

SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Europe Ltd.		
Name of Finished Product: FK506E (MR4, Advagraf®)		
Name of Active Ingredient: Tacrolimus		
Title of Study: A Multicenter, Open, Single Sequence Crossover Study to Assess the Safety and Efficacy of a Tacrolimus Modified Release, FK506E (MR4), Based Immunosuppressive Regimen in Stable Kidney Transplant Patients Converted From a Prograf® Based Immunosuppressive Regimen		
Responsible Medical Officer: Dr. [REDACTED], Astellas Pharma Europe Ltd., [REDACTED] [REDACTED]		
Coordinating Investigator: Dr. [REDACTED] [REDACTED]		
Investigator(s): [REDACTED]		
Study Center(s): 15 European centers participated in the study: Germany (2), Spain (5), France (3), Great Britain (1), The Netherlands (2), Poland (2).		
Publication (reference): None available to date.		
Study Period: Date of First Enrollment: 20 October 2006 Date of Last Evaluation: 11 July 2007		Phase of Development: Phase IIIb
Objectives: The primary objective was to assess the safety of a tacrolimus modified release, MR4 (Advagraf®), based immunosuppressive regimen in stable kidney transplant subjects converted on a 1:1 (mg:mg) basis from a Prograf® based immunosuppressive regimen. Non-inferiority for creatinine clearance was assessed. The secondary objective was to assess the safety and the efficacy of this treatment.		
Study Design: This was a multicenter, open, single sequence crossover study. On study enrollment (Week -6), the twice daily Prograf® regimen was replaced by a twice daily Prograf regimen as study medication. Subjects entered the 6-week Prograf-Treatment Phase to confirm compliance to regimen stability requirements and collect data under Prograf therapy. On completion of the Prograf-Treatment Phase and qualifying for entry into the MR4-Treatment Phase, Prograf total daily dose (morning and evening dose) was converted to MR4 once daily (morning dose) on a 1:1 (mg:mg) basis on Day 1 of the MR4-Treatment Phase. Subjects continued taking MR4 once daily treatment and were followed for 12 weeks with study assessments for safety and efficacy to evaluate the primary and secondary variables. All concomitant immunosuppressive medications used in combination with Prograf® prior to enrollment were maintained at a constant dose throughout the duration of the study.		
Diagnosis and Main Criteria for Inclusion: Male or female subjects with minimum 18 years of age; stable condition following a kidney transplantation at least 12 months prior to study enrollment; unchanged dose of Prograf® over 12 weeks prior to enrollment; tacrolimus blood trough level between 5–15 ng/mL. Additional inclusion criteria to enter the MR4-Treatment Phase were: stable dose of Prograf; unchanged dose of concomitant immunosuppressive medications during the Prograf-Treatment Phase; mean tacrolimus blood trough levels werewithin the recommended range of 5–15 ng/mL during the Prograf-Treatment Phase.		
Number of Subjects (planned and analyzed): Assuming a decrease in creatinine clearance of 5% using MR4 treatment (corresponding to 3.5 mL/min) and a standard deviation for the pre-post		

difference of 15% (10.5 mL/min) of the reference mean (Prograf), a total of 100 subjects would have a power of more than 90% to assess non-inferiority of MR4 with a 10% pre-defined non-inferiority margin. Assuming 20% as the rate of subjects to be excluded from the per protocol population, the analysis set for the primary analysis, approximately 125 subjects were to be enrolled to yield 100 evaluable subjects. The analyzed per protocol population consisted of 91 subjects.

Test Product, Dose And Mode of Administration:

Prograf 0.5 mg, 1.0 mg and 5.0 mg capsules.

Prograf administered orally:

Prograf capsules were administered twice daily (morning and evening).

Prograf dosing:

During the Prograf-Treatment Phase, the Prograf dose was to remain unchanged and the mean tacrolimus blood trough levels were to be between 5–15 ng/mL for the subject to enter into the MR4-Treatment Phase. Prograf was administered for the first 6 weeks of the study during the Prograf-Treatment Phase.

MR4: 0.5 mg, 1 mg and 5 mg capsules.

MR4 administered orally:

The total daily dose of Prograf at Day -1 was to be converted at 1:1 (mg:mg) on Day 1 to MR4 administered once daily in the morning.

MR4 dose modification:

Following conversion to MR4, tacrolimus blood trough levels were to be monitored and dose adjustments made to maintain a similar systemic exposure. Attempts were to be made to maintain a constant dose of MR4 for the duration of the study. Dose modifications could only be made if:

- indicated by clinical signs, and/or
- tacrolimus blood trough levels deviated by greater than 20% from the mean of the levels taken during the Prograf-Treatment Phase.

Recommended tacrolimus blood trough levels during the MR4-Treatment Phase were 5–15 ng/mL.

Lot Numbers: FK506: 0.5 mg, [REDACTED]; 1.0 mg, [REDACTED]; 5.0 mg, [REDACTED].

MR4: 0.5 mg, [REDACTED] ([REDACTED]); 1.0 mg, [REDACTED] ([REDACTED]); 5.0 mg, [REDACTED] ([REDACTED]).

Duration of Study and Treatment: Subjects were followed for 6 weeks during the Prograf-Treatment Phase of the study. Four assessment visits took place during this phase. Following conversion to MR4, subjects were followed for 12 weeks during which seven assessment visits took place.

Criteria for Evaluation: The primary study variable was the change in calculated creatinine clearance (Cockcroft and Gault formula) between Prograf and MR4 at steady state. The secondary variables assessed were: change in blood pressure and change in HbA_{1c} between Day -1 and Week 12; incidence of adverse events (AEs); frequency of biopsy-proven acute rejection episodes (BPAR); subject and graft survival.

Statistical Methods:

Analysis sets: Full analysis set (FAS): All subjects who received at least one dose of study drug in each treatment phase (Prograf and MR4) with sufficient data to derive the primary variable at least once during each treatment phase.

Per protocol set (PPS): All subjects in the FAS without major protocol violations and with sufficient data for the primary variable at least once during the steady state phase for each treatment (Week -6 to Day -1 for Prograf, and Week 6 to Week 12 for MR4).

Safety analysis set (SAF): All subjects who received at least one dose of study drug with any data reported thereafter.

Analysis of the primary variable as well as of relevant baseline characteristics was based on the FAS and PPS. The primary analysis was based on the PPS; an analysis based on the FAS was used to assess the robustness of the results of the primary analysis. Analysis of subject survival, graft survival and AEs was based on the SAF. Analysis of all other secondary variables was based on the FAS.

If non-inferiority is shown for any analysis set, then a test for superiority will be performed for the FAS and PPS sets [in accordance with CPMP/EWP/482/99: Points to Consider on Switching Between Superiority and Non-Inferiority, July 2000].

Primary variable: Creatinine clearance was calculated using the Cockcroft and Gault formula.

The comparison of creatinine clearance was based on the lower limit of the two-sided 95% confidence interval (CI) (corresponding to a one-sided significance level of $\alpha = 2.5\%$) for the relative difference of population means $((\mu_{MR4} - \mu_{Prograf}) / \mu_{Prograf})$, which should lie above the acceptance limit of -10% of the Prograf mean for concluding non-inferiority. Analysis was performed using an appropriate ANOVA for repeated measurements of non-transformed data with Prograf as reference that included the data from scheduled visits Week -6 to Day -1 and Week 6 to Week 12.

Secondary variables: All safety parameters were summarized for the Prograf-Treatment Phase and the MR4-Treatment Phase using appropriate descriptive statistics. All time related analyses referred to the first day of the respective treatment during the study.

The change from Day -1 to Week 12 in blood pressure and HbA_{1c} was summarized for the FAS. The incidences of AEs were summarized for the SAF by MedDRA preferred term. A biopsy of the renal graft was to be performed if clinical or laboratory signs indicated the occurrence of a rejection episode. Subject and graft survival were summarized for the SAF by overall frequencies. Tacrolimus blood trough levels were summarized over time for the PPS and FAS populations.

RESULTS:

Analysis Sets and Subject Disposition:

The number of subjects included in each of the sets used for study analysis is presented in the following table:

Table 1: Disposition of Subjects

	Number of Subjects
Enrolled	128 (100.0)
Safety analysis set (SAF)	127 (99.2)
Full analysis set (FAS)	115 (90.6)
Per protocol analysis set (PPS)	91 (79.1)
Completers	114 (89.8)
Premature study withdrawal:	14 (10.2)
Before Prograf-Treatment Phase	1 (0.7)
During Prograf-Treatment Phase	11 (8.0)
During MR4-Treatment Phase	2 (1.4)

Twelve subjects (9.4%) were not included in the FAS because they either did not receive Prograf (1 subject) or MR4 (11 subjects). Further, 24 subjects (20.9%) in the FAS were excluded from the PPS. Reasons for exclusion from the PPS were: change of immunosuppressive medication for ≥ 7 consecutive days (5/4.3%), change of immunosuppressive regimen within 12 weeks prior to enrollment (1/0.9%), inappropriate enrollment (1/0.9%), major violation of inclusion or exclusion criteria (4/3.5%), non-compliance to tacrolimus dose adjustment schedule (13/11.3%).

For purposes of this report and in adherence to the study protocol, results of the primary variable, study population demographics, and immunosuppressive therapy are reported for the PPS. Results of subject and graft survival and AEs are presented for the SAF. Results of all other secondary variables are presented for the FAS.

Demographics:

The mean (\pm SD) age of subjects was 48.9 years (\pm 11.8), 73.6% of subjects were male, 98.9% were Caucasian, and 80.2% had received an organ from a deceased donor. CMV status of donors (D) and recipients (R) was D+/R- 54.8%/34.8%. The mean time since kidney transplant was 48.9 months (\pm 28.6). An overwhelming majority of subjects presented with a medical history of hypertension (90.1%) followed by hypercholesterolemia (29.7%) and hyperlipidemia (11.0%) which were on-going at the time of transplantation.

Study Drug Exposure:

The mean daily dose of Prograf at Day -1 after 6 weeks of treatment was 0.06 mg/kg (\pm 0.03). Similarly, the mean daily dose of MR4 at Week 12 after 12 weeks of treatment was 0.07 mg/kg (\pm 0.03). During the MR4-Treatment Phase seven subjects required a decrease in the dose of study drug: six subjects required one dose adjustment and one subject required two dose adjustments. Forty-four subjects required an increase in MR4 dose: 29 required one adjustment, nine required two adjustments, and six required three dose adjustments.

Mean tacrolimus trough levels were at the lower levels of the recommended range during the Prograf-Treatment Phase. Mean trough levels were lower one week after switching to MR4 then showed a slight increasing trend during the MR4-Treatment Phase, but remained at the lower level of the recommended range during this treatment phase as depicted in the following table:

Table 2: Tacrolimus Trough Levels (ng/mL) during Study Time Periods (PPS)

Visit	N	Mean (SD)	Minimum	Median	Maximum
<i>Prograf- Treatment Phase</i>					
Week -6	91	7.32 (2.26)	4.0	7.1	15.0
Week -4	87	6.96 (1.91)	3.7	6.4	14.0
Week -2	87	7.11 (1.73)	4.0	7.1	11.6
Day -1	84	7.21 (2.09)	3.4	6.7	14.1
<i>MR4- Treatment Phase</i>					
Week 1	90	6.29 (1.99)	2.8	6.1	13.2
Week 2	87	6.10 (1.82)	1.9	6.0	10.4
Week 4	91	6.28 (1.88)	3.1	5.7	11.6
Week 6	90	6.42 (1.93)	1.5	6.5	11.5
Week 8	90	6.62 (1.82)	3.1	6.5	13.9
Week 10	86	6.75 (1.89)	2.6	6.4	13.4
Week 12	88	7.00 (2.13)	3.2	6.7	13.8

Primary Variable: Non-inferiority of MR4 against Prograf was demonstrated with a relative difference in mean calculated creatinine clearance of -0.7% (\pm 5.33), the 95% CI for relative difference [-1.8; 0.5] was well above the set non-inferior margin of -10% of the Prograf mean (PPS population). Superiority of MR4 against Prograf was not shown as the CI crossed 0. Results of the primary variable are presented in Table 3.

Table 3: Mean Creatinine Clearance during Steady State Phase: Results of the Test Procedure for Non-Inferiority (PPS)

	Steady State Phase		Absolute Difference MR4 – Prograf (mL/min)	Relative Difference MR4 – Prograf (%)
	Prograf-Treatment Phase ^a (mL/min)	MR4-Treatment Phase ^b (mL/min)		
N	91	91	91	91
Mean (SD)	72.5 (20.9)	72.1 (21.7)	-0.4 (4.0)	-0.7 (5.3)
Minimum	42.3	40.2	-9.2	-14.6
Median	71.0	70.1	-0.6	-0.7
Maximum	162.3	177.7	15.5	12.2
95% CI ^c	[68.2; 76.9]	[67.6; 76.7]	[-1.2; 0.4]	[-1.8; 0.5]

^a Week -6 to Day -1; ^b Week 6 to Week 12; ^c arithmetic mean.

Efficacy Results:

There were no incidences of BPAR during either the Prograf-Treatment Phase or during the MR4-Treatment Phase. There were no incidences of clinical acute rejection (diagnosed per signs and symptoms) during either treatment phase.

Safety Results:

Subject survival: The estimated subject survival rate (Kaplan-Meier method) was 100% at the end of the study (based on the SAF population).

Graft survival: The estimated graft survival rate (Kaplan-Meier method) was 100% at the end of the study (based on the SAF population).

Adverse events: The incidence of serious AEs was very low in each group. There were no incidences of AEs which lead to dose modification or to study withdrawal during either treatment phase.

Table 4: Overall Summary of the Incidence of Adverse Events (SAF)

	Prograf-Treatment Phase N=126		MR4-Treatment Phase N=116	
	N (%)	Nr. events	N (%)	Nr. events
Adverse events	28 (22.2)	33	29 (25.0)	41
Causally-related adverse events	8 (6.3)	9	7 (6.0)	9
Serious adverse events	1 (0.8)	1	2 (1.7)	9
Causally-related serious adverse events	0 (0.0)	0	0 (0.0)	0

The incidence of the most commonly reported AEs for the SAF set was generally higher during the MR4-Treatment Phase; however the duration of this treatment was 12 weeks compared with 6 weeks for the Prograf-Treatment Phase. Similar types of AEs were reported during both treatment phases. Infection was the most commonly reported adverse event during both of the treatment phases and was followed by metabolism/nutritional disorders and vascular disorders. The AEs reported during the study are consistent with the established safety profile of tacrolimus.

Table 5: Most Frequently Reported ^a Adverse Events Regardless of Relationship to Study Medication (SAF)

MedDRA Primary SOC MedDRA High Level Term <i>MedDRA Preferred Term</i>	Prograf Treatment-Phase N=126		MR4 Treatment-Phase N=116	
	N (%)	Nr. events	N (%)	Nr. events
Infections/infestations	7 (5.6)	7	14 (12.1)	15
Upper respiratory tract, pathogen unspecified	2 (1.6)	2	6 (5.2)	6
Metabolism/nutrition disorders	5 (4.0)	5	3 (2.6)	3
Vascular disorders	1 (0.8)	1	6 (5.2)	7
Vascular hypertension disorders NEC	1 (0.8)	1	5 (4.3)	5
<i>Hypertension</i>	1 (0.8)	1	5 (4.3)	5
Respiratory/thoracic/mediastinal disorders	4 (3.2)	4	0 (0.0)	0

^a Reported in at least 3% of subjects during either treatment phase. Coded using MedDRA version 6.1.
SOC=system organ class. NEC=not elsewhere classified.

There were no AEs or serious AEs of causal relationship to the study medication, as assessed by the investigator, which were reported in $\geq 3\%$ of subjects during either treatment phase.

There was no clinically relevant difference found in mean blood pressure measurements (derived from 24-hour ambulatory blood pressure monitoring) between Week 12 and Day -1. Changes in HbA_{1c} in subjects who were non-diabetic were unremarkable.

Table 6: Mean (SD) Differences in Blood Pressure and HbA_{1c} from Week 12 to Day -1 (FAS)

	Arterial Blood Pressure (mmHg) ^a	HbA _{1c}
N	107	54 ^b
Day -1	101.3 (10.1)	5.2 (0.8)
Week 12	100.9 (10.1)	5.3 (0.8)
<i>Difference</i>	-0.3 (5.9)	0.04 (0.2)

^a Derived from 24-hour ambulatory blood pressure monitoring. ^b Non-diabetic subjects.

CONCLUSIONS:

Non-inferiority of MR4 against Prograf was demonstrated using mean calculated creatinine clearance. Results of both safety and efficacy were excellent following treatment with Prograf for 6 weeks and MR4 for 12 weeks in this population of renal transplant recipients. The type of AEs reported during both treatment phases is consistent with the established safety profile of tacrolimus. The incidence of the most commonly reported AEs was generally higher during the MR4-Treatment Phase; however the duration of this treatment was twice as long as that for the Prograf-Treatment Phase.

Immunosuppressive coverage was sufficient during both treatment phases as evidenced by no incidences of BPAR. Mean tacrolimus levels were stable during the Prograf-Treatment Phase, were lower one week after switching to MR4, then showed a slight increasing tendency during the MR4-Treatment Phase. Although approximately 48% of subjects required an increase in dose of MR4, mean levels were at the lower level of the recommended range.

Date of Report: 31 October 2008