SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Europe B.V. / Europe Ltd.		
Name of Finished Product: FK506E (MR4)		
Name of Active Ingredient: Tacrolimus		

Title of Study: A Multicenter, Single-arm, Open, Conversion Study from a Cyclosporine (CyA) Based Immunosuppressive Regimen to a Tacrolimus Modified Release, FK506E (MR4), Based Immunosuppressive Regimen in Kidney Transplant Subjects (CONCERTO: ***Con***verting ***C***yclosporine to FK506***E*** (MR4) in ***R***enal ***T***ransplantati***o***n)

Responsible Medical Officer: Dr. [redacted] Astellas Pharma Europe Ltd., [redacted]

Investigator(s):
[redacted]

Study Center(s): The study was conducted at 48 clinical sites in 12 European countries which were: Austria, Belgium, Switzerland, Czech Republic, Germany, Spain, Finland, France, Hungary, Italy, Poland, and Sweden.

Publication (reference): None available to date.

Study Period: **Date of First Enrollment:** 16 April 2007 **Date of Last Evaluation:** 16 April 2009	**Phase of Development:** Phase IIIb

Objectives: Primary objective was to assess changes in kidney function in kidney transplant subjects converted from a cyclosporine A (CyA) based immunosuppressive regimen to a tacrolimus modified release, FK506E (MR4, Advagraf®), based immunosuppressive regimen. Reason for conversion was the occurrence of CyA-related side effects such as hyperlipidemia, hypertrichosis/hirsutism, arterial hypertension, gingival hyperplasia.

The secondary objective of the study was to assess the safety and the efficacy of an Advagraf-based immunosuppressive regimen in kidney transplant subjects converted from a CyA-based immunosuppressive regimen because of CyA-related side effects.

Study Design: Multicenter, single-arm, open, phase IIIb conversion study in which a CyA-based immunosuppressive regimen was replaced by the administration of tacrolimus modified release formulation, Advagraf, once daily (morning dose only) in stable renal transplant subjects.

Diagnosis and Main Criteria for Inclusion: Adult kidney transplant subjects aged 18 years and older on a stable CyA-based immunosuppressive regimen experiencing CyA-related side effects (hyperlipidemia, hypertrichosis/hirsutism, arterial hypertension, gingival hyperplasia). Kidney transplant was at least 12 months prior to enrollment and serum creatinine was < 200 µmol/L (< 2.3 mg/dl) at enrollment.

Number of Subjects (planned and analyzed): The total number of subjects to be included in the trial was 380; results of previous conversion trials were used as reference for the sample size estimation which was based on the following assumptions: a) Type I error: $\alpha = 0.625\%$ (adjusted for multiple testing of four comparisons to be done to control the overall error rate of one-sided $\alpha = 2.5\%$); b) Type II error: ß = 20%; c) Non-inferiority margin: $\Delta = -10\%$ of the mean creatinine clearance for CyA; d) Relative change of creatinine clearance under Advagraf treatment compared to baseline value under CyA: -3% ± 17.5% (mean ± SD); e) Test procedure: two-sided confidence interval based on one-sample t-test; f) n required: n = 75 per group providing a total n = 300 to show non-inferiority in all four groups of CyA-related side effects. The number of subjects enrolled in this study was 346 and the number analyzed was 339 in the Full Analysis Set (FAS), 301 in the Per Protocol Set (PPS) and 343 in the Safety Set (SAF).

Test Product, Dose and Mode of Administration: The CyA immunosuppressive medication was replaced at baseline (day 1) by the initial recommended oral dose of 0.1 mg/kg/day Advagraf administered once a day in the morning. The first dose of Advagraf was administered 12 hours after the last dose of CyA.
Following conversion to Advagraf at the recommended initial dose, tacrolimus trough levels were monitored and dose adjustments made to reach a trough level of 10 ng/ml (range 5 to 15 ng/ml) for the first 4 weeks. Trough levels were progressively reduced to 7 ng/ml (range 4 to 10 ng/ml) until the end of the study.

Lot Numbers:
Advagraf 0.5 mg: [redacted] and [redacted]; Advagraf 1.0 mg: [redacted] and [redacted];
Advagraf 5.0 mg: [redacted] and [redacted]

Duration of Study and Treatment: A study duration of 24 weeks was considered to be appropriate to assess changes in kidney function in subjects and to evaluate the changes in CyA-related side effects.

Criteria for Evaluation: The primary study variable was the change in calculated creatinine clearance (Cockcroft and Gault method) between baseline (day 1) and week 24 (End of Study [EOS]) for each specific CyA-related side effect group (hyperlipidemia, Group A; hypertrichosis/hirsutism, Group B; arterial hypertension, Group C; gingival hyperplasia, Group D).

Secondary variables assessed were: Change in calculated creatinine clearance (Cockcroft and Gault method) between baseline (day 1) and week 24 (EOS) in all subjects; changes in mean lipid levels (total cholesterol, TG, LDL and HDL) and the number of lipid lowering medications used between baseline (day 1) and week 24 (EOS) for Group A and all subjects; changes in mean arterial blood pressure and number of antihypertensive medications used between baseline (day 1) and week 24 (EOS) for Group C and all subjects; investigator rating of subject's clinical status at week 24 (EOS) for each specific CyA-related side effect group; subject rating of clinical status at week 24 (EOS) for those subjects in Group B and Group D; overall frequency of biopsy-proven acute rejection episodes for each specific CyA-related side effect group and in all subjects. The safety of the implemented treatment was assessed by evaluating subject and graft survival, incidence of treatment emergent adverse events (TEAEs), clinical laboratory variables and vital signs.

Statistical Methods: *Analysis sets:* The full analysis set (FAS) includes all subjects who received at least one dose of Advagraf after conversion from a CyA-based immunosuppressive regimen and at least one assessment thereafter. The per protocol set (PPS) includes all subjects from the FAS who were not withdrawn from the study prematurely and did not have any major protocol violations. The safety analysis set (SAF) includes all subjects who took at least one dose of Advagraf after conversion.

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 secondary study variables was based on the PPS and the FAS. The SAF was used for the statistical summary of the safety data.

Primary variable: The null and alternative hypotheses for this study were:

$H_{0i} : r_i \leq \Delta$ versus $H_{1i} : r_i > \Delta$

Where r_i is the relative change in creatinine clearance (Cockcroft and Gault method) in group *i* (*i*=1, 2, 3, 4) and Δ = non-inferiority margin, specified as -10% of the mean creatinine clearance for the CyA phase. Relative changes were analyzed using an ANOVA model with CyA-related side effect and center as fixed factors. Centers were pooled based on the number of recruited subjects: small (≤ 5 subjects enrolled), medium (6 to 15 subjects enrolled), and large (> 15 subjects enrolled).

For each hypothesis $H_{(i)}$ two sided confidence interval $CI_{(i)}$ adjusted for multiplicity using the Bonferroni-Holm method, which controls the family-wise 2-sided error rate at the $\alpha = 0.05$ level, were calculated.

If non-inferiority was shown in any particular CyA-related side effect group, then a test for superiority was to be performed (in accordance with CPMP "Points to consider on switching between superiority and non-inferiority", July 2000) without further alpha level adjustment on the FAS.

Due to increasing clinical importance of the MDRD formula (Modification of Diet in Renal Disease), renal function was assessed by calculated glomerular filtration rate (GFR) using this formula. Exploratory analysis on GFR was conducted in a similar way as for the primary variable.

Secondary variables: Secondary variables were analyzed in a descriptive manner. Kaplan-Meier estimates and confidence intervals (Greenwood formula) were calculated for all categories of acute rejection defined as secondary endpoints as well as for subject and graft survival.

RESULTS:

Analysis Sets and Subject Disposition:

Of the 346 subjects enrolled in the study, 3 subjects enrolled in Group D were not eligible for study participation as they were not converted from CyA to Advagraf. A total of 4 subjects were included in the SAF but excluded from the FAS because of a missing creatinine clearance after baseline (1 subject) and not exhibiting any of the designated CyA-related side effects at enrollment (3 subjects). These subjects did receive one dose of Advagraf and were therefore included in the SAF.

Table 1: Populations for Analysis

	Hyperlipidemia Group A	**Hypertrichosis Group B**	**Arterial hypertension Group C**	**Gingival hyperplasia Group D**	**Total**
Subjects enrolled	**49**	**114**	**93**	**87**	**346†**
Not converted	0	0	0	3	3
Safety analysis set	**49**	**114**	**93**	**84**	**343†**
Excluded from FAS	0	0	1	0	4 †
Full analysis set	**49**	**114**	**92**	**84**	**339**
Excluded from PPS	7	8	15	8	38
Per protocol set	**42**	**106**	**77**	**76**	**301**

A subject may have had > 1 reason for exclusion from a population. † 3 subjects were ineligible for study enrollment because of not exhibiting a primary CyA side effect at the time of study enrollment; they were, however, included in the total of subjects enrolled and in the SAF because they received one dose of Advagraf.

Approximately 92% of all subjects completed the study with similar percentages of subjects in each group completing the study. Twice as many subjects in Group A than in Groups B, C, or D were prematurely withdrawn from the study due to an adverse event. In no group was there one single adverse event which accounted for the majority of premature study discontinuations.

Table 2: Subject Disposition – Number (%) of Subjects - SAF

	Hyperlipidemia Group A N=49	Hypertrichosis Group B N=114	Arterial hypertension Group C N=93	Gingival hyperplasia Group D N=84	Total N=343
Completed	**44 (89.8)**	**108 (94.7)**	**85 (91.4)**	**78 (92.9)**	**315 (91.8)**
Died	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (1.2)**	**1 (0.3)**
During study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
After withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.3)
Premature discontinuation	**5 (10.2)**	**6 (5.3)**	**8 (8.6)**	**6 (7.1)**	**28 (8.2)†**
Inappropriate enrollment	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	2 (0.6)
Adverse event‡	5 (10.2)	4 (3.5)	3 (3.2)	4 (4.8)	17 (5.0)
Consent withdrawn	0 (0.0)	2 (1.8)	4 (4.3)	0 (0.0)	7 (2.0)
Non-compliance	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.2)	2 (0.6)

† 3 subjects were ineligible for study enrollment but were included in the total of subjects enrolled and in the SAF because they received one dose of Advagraf. ‡ Other than death or graft loss.

Demographics:

The mean age of all subjects included in the FAS was 51.4 ± 12.2 years and the majority was male (59.6%) Caucasian (96.5%). The median time since transplant for all subjects was 87.3 months or approximately 7 years and ranged from 66.6 to 96.9 months in the groups. The median (min, max) duration of CyA-related side effects in months in Groups A, B, C, and D, respectively, was: 48.2 (2, 215), 66.3 (0, 247), 112.2 (0, 447), and 16.8 (0, 207).

Study Drug Exposure:

The median (min, max) total daily dose and median (min, max) trough levels of Advagraf for all groups are presented in Table 3. During the first 4 weeks, tacrolimus trough levels were well within the targeted range of 5 to 15 ng/mL in all groups. At month 6, median trough levels were within the protocol-defined range of 4 to 10 ng/mL in all groups.

Table 3: Advagraf Exposure - SAF

	Hyperlipidemia Group A N=49	Hypertrichosis Group B N=114	Arterial hypertension Group C N=93	Gingival hyperplasia Group D N=84
Total daily dose at week 24 (mg/kg), Median (min, max)	0.068 (0.02, 0.22)	0.064 (0.01, 0.17)	0.062 (0.01, 0.19)	0.071 (0.01, 0.17)
Mean tacrolimus trough level (ng/mL), Median (min, max):				
Week 1	11.9 (1.0, 27.6)	8.5 (1.0, 44.8)	11.0 (1.0, 30.0)	12.0 (3.3, 25.1)
Week 4	6.8 (3.4, 20.9)	8.9 (4.0, 16.2)	8.8 (3.2, 17.7)	8.0 (1.9, 17.9)
Month 2	7.3 (3.5, 13.6)	7.3 (2.3, 12.8)	7.9 (1.2, 19.4)	8.0 (1.3, 16.3)
Month 3	5.8 (2.9, 12.2)	6.6 (2.5, 16.7)	7.0 (2.9, 20.0)	7.9 (4.0, 14.6)
Month 4	6.1 (3.6, 11.4)	7.4 (3.4, 16.1)	7.2 (1.9, 18.0)	7.4 (3.4, 12.9)
Month 5	7.0 (3.7, 11.8)	6.8 (4.3, 13.9)	6.9 (3.8, 13.5)	8.1 (4.1, 14.0)
Month 6	6.4 (2.3, 12.3)	7.0 (1.3, 15.9)	6.9 (1.2, 13.7)	7.6 (2.1, 16.0)

An adjustment in dose of Advagraf was permitted to either maintain or attain the targeted trough level of tacrolimus. The majority of all subjects required 1 or 2 adjustments in dose (increases or decreases) to achieve targeted levels. The majority of subjects requiring ≥ 3 dose adjustments required a decrease in tacrolimus dose. In very few subjects was it necessary to interrupt Advagraf and in the majority of incidences of dose interruption, 1 interruption of dose was necessary. A change in immunosuppressive regimen from baseline to week 24 was made in 10 subjects; changes were restricted to an addition or deletion of an adjunct immunosuppressive agent.

Efficacy Results:

Primary efficacy variable. Calculated creatinine clearance values (Cockcroft and Gault method) at week 24 using Advagraf did not on average lead to a substantial reduction in renal function, i.e., a decrease of 10% in calculated creatinine clearance as measured by the Cockcroft and Gault method. This result was found in all four groups using the PPS and is confirmed by the *P*-values reached during analysis. Superiority of creatinine clearance values at week 24 using Advagraf compared to baseline creatinine clearance values using CyA was not confirmed in any of the groups.

An analysis of the primary variable was performed on the FAS to assess the robustness of the testing performed on the PPS: FAS results supported those found using the PPS.

Table 4: Primary Endpoint Analysis: Relative Change in Creatinine Clearance from Baseline to Week 24 (Cockcroft-Gault Method) - PPS

	Hyperlipidemia Group A N=42	**Hypertrichosis Group B N=106**	**Arterial hypertension Group C N=77**	**Gingival hyperplasia Group D N=76**
Relative change, LS mean (SE)	-5.28 (2.192)	0.93 (1.401)	-0.06 (1.555)	-0.99 (1.614)
Confidence interval†	-9.59 to -0.97	-2.59 to 4.45	-3.80 to 3.68	-4.63 to 2.65
Significance level†	0.025	0.00625	0.00833	0.0125
***P*-value ‡**	0.0161	< 0.0001	< 0.0001	< 0.0001
Increasing order of *P*-values	4	1	2	3
***P*-value §**	0.9917	0.2537	0.5155	0.7298

†Obtained using the Bonferroni-Holm method for testing multiple comparisons. ‡Test for non-inferiority (non-inferiority margin: -10%) for the relative change in creatinine clearance from baseline to week 24 by means of an ANOVA model with CyA-related side effect group and pooled center as fixed factors. §Test for superiority for the relative change in creatinine clearance from baseline to week 24 by means of an ANOVA model with CyA-related side effect group and pooled center as fixed factors.

Using the MDRD formula, the calculated creatinine clearance values at week 24 using Advagraf did not show a difference of > -10% from baseline using CyA for all four groups in the PPS. Superiority of creatinine clearance values at week 24 using Advagraf compared to baseline using CyA was not confirmed in any of the groups. There were slight differences in relative changes in creatinine clearance using the MDRD formula compared with the Cockcroft-Gault formula, most notably in Groups B and C. In both groups, the relative change in calculated creatinine clearance was greater using MDRD as compared with Cockcroft-Gault: Group B, 1.64 vs. 0.93%; Group C, 1.31 vs. -0.06%.

Secondary efficacy variables. Relative change from baseline to week 24 in creatinine clearance was < 1.0% and mean absolute change was a decrease of 1.0 mL/min in All Subjects (Groups A, B, C, D). Both absolute and relative changes in mean creatinine clearance showed the greatest decrease in Group A as depicted in Table 5 below.

Table 5: Change in Creatinine Clearance (Cockcroft-Gault Method) between Baseline and Week 24 – FAS

	Hyperlipidemia Group A N=49	Hypertrichosis Group B N=114	Arterial hypertension Group C N=92	Gingival hyperplasia Group D N=84	All Subjects N=339
Baseline, Mean (SD), mL/min	59.4 (19.6)	63.6 (21.0)	59.0 (19.7)	64.3 (19.8)	61.9 (20.2)
Week 24, Mean (SD), mL/min	55.8 (17.4)	63.7 (20.9)	57.9 (20.5)	63.5 (20.5)	60.9 (20.4)
Absolute change †, Mean (SD), mL/min Confidence interval	-3.58 (10.0) -6.4 to -0.7	-0.13 (8.7) -1.5 to 1.7	-1.12 (8.6) -2.9 to 0.6	-0.82 (9.3) -2.8 to 1.2	-0.98 (9.1) -2.0 to -0.0
Relative change ‡, Mean (SD), %	-4.94 (15.0)	0.94 (13.8)	-1.36 (15.7)	-0.17 (16.6)	-0.81 (15.3)

† Individual absolute change from baseline to week 24. ‡ Individual relative change from baseline to week 24.

In Group A (Hyperlipidemia), mean absolute change in serum lipids from baseline to week 24 was < 1.0 mmol/L. Mean relative changes in total cholesterol, triglycerides and LDL showed a decrease over time of 11-12% and HDL a decrease of 4%. In All Subjects (Groups A, B, C, and D) decreases in serum lipids from baseline to week 24 were negligible. In subjects in Group A as well as All Subjects (Groups A, B, C, and D), no change over time was found in either the proportion of subjects taking lipid-lowering medications or in the number of lipid-lowering medications being taken.

A mean decrease of approximately 8 mmHg in mean arterial hypertension from baseline to week 24 was found in Group C (Arterial hypertension) and a decrease of approximately 5 mmHg in mean arterial hypertension in All Subjects (Groups A, B, C, D). In subjects in Group C as well as All Subjects, no change over time was found in either the proportion of subjects taking antihypertensive medications or in the number of antihypertensive medications being taken.

At baseline, investigators rated symptoms of hypertrichosis as being “strongly” or “completely” evident in 45% of subjects in Group B (Hypertrichosis) and “not at all” or “barely” evident in 5%. By week 24/study withdrawal, hypertrichosis was “strongly” or “completely” evident in 5% while it was “not at all” or “barely” evident in 61% of subjects in Group B. Similarly, at baseline investigators rated symptoms of gingival hyperplasia as being “strongly” or “completely” evident in 51% of subjects in Group D (Gingival hyperplasia) and “not at all” or “barely” evident in 2%. By week 24/study withdrawal, the proportion of subjects in which gingival hyperplasia was “strongly” or “completely” evident decreased to 4% and the proportion of subjects in which it was “not at all” or “barely” evident increased to 75% of subjects in Group D.

At baseline approximately 48% of subjects in Group B (Hypertrichosis) indicated that they “strongly” or “very strongly” suffered from hypertrichosis. This proportion decreased to 5% at week 24/study withdrawal. Conversely, 6% of subjects indicated that they did not suffer or “barely” suffered from hypertrichosis at baseline. This proportion increased to 60% at week 24/study withdrawal. Similarly, at baseline approximately 47% of all subjects with hypertrichosis (n=126 [FAS]) indicated that they “strongly” or “very strongly” suffered from this symptom. This proportion decreased to 7% by week 24/study withdrawal.

At baseline 53% of subjects in Group D (Gingival hyperplasia) indicated that they “strongly” or “very strongly” suffered from gingival hyperplasia. This proportion decreased to 5% at week 24/study withdrawal. Conversely, approximately 2% of subjects in Group D indicated that they did not suffer or “barely” suffered from hypertrichosis at baseline and this proportion increased to 72% at week 24/study withdrawal. Similarly, at baseline approximately 46% of all subjects with gingival hyperplasia (n=165 [FAS]) indicated that they “strongly” or “very strongly” suffered from this

symptom. This proportion decreased to 3% by week 24/study withdrawal.

There were no incidences of biopsy-proven acute rejection in any subject during the study.

Safety Results:

No subject in any of the four groups died during the study. One subject in Group D died after study withdrawal, 25 days after discontinuation of Advagraf. The cause of death was lymphoma. Using the Kaplan-Meier method and including subject deaths after study withdrawal, the subject survival rate at 6 months for all subjects included in the SAF (N=343) was 99.7%.

No kidney grafts were lost during the study. After premature study withdrawal, 1 graft loss was reported in Group C (secondary to dialysis which began on day 35 after conversion) and 1 in Group D (due to death of subject). Using the Kaplan-Meier method, the graft survival rate at 6 months for all subjects included in the SAF (N=343) was 100.0%.

Overall, TEAEs occurred with similar frequency in the four treatment groups. Approximately one-third of all TEAEs were classified as mild in severity and the incidence of severe TEAEs was low (5-8%) in all groups. The incidence of drug-related TEAEs and serious TEAEs was comparable across the four groups and there were no TEAEs which led to death in any of the four groups.

Table 6: Summary of Treatment Emergent Adverse Events - SAF

	Hyperlipidemia Group A N=49	**Hypertrichosis Group B N=114**	**Arterial hypertension Group C N=93**	**Gingival hyperplasia Group D N=84**
	Number (%) of Subjects / Number of Events			
Adverse events	34 (69.4) / 93	76 (66.7) / 218	65 (69.9) / 184	46 (54.8) / 115
Mild	16 (32.7)	39 (34.2)	34 (36.6)	20 (23.8)
Moderate	14 (28.6)	30 (26.3)	25 (26.9)	22 (26.2)
Severe	4 (8.2)	7 (6.1)	6 (6.5)	4 (4.8)
Serious adverse events	14 (28.6) / 25	13 (11.4) / 25	11 (11.8) / 17	9 (10.7) / 12
Drug-related adverse events†	18 (36.7) / 45	40 (35.1) / 99	42 (45.2) / 79	21 (25.0) / 41
Drug-related serious adverse events†	3 (6.1) / 8	6 (5.3) / 10	5 (5.4) / 6	3 (3.6) / 4
Adverse events leading to premature discontinuation	5 (10.2) / 8	4 (3.5) / 4	3 (3.2) / 3	4 (4.8) / 4
Adverse events leading to death	0 (0.0) / 0	0 (0.0) / 0	0 (0.0) / 0	0 (0.0) / 0

† Drug-related is defined as missing, possible, or probably relationship to study medication as assessed by the investigator.

The incidence of TEAEs was comparable between the groups; there were no significant differences in the incidence of events across the four groups. The most common TEAE in all groups was gastrointestinal disorders which accounted for 22-31% of all TEAEs reported.

Table 7: Overall Incidence of Treatment Emergent Adverse Events Regardless of Relationship to Study Medication occurring in ≥ 5% of Subjects in any Group, Number (%) of Subjects - SAF

MedDRA Primary SOC MedDRA Preferred Term	**Hyperlipidemia Group A N=49**	**Hypertrichosis Group B N=114**	**Arterial hypertension Group C N=93**	**Gingival hyperplasia Group D N=84**
Any	34 (69.4)	76 (66.7)	65 (69.9)	46 (54.8)
Gastrointestinal disorders	11 (22.4)	30 (26.3)	29 (31.2)	19 (22.6)
Diarrhea	8 (16.3)	25 (21.9)	20 (21.5)	14 (16.7)
Infections	10 (20.4)	27 (23.7)	27 (29.0)	18 (21.4)
Urinary tract infection, bacterial	2 (4.1)	6 (5.3)	8 (8.6)	4 (4.8)
Bronchitis, bacterial	0 (0.0)	2 (1.8)	5 (5.4)	1 (1.2)
Nervous system disorders	7 (14.3)	18 (15.8)	11 (11.8)	8 (9.5)
Tremor	2 (4.1)	7 (6.1)	8 (8.6)	5 (6.0)
Headache	3 (6.1)	10 (8.8)	2 (2.2)	2 (2.4)
Investigations	10 (20.4)	9 (7.9)	16 (17.2)	7 (8.3)
Blood creatinine, increased	7 (14.3)	7 (6.1)	12 (12.9)	6 (7.1)
Metabolism/nutrition disorders	7 (14.3)	14 (2.3)	10 (10.8)	7 (8.3)
General disorders and administration site conditions	4 (8.2)	12 (10.5)	8 (8.6)	5 (6.0)
Pyrexia	2 (4.1)	1 (0.9)	5 (5.4)	1 (1.2)
Renal/urinary disorders	6 (12.2)	10 (8.8)	10 (10.8)	3 (3.6)
Skin/subcutaneous tissue disorders	3 (6.1)	10 (8.8)	10 (10.8)	4 (4.8)
Pruritus	1 (2.0)	5 (4.4)	5 (5.4)	0 (0.0)
Musculoskeletal and connective tissue disorders	5 (10.2)	5 (4.4)	9 (9.7)	7 (8.3)
Blood/lymphatic system disorders	2 (4.1)	11 (9.6)	8 (8.6)	3 (3.6)
Anemia	1 (2.0)	10 (8.8)	7 (7.5)	2 (2.4)
Vascular disorders	4 (8.2)	6 (5.3)	4 (4.3)	3 (3.6)
Injury, poisoning, procedural complications	3 (6.1)	5 (4.4)	3 (3.2)	2 (2.4)
Respiratory/thoracic/ mediastinal disorders	3 (6.1)	5 (4.4)	4 (4.3)	0 (0.0)
Cardiac disorders	1 (2.0)	1 (0.9)	5 (5.4)	0 (0.0)

Coded using MedDRA version 10.1.

Gastrointestinal disorders were the only TEAEs with an incidence ≥ 3% which led to premature study discontinuation. Gastrointestinal disorders led to study discontinuation in 3 (6.1%) subjects in Group A, 1 (1.1%) subject in Group C and 2 (2.4%) subjects in Group D.

Clinical hematology, biochemistry, and urinalysis values were comparable in all four groups at study completion. Median systolic and diastolic blood pressure values and median pulse rates were comparable between the groups at study completion.

CONCLUSIONS:

The results of the analysis of the primary efficacy variable showed that calculated creatinine clearance values at week 24 following conversion to Advagraf did not on average lead to a substantial reduction in renal function, i.e., a decrease of 10% in calculated creatinine clearance as measured by the Cockcroft and Gault method. These results were found using the PPS and confirmed by analysis of results from the FAS. Using the MDRD formula, the calculated creatinine clearance values were the same as those found using the Cockcroft and Gault method.

A small decrease in calculated creatinine clearance from baseline to 24 weeks following conversion from CyA to Advagraf was seen in All Subjects: the mean absolute decrease was 1.0 mL/min and the relative change was about 1%. Changes in calculated creatinine clearance were greatest in Group A (Hyperlipidemia) with negligible decreases in Groups B, C and D.

Mean absolute decreases in total cholesterol, triglycerides and LDL were seen in Group A (Hyperlipidemia). While arterial blood pressure decreased slightly from baseline to week 24 in Group C (Arterial hypertension), as to be expected in this population, use of antihypertensive medications remained unchanged over time.

There were no incidences of biopsy-proven acute rejection in any of the four groups. No subject died during the study however one death occurred after study withdrawal. No kidney grafts were lost during the study with 2 graft losses (1 due to subject death) reported after study withdrawal.

Investigator-rated clinical status of subjects' CyA-related side effects revealed a decrease in severity of symptoms at week 24. In Group D (Gingival hyperplasia), the proportion of subjects with severe symptoms (ratings of "strongly or "completely") decreased by 49% and the proportion of subjects with severe symptoms of hypertrichosis (Group B) decreased by 40% in week 24 to baseline comparisons

Subject-rated suffering from CyA-related side effects showed a decrease after conversion to Advagraf. In Group D, (Gingival hyperplasia), the proportion of subjects who indicated that they were "strongly" or "very strongly" bothered by gingival hyperplasia decreased by 48% and the proportion of subjects who indicated that they were "strongly" or "very strongly" bothered by hypertrichosis (Group B) decreased by 43% in week 24 to baseline comparisons.

Safety parameters remained stable following conversion. The low rate of TEAEs leading to study discontinuation provides evidence of the safety of the study drug. Following conversion from CyA to Advagraf few adjustments in dose were necessary to attain and maintain protocol-specified target tacrolimus trough levels.

In conclusion, conversion from CyA to Advagraf was both safe and effective in stable kidney transplant subjects. Renal function remained stable at week 24 after conversion. An improvement in CyA-related side effects following conversion was evident as rated by investigators as well as subjects.

Date of Report: January 2010