Synopsis

Drug Registration Applicant	Astellas Pharma (China) Inc.	
Test Drug	Tacrolimus Sustained-release Capsule Tacrolimus Capsule Cyclosporine A	
Study Title	A randomized, open-label, multi-center clinical trial to compare efficacy and safety of cyclosporine-based and switching cyclosporine to tacrolimus of two forms-based immunosuppressive therapy in renal transplant (KTx) recipients	
Study Sites	There were 7 sites in total [redacted]	
Principal Investigator	Prof. [redacted]	
Publications (References)	NA	
Study Duration	Initiation date: 23-Jul-2013	Completion date: 31-Mar-2015
Study Objectives	**Primary objective:** To explore the impact of two forms of tacrolimus on the renal functions of KTx recipients in comparison with cyclosporine A group **Secondary objectives:** To explore the impact of cyclosporine and the two forms of tacrolimus on patients' life quality To compare the efficacy of cyclosporine and the two forms of tacrolimus in KTx recipients To compare the safety of cyclosporine and the two forms of tacrolimus in KTx recipients	
Study Design	A prospective, randomized, controlled, multicenter, open-label clinical trial. ☐ Patients deemed eligible for enrollment after screening were randomly divided into three groups: ☐1. MR4Group: Tacrolimus Sustained-release Capsule ☐2. TACGroup: Tacrolimus Capsule ☐3. CSA Group: Cyclosporine A All enrolled patients were followed up and observed for 24 weeks. The groups	

	that used two forms of tacrolimus received tests at Week 0, 1, 2, 4, 8, 16 and 24 of administration to evaluate relevant indexes; the cyclosporine A group received tests at Week 0, 8, 16 and 24 to evaluate relevant indexes.
Sample Size	360 subjects were planned to be enrolled; in actual practice, 17 subjects were enrolled.
Inclusion Criteria	**Inclusion criteria:** 1. Age 18-65, male or female; 2. KTx ≥6 months; 3. Patients had received cyclosporine-based immunosuppressive therapy for more than 6 months, and had maintained a stable regimen for at least 8 weeks before enrollment; 4. The trough level of cyclosporine maintained at 50-200 ng/mL for at least 4 weeks before enrollment; 5. SCr < 200 μmol/l (2.3 mg/dl); 6. Women of childbearing age committed birth control during the trial; 7. Signed Informed Consent Form. **Exclusion criteria:** 1. Patients who had other solid organ transplantations; 2. 24 hours proteinuria>2 g; 3. SGPT/ALT, SGOT/AST or total bilirubin rising continuously to more than double the normal level; 4. Patients suffering from infection lesions that are difficult to control; 5. Patients had severe diarrhea or vomiting, active upper digestive tract ulcers or defective absorption; 6. Patients had severe heart, lung disease, abnormal glucose tolerance or malignant tumor history; 7. Allergy to tacrolimus or other basic drugs; 8. Pregnancy or lactating women; 9. Patients had participated in another clinical trial in the past month; 10. Patient refused to sign Informed Consent Form.
Withdrawal (Drop Out) Criteria	1. Patient not willing to continue in the study; 2. Poor compliance or lost to follow up; 3. Protocol violation; 4. Adverse event which had impact on patient's safety according to investigator's judgement or any incompatible safety issues that interfere with patient's continuing participation in this trial; 5. Pregnancy.
Test Drug and Dosing Regimen	☐ Cyclosporine A: according to the clinician's advice. ☐ Tacrolimus capsule: twice daily at 12-hour interval, one hour before meal or

	two hours after meal. ☐ Tacrolimus sustained-release capsule: once a day, one hour before breakfast. ☐ The initial dose for tacrolimus capsule and tacrolimus sustained-release capsule: 0.05-0.08 mg/kg/day or 1/30-1/50 of the dose of cyclosporine; the interval between the first dose of tacrolimus capsules or tacrolimus sustained-release capsule and the last dose of cyclosporine should be 12-24 hours. ☐ The recommended target concentration of tacrolimus is 5-10 ng/ml. For the switching groups, the regimen for other drugs did not change except cyclosporine.
Efficacy Endpoints	**Primary efficacy endpoints**: The impact of the three treatment regimens on estimated glomerular filtration rate (eGFR). **Secondary efficacy endpoints:** 1. For the three groups, the changes in renal functions (including serum creatinine, urine creatinine and urea nitrogen level) at Week 0, 8, 16 and 24 compared to baseline; 2. Comparison of the changes in life quality at Weeks 0, 8, 16 and 24 between the three groups; 3. Comparison between the three groups of the changes in blood pressure, plasma lipid, liver function and fasting blood glucose, as well as the changes in concomitant drugs used to control hypertension, diabetes and plasma lipid at Week 0, 8, 16, 24; 4. Comparison between the three groups of the changes in gingival hyperplasia and hypertrichiasis during 24 weeks administration; 5. The rejection rate throughout the study period; 6. For the two groups that switched to tacrolimus treatment, the changes in the trough concentration of the drug at Week 0, 1, 2, 4, 8, 16 and 24; 7. For the group that continued to use cyclosporine A, the changes in the trough concentration of the drug at Week 0, 8, 16 and 24; 8. Comparison of the incidence of adverse events between the three groups.
Safety Endpoint	Comparison of the incidence of adverse events between the three groups.
Statistical Methods	Full Analysis Set (FAS): All subjects who met all inclusion/exclusion criteria, were enrolled, had received the medicine at least once and could supply an efficacy assessment after baseline constituted the FAS of the study. The FAS population was used in the analysis of demographics, baseline features and efficacy. Per-protocol Set (PPS): All the patients who were enrolled and completed the whole study according to the protocol without any protocol violation (including inclusion criteria) constituted the PPS of the study. The PPS set was used for adjuvant efficacy assessment. Safety Set (SS): All the patients who were enrolled, received the medicine at least once and could supply a safety assessment constituted the SS of the study. The SS population was used for the safety assessment. All statistical analysis should be performed using SAS 9.1 or newer versions.

	Unless otherwise specified, all statistical tests were two-sided tests with α=0.05, and two-sided 95% confidence intervals were calculated. Descriptive statistics were used, including number of cases, mean, median, standard deviation, maximum and minimum, to summarize continuous variables. Categorical endpoints were described based on the case number and percentages of each category. ☐ Statistical analysis were further explained in the Statistical Analysis Plan (SAP), and the SAP were finalized before the database lock. ☐ The demographics and baseline features of each treatment group and in the whole sample were described and summarized using statistics. ☐ ANCOVA analysis were used to compare the difference between the treatment groups based on the primary observational endpoints, eGFR. The dependent variable in the ANCOVA model was the change in eGRF compared to baseline, and explanatory variables included the patients' trial group and their eGFR level at baseline. The two-sided p values for the MR4 Group compared to the CSA Group were firstly obtained based on the ANCOVA model. If the two-sided p values for the MR4 Group compared to the CSA Group was less than 0.05, then the two-sided p values for the TAC Group compared to the CSA Group should be obtained. Additionally, the two-sided 95% confidence intervals for MR4 Group compared to CSA Group and for TAC Group compared to CSA Group should be obtained from ANCOVA model. ☐ For the continuous variables in the secondary observational endpoints, the same methods of analysis with the primary outcome measure were used. The rejection rates were compared using χ-square test, and two-sided 95% asymptotic confidence intervals were calculated for the rejection rate of each trial group. Adverse events were coded with MedDRA dictionary. Adverse event analysis will be conducted based on treatment-emergent adverse events (TEAEs). A TEAE was defined as an adverse event that occurred during the treatment period or aggravated during the treatment period compared to the pre-treatment condition. The incidence of TEAEs was described according to the System Organ Class (SOC) and Preferred Terms (PT). Meanwhile, similar summary and listings were provided for serious adverse events (SAEs) and adverse events leading to study discontinuation. Listings and applicable descriptive summaries were also provided for other safety assessment endpoints.
Results	**<u>Subjects</u>** In this clinical study, 17 patients were randomly placed in the tacrolimus sustained-release capsule group (6 cases), tacrolimus capsule group (6 cases) and cyclosporine A group (5 cases); among these groups, 5 cases (83.33%), 6 cases (100%), and 4 cases (80%) were included into the FAS respectively. 3 patients (60%) completed the trial in the tacrolimus sustained-release capsule group, 4 (66.67%) in the tacrolimus capsule group and 4 (100%) in the cyclosporine A group. The main reasons for not completing the trial were loss to follow up and missing data. **<u>Efficacy results</u>** **Primary efficacy endpoints:** In the FAS, the average eGFR values of the three treatment groups at baseline were: 58.050 ml/min•1.73m^2 for tacrolimus sustained-release capsule group, 65.896 ml/min•1.73m^2 for the tacrolimus capsule group, and 86.033 ml/min•1.73m^2 in the cyclosporine A group. The average eGFR values of the three

	treatment groups at the end of the treatment were: 69.590 ml/min•1.73m^2 for the tacrolimus sustained-release capsule group, 55.792 ml/min • 1.73m^2 for the tacrolimus capsule group and 71.380 ml/min•1.73m^2 for the cyclosporine A group. In the PPS, the average eGFR values at baseline were: 54.457 ml/min•1.73m^2 for the tacrolimus sustained-release group, 68.537 ml/min • 1.73m^2 for the tacrolimus capsule group, and 86.033 ml/min•1.73m^2 for the cyclosporine A group. At the end of treatment, the average eGFR value for each group was: 69.590 ml/min • 1.73m^2 for the tacrolimus sustained-release group, 62.203 ml/min•1.73m^2 for the tacrolimus capsule group, and 71.380 ml/min•1.73m^2 for the cyclosporine A group. **Secondary efficacy endpoints:** Since this study was terminated in advance and the limited subjects, the secondary endpoints were not statistical significant. **Safety results** In this trial, among the 15 patients who were included in the FAS, there was 1 case of adverse event (6.7%), which was also a serious adverse event (6.7%). The adverse event occurred in the tacrolimus sustained-release group (20%), and was elevated serum creatinine. The degree of severity was mild, and the relationship with the trial drug was "possibly related". This case of adverse event had relieved before the end of the trial. No death or other significant adverse event occurred.
Conclusion	**Conclusion:** Since this study was terminated in advance, there was limited data. The efficacy of tacrolimus sustained-release capsule or tacrolimus capsule in KTx patients receiving immunosuppressive therapies and the difference in efficacies between each treatment group could not be evaluated.
Report Date	08-July-2015