SYNOPSIS

Title of Study:

A Multicenter, Open-label, Single-arm, Non-inferiority Study to Assess the Safety and Efficacy of a Tacrolimus Modified Release, ADVAGRAF®, based Immunosuppressive Regimen in Stable Kidney Transplant Patients Converted from a PROGRAF® based Immunosuppressive Regimen

Investigators/Coordinating Investigator:

Study Center	Role	Department	Name
[redacted]	[redacted]	[redacted]	[redacted]

Study Center(s):

Study Center
[redacted]

Publication Based on the Study: NA

Study Period: 2Q 2010 ~ 1Q 2013

Study Initiation Date (Date of First Enrollment): 31 Aug 2010

Study Completion Date (Date of Last Evaluation): 31 Jan 2013

Phase of Development: Phase IV

Objectives:

The primary objective of this study was to evaluate the efficacy of conversion from Prograf®-based immunosuppressant therapy to tacrolimus modified release, Advagraf® (MR4), based immunosuppressive regimen on a 1:1 (mg:mg) total daily dose basis.
The secondary objective was to evaluate the safety and efficacy of Advagraf®-based immunosuppressive regimen

Methodology:

This study is a multi-center, open-label, single-arm, non-inferiority phase 4 study to assess the safety and efficacy of a tacrolimus modified release, Advagraf® (MR4), based immunosuppressive regimen in stable kidney transplant patients.
It was designed to compare the safety and efficacy after converting from Prograf®-based immunosuppressant therapy twice daily to tacrolimus modified release, Advagraf® (MR4), based immunosuppressive regimen once daily in stable patients on a 1:1 (mg:mg) total daily dose basis. In order to observe the stability and efficacy before and after conversion to Advagraf® (MR4), the subjects were observed for 24 weeks following Advagraf® (MR4).
Stable adult kidney recipients (over 12 months after transplant) who were being treated with Prograf® and met the inclusion and exclusion criteria were be enrolled. The dose of Advagraf® was converted to Prograf® on a 1:1 (mg:mg) total daily dose basis at Day 1 and Prograf® was administered once daily (only in the morning). The subjects maintained Advagraf® (MR4) once daily and the safety and efficacy were followed up and observed during a 24-week study period to assess the primary and secondary variables.
The investigators maintained the dose of tacrolimus during the study. The recommended range of blood trough level was 3 to 10 ng/mL during the maintenance therapy.

Number of Patients (Planned, Enrolled and Analyzed):

One hundred forty two patients underwent the screening process in nine study centers (except [redacted]), and the eligible 138 were enrolled in the study after the assessment based on the inclusion/exclusion criteria. Of the 138 subjects, 135 were made to take the study drug and were included in the safety analysis set (SAF). Fourteen subjects (10.14%) were withdrawn from the study, and 124 subjects (89.86%) completed the study. A total of 123 subjects were included in the full analysis set (FAS), excluding the withdrawn 14 subjects and one subject who completed the study but did not have enough records for the assessment of the primary variable. Nine subjects violated the study protocol. Thus, 114 subjects, excluding those nine, were included in the per-protocol set (PPS).

Diagnosis and Main Criteria for Inclusion:

1. Male and female patients who are over 20 years.
2. Patients received a kidney transplant at least 12 months ago prior to enrollment.
3. Patients have taken unchanged dosage of Prograf® and remained stable serum level of tacrolimus (3-10 ng/mL) at least for 12 weeks prior to enrollment.
4. Patients have kept in unchanged immunosuppressive therapy (combination therapy) at least for 12 weeks prior to enrollment.
5. Female patients of childbearing potential must have a negative urine or serum pregnancy test prior to enrollment, and agreed to the deliberate prevention of conception during the trial.
6. Patients are considered clinically stable by investigator's judgment.
7. Patients understood the purpose and risk of participating thethe trial and signed on the written consent.

Test Product, Dose and Mode of Administration, Batch Numbers:

Advagraf® (MR4) was provided in the form of a hard gelatin capsule containing 0.5mg, 1mg and 5mg of tacrolimus. Other ingredients are lactose, HPMC(hydroxypropyl methylcellulose) 2910, ethyl cellulose and magnesium stearate.

0.5 mg capsule	The 0.5 mg strength is encapsulated in a size 5 hard gelatin capsule composed of light yellow cap and orange body with "[f] 0.5 mg" imprinted in red on the cap and the body.
1 mg capsule	The 1 mg strength is encapsulated in a size 4hard gelatin capsule composed of white cap and orange body with "[f] 1 mg" imprinted in red on the cap and the body.
5 mg capsule	The 5 mg strength is encapsulated in a size 0hard gelatin capsule composed of gray-red cap and orange body with "[f] 5 mg" imprinted in red on the cap and the body.

Duration of Treatment (or Duration of Study, if applicable):

24 weeks (6 Month)

Reference Product, Dose and Mode of Administration, Batch Numbers:

Prograf® is provided in the form of a hard gelatin capsule containing 0.5mg or 1mg tacrolimus. Other ingredients are lactose, HPMC (hydroxypropyl methylcellulose) 2910, ethyl cellulose and magnesium stearate.

0.5 mg capsule	a size 5 hard gelatin capsule composed of light yellow cap and body with “0.5 mg” imprinted in red on the cap and body.
1 mg capsule	a size 4 hard gelatin capsule composed of white cap and body with “1 mg” imprinted in red on the cap and body.

Criteria for Evaluation:

Primary Efficacy Variable

Change in GFR at Week 24 from baseline (Day -1)
(GFR at Week 24 –GFR at baseline)

Secondary Efficacy Variable

- Change in BP at Week 24 from baseline (Day -1)
- Change in HbA1c at Week 24 from baseline (Day -1)
- Change in tacrolimus blood trough level at Week 24 from baseline (Day -1)

Safety Variables

Physical examination, vital signs, laboratory tests, adverse events, serious adverse events and overall frequency of acute rejection

Statistical Methods:

Full Analysis Set (FAS):
All the subjects who have received the study drug [Advagraf® (MR4)] in the each dosing stage and have enough records to evaluate the primary variable at least once in each dosing stage

Per protocol Set (PPS):
All the subjects who have not committed major protocol violation such as inclusion/exclusion criteria or tacrolimus dose adjustment regulations violations (see Section 5.1) and have enough records to evaluate the primary variable

Safety analysis set (SAF): All the subjects who have received the study drug at least once

Not only characteristics of baseline (demographic statistics and immunosuppressant therapy including tacrolimus blood trough level) based on FAS and PPS but also the primary variable will be analyzed, The

analysis of the primary variable will be based on PPS. The analysis of the subject's survival, graft survival and AEs will be based on SAF. The analysis of all the secondary variables will be based on FAS.

Summary of Results/Conclusions:

Advagraf®-based therapy was proven not to be inferior to Prograf®-based therapy after conversion in stable kidney transplant. It is expected that the use of Advagraf® will help kidney transplant patients as much as Prograf® does.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

The primary objective of this study was to confirm whether the GFR was decreased by ≥6.25(mL/min per 1.73m2)at week 24 after conversion from Prograf®-based immunosuppressant therapy to Advagraf®-based immunosuppressant regimen. The analysis results in PPS are presented in Table13and 14and in Figure2 and3.

The mean GFR at baseline (day -1) was 67.79(±16.87) mL/min, and that at week 24 after the conversion to Advagraf®-based immunosuppressant regimen was 68.13(±17.73) mL/min, which showed an increase but one that was not statistically significant (p-value=0.3251). The change in GFR at week 24 from baseline was 0.34(±8.07)mL/min, and the one-sided 95% confidence level was -0.91mL/min. As the value was above the maximum change value required to conclude that Advagraf® is inferior to Prograf® (-6.25mL/min per 1.73m2), it was confirmed that Advagraf® is not inferior to Prograf® based on the results of this study.

[Table1] Change in GFR at Each Visit (PPS=114)

GFR[mL/min]	Mean±SD
Baseline (Day -1)	67.79±16.87
Week 24	68.13±17.73
Change in CFR at Week 24 compared to Baseline	0.34±8.07
95% one-sided confidence interval	(-0.91, ∞)
P-value[1)]	0.3251

[1)]A paired t-test (one-tailed) was performed to analyze the significance of change.

Two acute rejections occurred in two subjects during the study period, and the incidence of acute rejection was 1.48%[Table 25]. The detailed data of the subjects who developed acute rejection are listed in Table26.

[Table 2] Summary of Acute Rejections (SAF=135)

	N(%),[No. of Cases]	95% CI
Acute Rejection	**2(1.48),[2]**	**(0.18, 5.25)**

[Table3] Detailed Acute Rejections (SAF=135)

Site	Subject No.	First Administration of Study drug	Onset Date of Acute Rejection	Period of Event (Days)†	Biopsy of Transplanted Organ	
					Date	Findings
[redacted]	[redacted]	[redacted]	[redacted]	149	[redacted]	Banff IB
[redacted]	[redacted]	[redacted]	[redacted]	7	[redacted]	Banff IA

† Period before the initial acute rejection development (days): from day 1 of study drug administration to the onset date of acute rejection

Safety Results:

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any

unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug. The adverse events were coded based on system organ class (SOC) and Preferred term of MedDRA 15.0 and were listed from the highest to lowest frequency of SOC.

Ninetyone (67.41%) of the 135 subjects showed 183 AEs (mild: 169 cases; moderate: 12 cases; and severe: 2 cases), and the AEs whose causal relationship with the study drug could not be ruled out numbered 26 in 20 subjects (14.81%).

Fourteen SAEs under the "hospitalization or leads to prolongation of hospitalization" criterion were reported in 12 subjects (8.89%). There were four serious ADRs in three (2.22%) subjects. Three subjects (2.22%) were withdrawn from the study due to AEs, and there was no death case.

CONCLUSIONS:

This clinical trial is an open-label, multicenter, comparative, phase IV study. Male or female patients who had kidney transplant at least 12 months before the study and aged 20 years old or more signed the informed-consent forms and participated in this study. Their Prograf® doses were maintained, and their blood tacrolimus trough levels were within 3-10 ng/mL. They continued their immunosuppressive therapy for at least 12 months after the transplantation.

One hundred forty two subjects were screened from August 31, 2010 to January 31, 2013 in ten study centers, including [redacted] Of the 142 subjects, 138 were enrolled in the study, and four patients were excluded as they failed to meet the inclusion/exclusion criteria.

In this study, the GFR was calculated using the MDRD equation to evaluate the kidney graft function. The mean GFR at baseline (day -1) was 7.79 (±16.87) mL/min, and it increased to 68.13(±17.73)mL/min after the conversion to Advagraf®, but the change was not statistically significant. A previous long-term observation study reported a significantly increased GFR 24 weeks after converting from Prograf®-based immunosuppressive therapy to Advagraf®-based therapy.20 The primary efficacy variable was change in CFR 24 weeks after the conversion compared to baseline. The lower limit of 95% one-sided confidence interval was -0.91 mL/min, which was over the maximum change required to conclude that Advagraf® is inferior to Prograf®(-6.25mL/min per 1.73m2). As such, this study confirmed the non-superiority of Advagraf ®.

The second efficacy variable was the change in BP, HbA1, and blood tacrolimus trough level. Diabetes and hypertension after transplantation is a major cardiovascular complication with the use of tacrolimus. A couple of previous studies suggested that the significant decrease in HbAlc level for a brief period after converting from Prograf®-based immunosuppressive therapy to Advagraf®-based therapy could be interpreted as a possible decreased frequency of cardiovascular complications such as diabetes after transplantation. In this study, the mean systolic and diastolic BP were 123.07(±14.59)mmHg and 80.18(±8.65)mmHg at baseline, and those at 24 weeks after the conversion to Advagraf® were 123.28(±14.74)mmHg and 79.88(±9.23)mmHg. The mean systolic BP increased by 0.33(±16.19)mmHg, and the mean diastolic BP decreased by 0.34(±10.79)mmHg, but such changes were not significant. The mean HbAlc was 6.01% (±0.85) at baseline (day -1) and 6.05% (±0.96) at 24 weeks after the conversion, which increased by 0.04% (±0.52),but the increase was not significant.

The mean blood tacrolimus trough level was 5.78 (±1.58) ng/mL at baseline and 4.79(±1.56)ng/mL at 24 weeks after the conversion, which showed a significant decrease of 1.04(±1.95)ng/mL.

Ninety one (67.41%) of the 135 subjects who were enrolled in this study and to whom the study drug was administered at least once showed 183 AEs, and the AEs whose causal relationship with the study drug could not be ruled out numbered 26 in 20 subjects (14.81%).

Fourteen SAEs under the “hospitalization or leads to prolongation of hospitalization” criterion were reported in 12 subjects (8.89%). There were four serious ADRs in three (2.22%) subjects. The safety and efficacy of converting from Prograf®-based immunosuppressive therapy to Advagraf®-based therapy in kidney transplant patients have already been reported.22-25The ADR with an over 5% occurrence was upper respiratory tract infection (8 cases, 8 subjects, 5.93%) under the infections and infestations category. The other ADRs included dyspepsia (3 cases) under the gastrointestinal disorders and blood creatinine increase category (3 cases) under investigation, and most of them were expected ADRs.Acute rejection was confirmed in the part of safety assessment. Two acute rejections occurred in two subjects during the study period, and the incidence of acute rejection was 1.48%. Tacrolimus has already been proven to be superior to cyclosporins in terms of acute rejection. This study, however, did not compare the Prograf®-maintained therapy and conversion to Advagraf® groups, and as such, the acute rejections of the two products were not compared.

Of the hematology test items, the hemoglobin level at week 16 was significantly lowered compared to baseline, and the hematocrit level at weeks 1, 2, 16, and 24 was also significantly lowered. The WBC level at weeks 2, 12, and 16, and the platelet level at weeks 2, 8, 12, and 16, became significantly higher compared to baseline. Of the blood chemistry items, the γ-GT (gamma glutamyl transpeptidase) at weeks 1, 2, and 4, and the LDL at week 1, significantly decreased compared to baseline. The HDL level at weeks 4, 8, and 16 became significantly higher compared to baseline.

In conclusion, Advagraf®-based therapy was proven not to be inferior to Prograf®-based therapy after conversion in stable kidney transplant. It is expected that the use of Advagraf® will help kidney transplant patients as much as Prograf® does.

Date of Report: 31 Oct 2013