

## A Phase 1 Rectal Safety and Acceptability Study of UC781 Microbicide Gel

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**Background:** Vaginal microbicides, when widely available, will inevitably be used rectally by men who have sex with men (MSM) and women. It is critical that the development path of vaginal microbicides include both rectal and vaginal safety studies, especially given the history of nonoxynol-9. We report safety and mucosal immuno-toxicity results from the first phase 1 rectal safety study of the vaginal formulation of the NNRTI UC781 gel (0.1% vs. 0.25% vs. placebo) in 36 sexually abstinent HIV-seronegative adults. The primary safety endpoint is the frequency of >grade 2 adverse events and an extensive panel of assays to assess potential mucosal injury and ex vivo efficacy.

**Methods:** Eligible participants were enrolled and had a baseline flexible sigmoidoscopy with stool and rectal fluid sampling. The same procedures occurred following a single-dose rectal exposure and 7 once-daily rectal exposures. Mucosal indices included: epithelial sloughing; histopathology (10 and 30 cm); microflora changes; mucosal mononuclear cell (MMC) phenotype (10 and 30 cm) by flow cytometry; mucosal cytokine profile (secreted and tissue mRNA); secreted mucosal immunoglobulins; fecal calprotectin indicating mucosal inflammation; explant specimens (10 and 30 cm) for direct HIV challenge of mucosa ex vivo; and acceptability data.

**Results:** Of the 146 participants, who volunteered, 55 were screened, 36 were enrolled, and 36 completed (26 men, 10 women). In 5 of 36 subjects, 84 grade 1 and 8 grade 2 adverse events were reported. Of these 4 grade 2 adverse events occurred in 1 individual at 1 visit; possibly related symptoms were fever, cramps, flatulence, diarrhea; 2 subjects had limited diarrhea, possibly related; 1 had isolated transient thrombocytopenia, not related; and 1 had a spider bite, not related. There were no procedure-related adverse events (108 procedures completed with 3024 intestinal biopsies) or any grade 3 adverse events. Extensive indices of mucosal injury showed no differences when comparing before vs. after product exposure or between treatment groups. Explant and acceptability results are presented elsewhere.

**Conclusions:** This first phase 1 rectal safety trial assessing the vaginal microbicide UC781 showed the product to be safe and well tolerated. Participants were highly compliant and all procedures completed. No significant differences were seen in mucosal injury assays between high dose (0.25%), low dose (0.1%), or placebo groups.