Name of Sponsor/Company: Astellas Pharma Europe, Ltd		
Name of Finished Product: Modigraf®		
Name of Active Ingredient: Tacrolimus Granules		

SYNOPSIS

Title of Study: A Long-term, Open-label, Non-comparative Study to Evaluate the Safety and Efficacy of a Modigraf® Based Immunosuppression Regimen in Paediatric Solid Allograft Recipients, Part B

Investigators/Coordinating Investigator: [redacted]

Study Center(s): This multicenter study was conducted at 4 contracted sites in a total of 3 countries including Germany (2 sites), Spain (1 site) and the United Kingdom (1 site).

Publication Based on the Study: Not applicable

Study Period: 6.8 years

Study Initiation Date (Date of First Enrollment): 24 Jun 2011

Study Completion Date (Date of Last Evaluation): 02 Apr 2017

Study Termination Date: 31 Oct 2017

Phase of Development: 4

Objective: The objective of the study was to monitor dose changes and tacrolimus whole blood trough levels after conversion from a Modigraf-based immunosuppression regimen to a Prograf-based immunosuppression regimen.

Methodology:

This was a multicentre, open-label, single arm study. Pediatric patients who had undergone liver, kidney or heart transplantation and met the inclusion criteria and complied with the exclusion criteria prior to initiation of tacrolimus therapy were enrolled. All patients had previously participated in Studies F506-CL-0403 and F506-CL-0404A. All patients entering Study F506-CL-0404B were on a Modigraf-based immunosuppressive regimen at the time of enrollment.

Patients continued to be treated with a Modigraf-based immunosuppression regimen, administered twice daily, until such time as their treating physician deemed it appropriate to convert them to a twice daily Prograf regimen (stable patients only). One day prior to conversion from a Modigraf-based regimen to a Prograf-based regimen, patients were enrolled in Study F506-CL-0404B. Shortly before and following conversion, the number of dose changes and whole blood tacrolimus trough level measurements were recorded for a period of 1 month. A minimum of 4 blood tacrolimus trough level measurements were taken between days 3 and 16. At the end of the 1 month period, an end of study visit was performed.

Number of Patients (Planned, Enrolled and Analyzed): No sample size calculations were performed. This study was a follow up for the pharmacokinetic Study F506-CL-0403 and extension Study F506-Cl-0404A and, as such, the sample size was comprised of the number of patients who were subsequently enrolled in Study F506-CL-0404B.

Of the 52 patients who received a kidney, liver or heart transplant and received treatment in Study F506-CL-0403, 47 patients were enrolled in Study F506-CL-0404A and 6 patients were enrolled in Study F506-CL-0404B as of 31 Oct 2017, the date the study was terminated.

Diagnosis and Main Criteria for Inclusion: A patient was eligible for the study if all of the following applied:

1. Patient received at least 1 dose of Modigraf in Study F506-CL-0403.
2. Patient participated in Study F506-CL-0404A.
3. Patient had continuously been dosed with twice daily Modigraf since the end of study visit from Study F506-CL-0404A.
4. In the opinion of the patient's investigating physician, the patient would benefit from conversion to Prograf.
5. The patient's parent(s) or their legal representative(s) had been fully informed and had given written informed consent to patriciate in the study. The patient had given assent where applicable.

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

Patients were treated with Prograf oral hard capsules containing 0.5 mg, 1 mg or 5 mg of tacrolimus per capsule. The Prograf lot numbers were: [redacted], [redacted] (0.5 mg); [redacted], [redacted] (1 mg) and [redacted], [redacted] (5 mg).

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

- Minimum time on study drug: 29 days.
- Maximum time on study drug: 34 days.

Reference Product, Dose and Mode of Administration, Batch Numbers: Not applicable

Criteria for Evaluation:

Safety: The safety and tolerability of the study drug was assessed using adverse events (AEs), vital signs and clinical laboratory tests.

Statistical Methods:

No summary statistics were generated for this study because of the small number of patients enrolled (n = 6). All listings were created using SAS® Version 9.1.3 or higher on a Unix system.

Population for Analysis: All patients enrolled in Part B who took at least 1 dose of Prograf study drug were included in the conversion analysis set.

Exposure: Duration of exposure and total daily dosing for each patient were presented in a listing.

Safety: The coding dictionary for this study used to categorize AEs was MedDRA v15.0. By-patient listings of treatment-emergent adverse events (TEAEs), drug-related TEAEs, serious TEAEs and TEAEs leading to permanent discontinuation of study drug were created.

Quantitative clinical laboratory variables, i.e., hematology and biochemistry, were presented in a listing.

Summary of Results/Conclusions:

Patient Disposition: Of the 52 patients who received a kidney, liver or heart transplant and received treatment in Study F506-CL-0403, 47 patients were enrolled in Study F506-CL-0404A and 6 patients were enrolled in Study F506-CL-0404B as of 31 Oct 2017, the date the study was terminated.

All 6 enrolled patients took at least 1 dose of Prograf study drug and were included in the conversion analysis set.

Demographics:

Overall, 4 of the patients were male and 2 of the patients were female; all patients were white. The age and weight at enrollment ranged from 4.0 years to 13.2 years and 18.0 kg to 45.8 kg, respectively.

The age at enrollment for the kidney transplant patients ranged from 7.00 years to 11.0 years; for the 2 liver transplant patients, their ages at enrollment were [redacted] years and [redacted] years; the age at enrollment of the 1 heart transplant patient was [redacted] years.

Efficacy Results:

Efficacy was not assessed in Study F506-CL-0404B.

Safety Results:

Two patients reported at least 1 TEAE and 2 patients experienced ongoing AEs (which had started prior to conversion to Prograf). None of these TEAEs/AEs resulted in study drug dose adjustment or study discontinuation. During the study, there were no deaths or SAEs reported. The observed safety profile is consistent with the known characteristics of tacrolimus and no new safety issues were identified.

CONCLUSIONS:

The data from this study suggest that following conversion, trough levels remained in the recommended target range. The observed safety profile throughout the study was consistent with the known characteristics of tacrolimus and no new safety issues were identified.

Date of Report: 22 Mar 2018