**Item S1. Detailed description of the genotyping and analytical methods used.**

**Genotyping**

Briefly, Assay-by-Design Taqman 5’ nuclease PCR primers and probes for the variant SNPs of interest (C__26201809_30 [CYP3A5*3, rs776746], C__30203950_10 [CYP3A5*6, rs10264272 and C___7586657_20 [ABCB1 C3435T, rs1045642]], were purchased from Applied Biosystems (Foster City, CA). PCR was performed using 5 ng of genomic DNA, specific PCR primers, two allele-specific probes, dNTPs, Taq DNA polymerase and buffer according to the manufacturer's specifications. After PCR results were graphed on a scatter-plot contrasting reporter dye florescence (i.e. allele X versus allele Y) using Applied Biosystem software (Life Technologies Corporation, Carlsbad, CA). Clustering boundaries for each variant-specific genotype were assigned in an automated fashion based on the position of the positive control within each cluster and spectral-specific plots specific to each genotype. Genotypes were called based on their corresponding location within each cluster. Sequence variants were called “undetermined” if they clustered in proximity to the negative (water) controls (<1 fluorescence units), showed an abnormal spectral plot (probe-specific fluorophore signal to internal control signal<1), or did not cluster tightly (outliers).

**Performance characteristics for the tacrolimus assay**

The analysis of Tacrolimus (Prograf) in blood is performed with High Performance Liquid Chromatography followed by tandem mass spectrometry detection (HPLC/MS/MS). Tacrolimus results are reported as ng/mL with a dynamic range of 1.0 to 30 ng/mL. HPLC/MS/MS provides ultimate sample-to-sample specificity, freedom from interferences by simultaneous detection of the Tacrolimus molecular ion (m/z 821.5) and a Tacrolimus-specific fragment ion (m/z 768.5).
To establish acceptable performance, all levels of QC controls must be tested at the beginning of each shift and at least one level QC must be assayed at the end of each run to bracket the patient samples. For additional runs, QC must be incorporated at approximately the following frequency while continuing to ensure that all patient samples are bracketed by QC. 15% Total Allowable Error Specifications for the most current allowable total error (Tea) or Optimal/Acceptable 10%CV. Verification of the Analytical Reportable Range (AMR) is performed when new calibrators are put into place. Calibration is performed daily. All calculation for the unknown sample is done through MultiQuant software. It is based on the calibration curve that generate with the batch. The curve R value has to be greater than 0.99 for any batch to be accepted. Any dilution must be multiple with the dilution factor and the instrument result is less than the linear range (30 ng/mL). SENSITIVITY AND LINEARITY: The assay is linear from 1 ng/mL to 30 ng/mL. Results >30 ng/mL should be diluted with negative whole blood control and rerun. Multiply result by appropriate dilution factor. Up to x4 dilution can be run. If results of dilution are still higher than linearity, report “> 120 ng/mL.” Results less than 1 should be reported as “< 1”.

1.1 Analytical Measurement Range (AMR)

1 ng/mL – 30 ng/mL

1.2 Precision

Within 15% or ±1 ng/ml of each other

1.3 Interfering Substances

There are no known interfering substances. Please refer to Matrix Effect Assessment study.

1.4 Clinical Sensitivity/Specificity/Predictive Values
LOQ (Limit of Quantification) is less than 1ng/mL; LOB (Limit of Blank) is less than 10x the noise SD; the predictive value of this method determined to be from 1ng/mL to 30 ng/mL.

1.5 Carryover: Twenty one specimens were injected with the low is the Tacrolimus free whole blood and the high concentration has a concentration of 42.2ng/mL. Alternate injections of negative and high samples were performed to determine the low-low mean result and high-low mean result. Positive carryover is defined as when the mean of high-low result minus the mean of low-low result and the different is greater than 3 times the low-low standard deviation. The study showed that carryover is zero. Thus, no carryover exists for this method.

1.6 Matrix Effect Assessment: A constant infusion method was used to detect any ion suppression or enhancement to both Tacrolimus and Ascomycin. Twenty samples were selected for a variety of plasma matrix. Difference matrix include: icteric, lipemic, hemolyzed, high white count, combination of icteric and lipemic, normal, and mobile phase were tested and shows no ion suppression at the retention time of Tacrolimus and the Ascomycin internal standard. Daily run review: the internal standard peak area for all samples should match within + one factor of 10.

**Statistical Analysis**

Plasma PK parameters were calculated by non-compartmental methods using Phoenix® WinNonlin® (Version 6.3, Pharsight Corporation, St. Louis, MO). Actual elapsed sampling times of blood samples were used for the estimation of PK variables. The maximum plasma concentration, Cmax, for the concentration-time profile was determined observationally as the peak concentration for each subject in each treatment. The time to maximum concentration, Tmax, was determined as the time to reach the corresponding Cmax. The area under the plasma
concentration-time curve ($\text{AUC}_{0-24}$) was calculated using the linear up/log down trapezoidal method. Continuous data were summarized using descriptive statistics. Categorical data were summarized using n and percentages. Differences in PK profiles between the two tacrolimus formulations were evaluated in two ways: relative bioavailability (RBA) of the test to the reference, and difference in kinetics parameters. Relative bioavailability analysis was performed on natural log transformed data for $\text{AUC}_{0-24}$, $C_{\text{max}}$, and $C_{\text{min}}$. The RBA examined two null hypotheses: (1) the ratio of the test mean to the reference (standard) mean is below 0.80, and (2) the ratio of test mean to the standard mean is above 1.25. The null hypotheses were evaluated via the framework of analysis of variance (ANOVA) for the cross-over design. The statistical model included fixed effects of treatment, sequence, and period (for comparisons between LCPT and IR-Tac) and random effect of patients (nest within sequence); difference in least squares mean (LSM, Test - Reference) and 90% confidence intervals for the difference, all in natural log scale, between two tacrolimus formulations were derived from the model; ratio of geometric means (RGMs) and 90% CIs for the RGMs were presented after anti-log transformation of the LSM difference and the 90% CIs. One would reject both null hypotheses if the 90% CIs were within the range of (0.80 to 1.25), inclusive. Relative bioavailability analysis was performed on observed and dose-adjusted PK parameters. The null hypotheses were evaluated using the same ANOVA model as for the RBA analysis, but the analysis was based on untransformed data for fluctuation, swing, and $C_{\text{max}}/C_{\text{min}}$. Difference in LSM between two treatments was derived and tested using a 2-sample t-test at the 0.05 significance level. Comparison of $t_{\text{max}}$ was based on 2-sided Wilcoxon two-sample rank sum test. Dose normalized $C_{\text{max}}$, $C_{\text{min}}$, and $\text{AUC}_{0-24}$ were derived by (observed parameter/tdd); dose normalized parameters were evaluated using the same approach as the observed parameters. Analysis at the study level used all 3 observations per
subjects. The analysis model and the estimates were based on FA0(2) Covariance Structure for this 3 period partially replicated study; whereas the analysis within a subgroup (e.g., difference between treatments within a genotype and difference between genotypes within a treatment), the average across periods 2 and 3 was calculated for each subject so the study design collapsed into a typical 2x2 crossover design. Effect of genotype was also examined within a treatment group using mixed effect ANOVA model that include mixed effect of genotype and period and random effect of patients (nest within sequence).