Title: Assessing the Association of Four Measurements of Adherence to Tacrolimus for Organ Transplant Recipients

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Keywords: organ transplantation, multiple measures, longitudinal measurement, validation

Body (500 word max):

Background: For end-stage solid organ disease patients, transplantation offers increased life span and quality of life. However, recipients must adhere to a complex regimen of immunosuppressant medications, particularly tacrolimus, to prevent rejection of the transplanted organ. There is not a standardized method of detecting medication adherence (MA) in solid organ transplantation. Assessments range from patient surveys and dosing diaries, electronic pill bottle caps, and biological measures of the levels of medication in a patient's blood. Each approach has advantages and disadvantages, thus a reasonable assessment strategy is to employ multiple validated measures. Understanding the comparability of multiple measures is critical for interpreting the results of studies involving adherence measure comparisons. As part of a FDA-sponsored, multicenter trial we will compare 300 adult and pediatric organ recipients' experiences receiving heart, liver, and kidney transplants with branded and generic tacrolimus in which MA is a secondary outcome. Furthermore, we will examine the comparability of four validated and non-validated measures of adherence over 36 months.

Methods: Assessments of adherence will be made at several time points over three years of follow-up post-transplantation. A validated, patient-reported MA scale, the Morisky Medication Adherence Scale (MMAS-8), will be assessed at 9-, 18-, and 36-months post-transplant; scale scores range between 0-8 (higher = better adherence). The coefficient of variation (CV), a validated measure of the level of tacrolimus in patient's blood, defines adherence as the standard deviation of patients' trough blood levels divided by the mean level across 11 points over 36 months, generating scores between 0%-100% (higher = better adherence). Daily measurement of MA will be conducted with a pill-by-pill utilization measurement cap device that appends to a pill vial called CleverCap®, and daily dosage diaries; these assessments will utilize the CleverScore™, a novel adherence metric formulated for the CleverCap® reporting and analytics platform and defined as the difference of the number of actual doses taken and non-prescribed doses taken divided by the number of prescribed doses taken, ranging between 0%-100% (higher = better adherence).

Associations between each of these measures will first be tested using correlations at 9-, 18-, and 36-months post-transplant, and each will be assessed for sensitivity to change in adherence levels over time. On the MMAS-8, categories of low (score of <6), medium (6-<8), and high adherence (8) will be tested for association with the CV (dichotomized at established cut-off of >40% = adherent, ≤ 40% = non-adherent), as well as data from the CleverCap® and diaries using chi-square and Wilcoxon rank-sum tests. Finally, receiver-operator curves will be

used to establish a meaningful adherence cut-off point for the CleverScore™. These analyses will help identify the most efficient and cost-effective measure of medication taking behavior.

Conclusions: The results of these analyses will establish and quantify the degree to which multiple measures of adherence are related in a novel study setting with adult and pediatric patients assessed over multiple time points, and create a basis for comparing their individual results in a single clinical trial across solid organ transplantation.

Acknowledgements: Funding for this research was made possible, in part by the Food and Drug Administration through grant 1U01FD005271-01, views expressed in written materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Food and Drug Administration or the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.