Probenecid-Boosted Tenofovir: A PBPK model informed strategy for on-demand HIV pre-exposure prophylaxis

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Supplemental Information: Source of observed clinical PK values for model verification

The observed pharmacokinetic data for TFV was obtained from a clinical trial entitled "Assessment of a new 'boosting' strategy for HIV pre-exposure prophylaxis in healthy volunteers" that was conducted and recently completed at the Indiana University Clinical Research Center. This healthy volunteers trial was a prospective, randomized, open-label, two-treatment, active-control, pivotal, cross-over, pharmacokinetic study designed to compare the plasma, urine, and peripheral blood mononuclear cells (PBMC) pharmacokinetics of single-dose PRO with TDF/FTC to the current 3-day IPERGAY HIV PrEP regimen. Study investigators randomized participants (SAS, PROC RANDOM, v. 9.4) by blocks of 4 to initially receive one of two sequences of treatments: (1) the test ("T") treatment (2g PRO and 600mg TDF / 400mg FTC on day 1 only) and (2) the control ("C") treatment IPERGAY (600mg TDF / 400mg FTC followed by day 1, 300mg TDF / 200mg FTC on days 2 and 3). The wash out was a period of at least 6 weeks before participants were assigned to the other study treatment. Samples collected included (1) blood (plasma, isolated PBMCs) and (2) urine (not shown here). Blood samples

were drawn (~10mL) at 0, 0.5, 1, 2, 4, 8, 12, 18, 24, 48, and 72 hours post-dose. Plasma was harvested for TFV bioanalytical and pharmacokinetic analysis. Peripheral blood mononuclear cell (PBMC) samples were obtained at 0, 24, 48, and 72 hours. The study was conducted at Indiana University Clinical Research Unit and the protocol was approved, in advance, by the Indiana University School of Medicine Institutional Review Board (IRB). This study was supported by the Campbell Foundation for AIDS Research. The full trial protocol can be found at the ClinicalTrials.gov (identifier #: NCT03202511).

A total of 14 subjects completed both phases of the study and the pharmacokinetic analysis of all subjects has been completed. A manuscript describing this pharmacokinetic DDI study has been accepted for publication: **Liu SN et al., Inhibitory Effects of Probenecid on Pharmacokinetics of Tenofovir Disoproxil Fumarate and Emtricitabine for On-Demand HIV PrEP.**