

Title: Pilot Clinical Pharmacokinetic and Pharmacodynamic Study of UC781 Vaginal Gel

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Background: In vivo application of microbicides followed by tissue sampling and ex vivo HIV challenge of the explants is a promising way to assess pharmacodynamics (PD). Several technical issues, however, remain to be resolved (e.g., site and size of biopsy and method of transport [frozen vs. medium]). In addition, tissue sampling to assess drug concentrations in the female genital tract is critical to the clinical evaluation of antiretroviral candidate microbicides but method development is challenging and requires sensitive assays. This pilot study was designed to address some of these technical issues. A pharmacokinetic (PK), PD safety study of UC781gel in women is planned.

Methods: This was a prospective study in which 15 women were enrolled in three groups of five to undergo three genital tract biopsies (cervical and/or vaginal) at the baseline visit and again 4 hours after intravaginal application of 0.1% or 0.25% UC781 (3.5 ml) at the treatment visit. Genital tract tissue was analyzed for UC781 levels and for HIV infectivity following ex vivo exposure of tissue explants to HIV-1_{BaL}. Explant infection was measured by in vitro supernatant p24 levels and UC781 tissue levels were measured by LC/MS/MS. The results of each group of five were used to inform the procedures in the following group.

Results: All baseline biopsies (40) showed productive HIV infection 7 days after an ex vivo explant challenge. Replication in cervical and vaginal tissues was not statistically different, with p24 medians normalized per tissue weight of 187 and 137 pg/mg, respectively. There appeared to be no significant differences between frozen tissue and tissue transported in medium or half versus whole biopsies (n=5). Median UC781 concentrations were 633 ng/g in vaginal biopsies (n=14) and 395 ng/g in cervical biopsies (n=15), and were higher with exposure to 0.25% compared to 0.1% UC781. Data on infectivity of UC781-exposed tissues are being collected.

Conclusions: These pilot data showed that it is feasible to freeze cervical and vaginal biopsies from human subjects prior to ex vivo HIV challenge and that viral replication results are similar with both transport methods. A recently validated assay for vaginal and cervical tissue concentrations of UC781 showed tissue levels orders of magnitude higher than its in vitro effective concentration, following a single dose of UC781 gel. The established methodology will be used in the upcoming expanded safety study of UC781 gel.