Poster Abstract Presentation Notification [A-0999-0021-01209]

Pharmacokinetics of Dapivirine Vaginal Ring during Ring Removals and Re-insertions

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BACKGROUND

HIV prevention methods should consider circumstances of non-adherence to evaluate effectiveness. The effect of multiple removals and (re-)insertions of Dapivirine Vaginal Ring at different time points during a 28-day period on local and systemic dapivirine exposure and dapivirine residual levels in used rings was evaluated to simulate possible scenarios of product non-adherence by women in Phase III clinical trials.

PHARMACOKINETIC RESULTS

(1) Ring removal within 24 hours after insertion resulted in 35% higher dapivirine plasma $AUC_{0\text{-}24h}$ on Day 0 compared to Day 27, likely due to the small burst of drug release observed with new rings, that is unlikely to occur with re-insertion of a used ring. Dapivirine vaginal fluid $AUC_{0\text{-}24h}$ on Days 0 and 27 were similar; the mean dapivirine vaginal fluid concentration before removal of the ring was approximately 25% lower on Day 1 compared to Day 28.

(2) Simulating ring removal during weekends resulted in similar mean AUCs and plasma concentrations prior to ring removals throughout. Dapivirine vaginal fluid AUCs and concentrations prior to ring removal decreased somewhat with each successive ring use period, consistent with the reduced amount of dapivirine remaining in the ring with each re-insertion.

(3) Ring removal at onset of menses and re-insertion after menses resulted in 30% lower plasma $AUC_{0\text{-}24h}$ on Day 0 compared to re-insertion, explained by the fact that dapivirine was not completely cleared from plasma during menses, as reflected in quantifiable mean plasma concentrations before re-insertion of the ring. Vaginal fluid $AUC_{0\text{-}24h}$ was 2.6-fold higher on Day 0 than after re-insertion at the end of menses.

DAPIVIRINE RING RESIDUAL LEVELS

- For all 3 ring use scenarios, mean dapivirine residual levels in used rings decreased with increased duration of ring use.
- Mean (range) dapivirine residual levels were 24.3 (23.9-24.6) mg, 21.4 (20.8-22.0) mg and 20.9 (20.0-21.7) mg for scenarios (1), (2) and (3), respectively.

SAFETY RESULTS

- No serious or product-related adverse events were reported.
- Safety findings were similar to those observed in earlier trials with Dapivirine Vaginal Ring.

METHODS

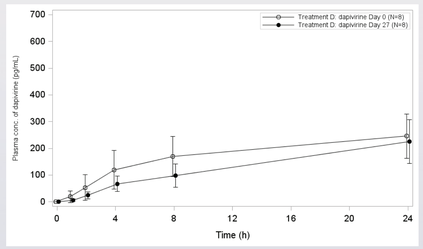
An open-label, randomized trial was conducted in 24 healthy, HIV-negative women, simulating 3 ring use scenarios:

(1) ring insertion on Day 0, removal 24 hours later (Day 1), with re-insertion on Day 27 and removal on Day 28;
(2) ring use during the week (Days 0-3, 7-10, 14-18 and 21-24) and removal during weekends; and
(3) ring use until expected onset of menses, 2 to 3 weeks after start of ring use, with re-insertion after menses until removal on Day 28.

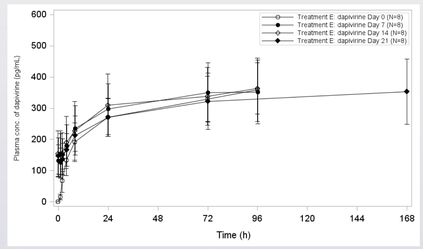
Dapivirine concentrations were determined in plasma and vaginal fluid, and dapivirine residual levels were assessed in used rings. Safety was evaluated throughout the trial.

FIGURE 1: DAPIVIRINE PLASMA CONCENTRATIONS (PG/ML)

Scenario 1



Scenario 2



Scenario 3

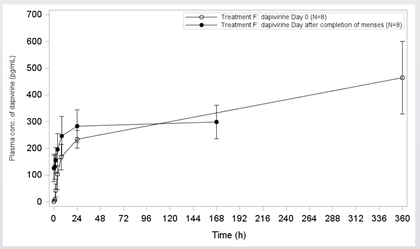
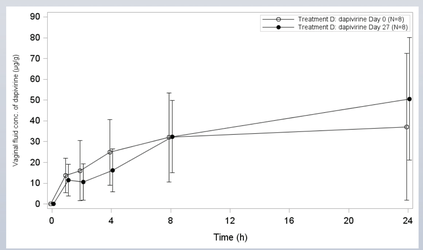
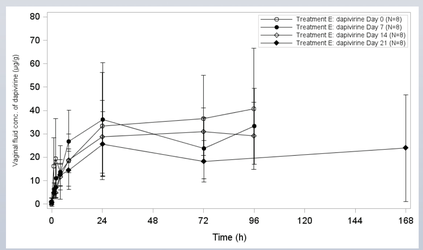


FIGURE 2: DAPIVIRINE VAGINAL FLUID CONCENTRATIONS (µG/G)

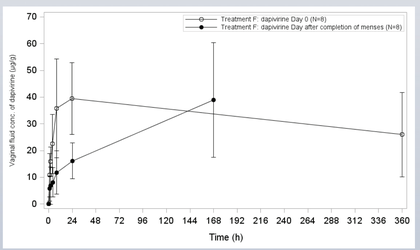
Scenario 1



Scenario 2



Scenario 3



CONCLUSION

Dapivirine release readily continued into vaginal fluids during all re-insertion scenarios. During ring use, dapivirine release rates decreased as drug levels present in the ring decreased, and also as duration of ring use increased.

Also see Poster Abstract Presentation Notification [A-0999-0021-00987]

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