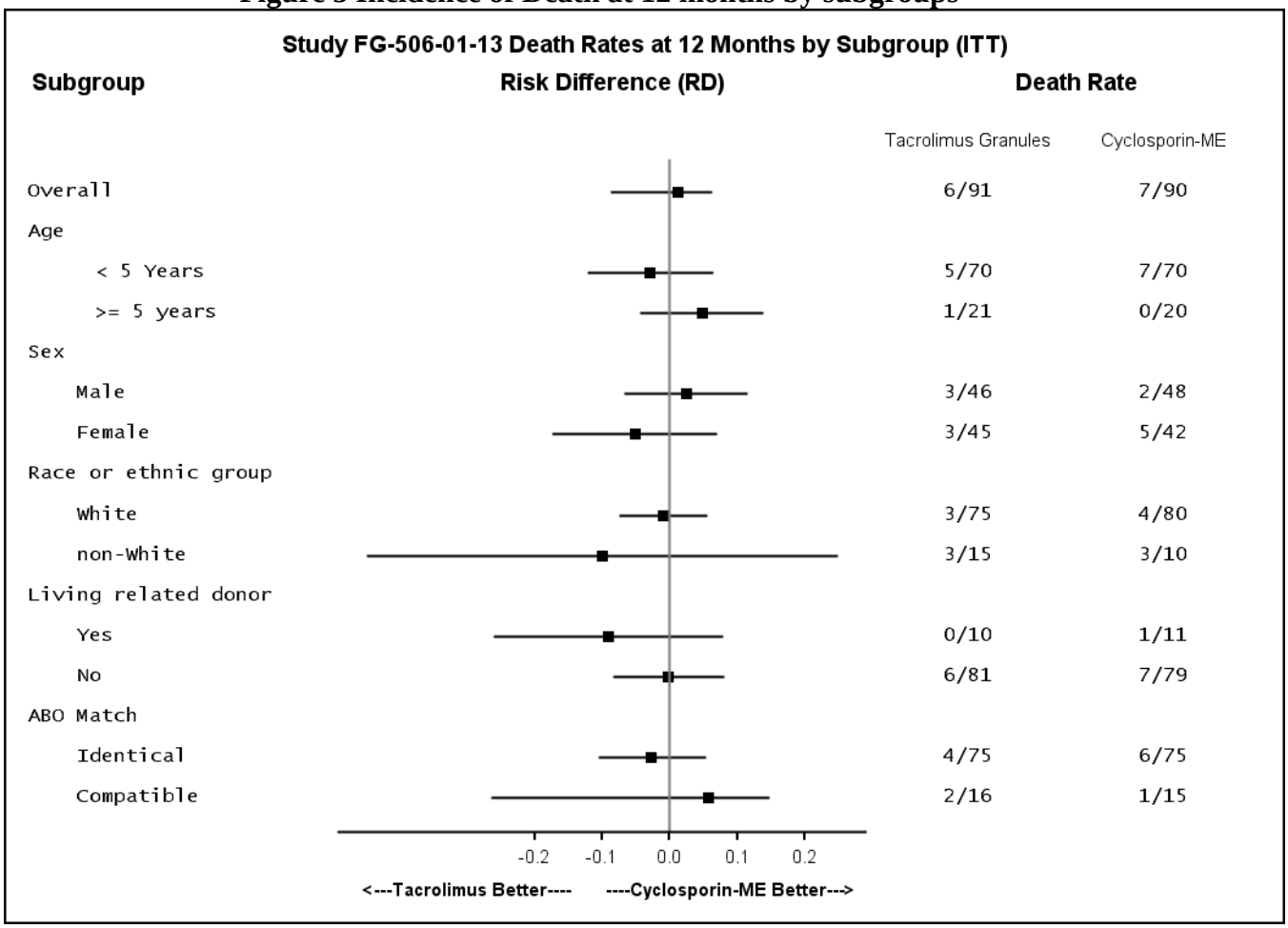
Figure 4 Incidence for BPAR at 12 months by subgroups



Note: One patient in tacrolimus granules group had missing race information and was not included in the subgroup analysis for race.
Source: Reviewer analysis

Figure 5 shows the forest plot for event of death by subgroups. None of the 95% of the difference of death rates between the tacrolimus granules and cyclosporin-ME groups in each subgroup considered in Figure 5 excluded 0. Note that conclusive statements regarding statistical significance could not be made on the magnitude of the treatment effect for any subgroup, as the study was not designed to test the treatment effect for any subgroup.

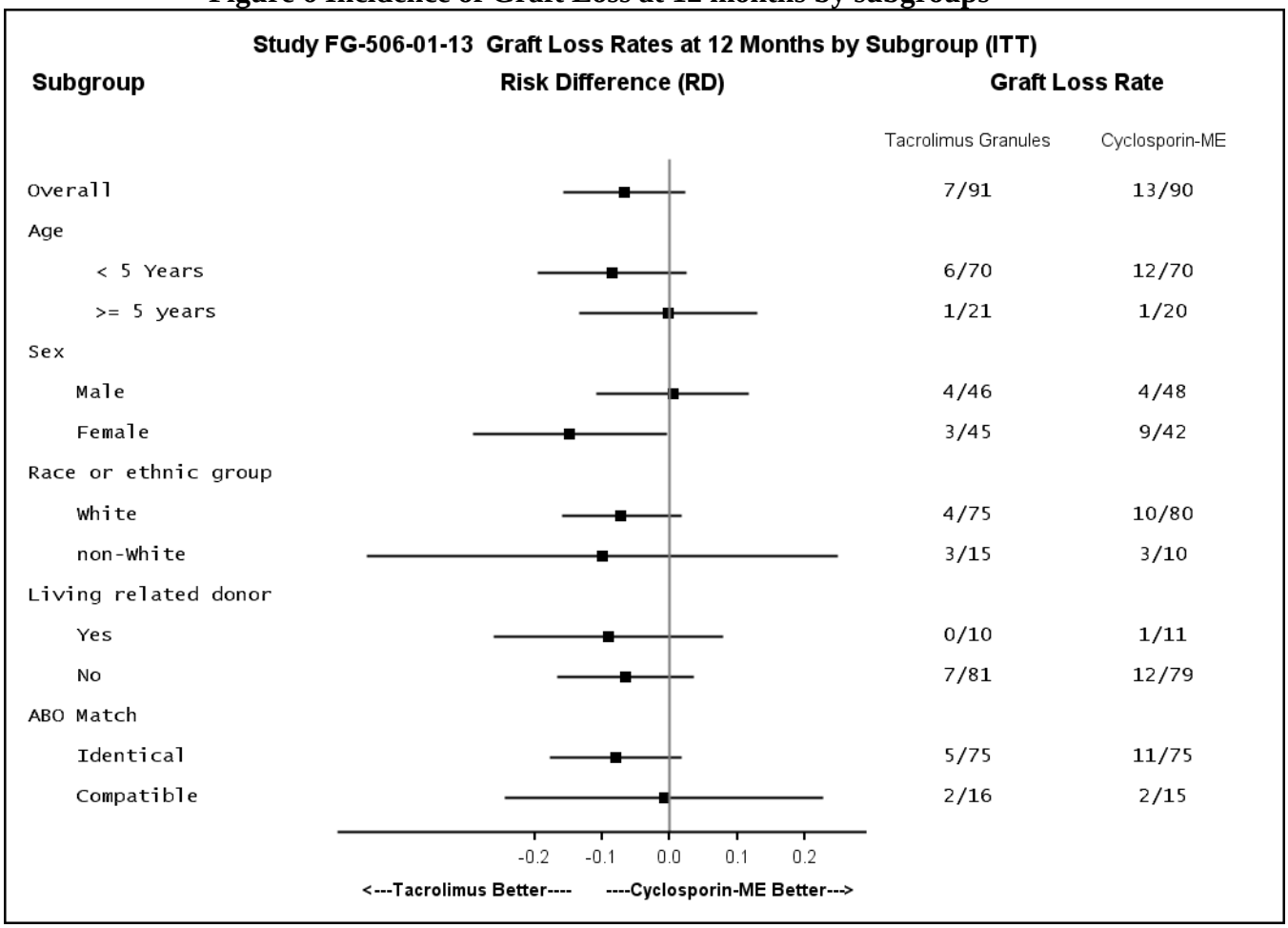
Figure 5 Incidence of Death at 12 months by subgroups



Note: One patient in tacrolimus granules group had missing race information and was not included in the subgroup analysis for race.
Source: Reviewer analysis

Figure 6 shows summary and comparison of Graft Loss endpoint at 12 months by gender, race, age, ABO match status and whether or not the recipient had a living related donor. The rate of graft loss among males was slightly higher (8.7%) in tacrolimus granules group than the rate (8.3%) in cyclosporin-ME group. Among females, the rate of graft loss in tacrolimus granules group (6.7%) was lower than the incidence rate in cyclosporin-ME group (21.4%). The 95% of the difference of the rates of graft loss between the tacrolimus granules group and cyclosporin-ME group among female patients was below 0 [(-29.2%, -0.4%)], which is in favor of tacrolimus granules group with respect to graft loss endpoint among female patients.

Figure 6 Incidence of Graft Loss at 12 months by subgroups



Note: One patient in tacrolimus granules group had missing race information and was not included in the subgroup analysis for race.
Source: Reviewer analysis

5 SUMMARY AND CONCLUSIONS

5.1 Collective Evidence

The applicant has submitted efficacy and safety data from the Study FG-506-01-13, a pediatric phase 3 study in primary liver allograft transplantation comparing a tacrolimus based (tacrolimus granules) dual drug immunosuppressive regimen with a cyclosporin-ME based triple drug immunosuppressive regimen. Specifically, the incidence rate at 12 months for composite endpoint of BPAR/GL/D (biopsy proven acute rejection/graft loss/death) was lower for the tacrolimus granules group than the incidence rate for the cyclosporin-ME group. There is no statistically significant difference on BPAR/GL/D between the two treatment groups based on either incidence rate or K-M estimate.

The incidence rate of AR (acute rejection) was lower in the tacrolimus granules group compared with the cyclosporin group. The incidence rate of BPAR was also lower in the tacrolimus granules group compared with the cyclosporin group. One more death occurred in the cyclosporin-ME group than in the tacrolimus granules group. The incidence rate of graft loss was also higher for the cyclosporin-ME group compared with the tacrolimus granules group.

5.2 Conclusions and Recommendations

In conclusion, the efficacy results of Study FG-506-01-13 are numerically in favor of tacrolimus granules group compared with the cyclosporin-ME group for both the FDA recommended composite endpoint of BPAR/GL/D and the protocol-defined primary endpoint of AR. For both endpoints, the upper limit of the 95% CI for the treatment difference in the incidence rates is less than 4%.

In the assessment of this reviewer, this study will provide useful information for healthcare professionals and patients regarding the efficacy and safety of tacrolimus treatment for pediatric liver patients, in addition to the two liver transplant studies (>12 years old) currently in the Prograf label. This reviewer recommends the addition of the safety and efficacy data of Study FG-506-01-13 in the PROGRAF® labeling (see Section 5.3 for the detailed recommendation).

5.3 Labeling Recommendations (as applicable)

The applicant proposes to add the results of Study FG-506-01-13 in Section of 14.2. The applicant's proposal for the efficacy results was discussed in Section 3.3 of this review. The following is the reviewer's proposal (the texts are from the applicant's proposed labeling):

Pediatric Liver Transplantation using PROGRAF Granules

The efficacy and safety of PROGRAF granules plus corticosteroids (b) (4) were compared with a triple regimen of cyclosporine/corticosteroids/azathioprine (b) (4) in a randomized, open-label study, in de novo pediatric liver transplant patients (b) (4)

(b) (4)

(b) (4). Doses throughout the 1 year study period were adjusted to maintain (b) (4) whole blood trough levels within 5-20 ng/mL [see Dosage and Administration (2.2)]. (b) (4)

(b) (4)

Table 26. Key Efficacy Results at 12 Months in Pediatric Liver Transplant Recipients Receiving PROGRAF for Oral Suspension or Cyclosporine

	PROGRAF granules N=91	**Cyclosporine-ME 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 Cyclosporin-ME (95% CI*)	-8.4% (-22.7%, 6.0%)	

*95% confidence interval calculated using normal approximation.

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

/s/

HONGLING ZHOU
05/15/2018

YAN WANG
05/15/2018
I concur.