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Abstract title: Characterization of In Vitro Release and In Vivo Delivery of TMC120 with an Intravaginal Ring: Implications for Microbicide Delivery

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Background: The conventional approach for vaginal delivery of microbicides for the prevention of HIV transmission is administration of semi-solid formulations with an applicator. An alternative approach that achieves longer term sustained release of a microbicide is the intra-vaginal ring (IVR). TMC120 is a non-nucleoside reverse transcriptase inhibitor currently in Phase I/II trials as a microbicide in a gel formulation.

Methods: In preliminary studies, TMC120 was formulated into alternative silicone elastomer reservoir type IVR's, and was characterized for release of drug in vitro in different dissolution media. Clinical evaluation of safety and delivery was achieved in a randomized, double-blinded placebo controlled 7 day phase I study of an IVR containing 25 mg of TMC120. Ten women received the TMC120 IVR and 3 received placebo IVR. Standard laboratory diagnostics, vaginal ecology cultures, and pelvic examinations were conducted for safety assessment. Delivery was assessed via determination of TMC120 levels in plasma, as well as in cervical and vaginal tissues obtained by biopsy.

Results: Overall it was shown that sustained release of drug in vitro was maintained for >30 days. No clinically relevant changes in lab parameters or vaginal ecology or pH were observed. One clinically relevant abnormality was revealed upon pelvic exam, but was designated as probably unrelated to drug product. The majority of the adverse events were mild and were doubtful in terms of relation to the drug. No deaths, SAE's or AE's resulting in early termination occurred. TMC120 was detected in vaginal fluids as early as 4 hours post-insertion, as determined with sno-strip collection. TMC120 levels were similar in samples from cervix, the vaginal ring area, and the vaginal introitus. Levels in plasma were below the lower limit of quantitation (5 pg/mL).

Conclusions: The study demonstrated that IVR delivery of TMC120 was safe and generally well tolerated, and release of drug in vivo could be achieved.