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

Pharmacokinetics of Dapivirine Vaginal Ring (25 mg) Co-administered with Clotrimazole

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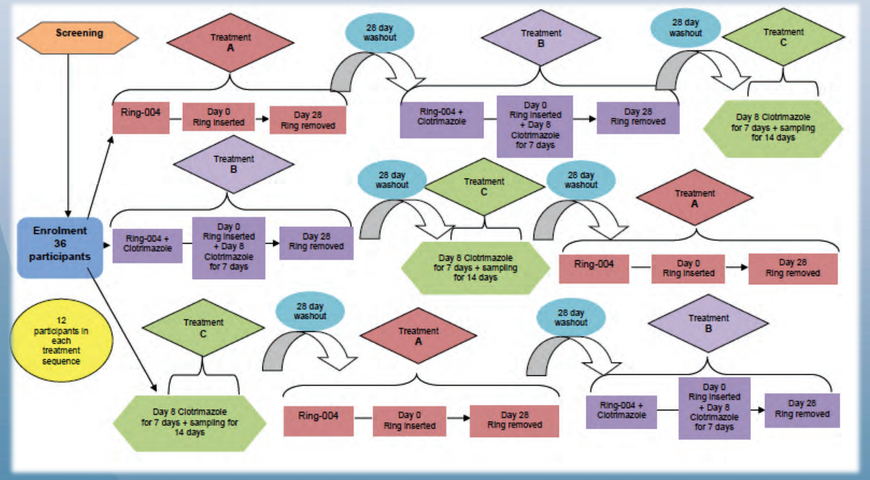
BACKGROUND

Dapivirine Vaginal Ring (25 mg) provides topical delivery of the microbicide, dapivirine, to the vagina. There is the potential of drug-drug interactions between dapivirine and other co-administered vaginal products. Clotrimazole, an imidazole derivative with a broad spectrum of antimycotic activity, is widely used in sub-Saharan Africa. This trial evaluated whether concomitant use of repeat vaginal doses of clotrimazole (10 mg/g [1%]; 50 mg/day) administered on 7 consecutive days with the Dapivirine Vaginal Ring affects the local and systemic pharmacokinetic (PK) profiles of dapivirine and clotrimazole. The safety of co-administration of the two drugs in healthy, HIV-negative women was also assessed.

TRIAL DESIGN

- Open-label, randomized, 3-period, 3-sequence crossover trial in 36 healthy HIV-negative women, aged 18-45 years.
- Participants used Dapivirine Vaginal Ring for 28 days, clotrimazole (5 g/day) for 7 days or both, with clotrimazole co-administered on Days 8-14, with 28-day washout periods between treatments (Figure 1).
- Dapivirine and clotrimazole concentrations were determined in plasma and vaginal fluid, and dapivirine residual levels assessed in used rings.
- Safety was evaluated throughout the trial.

FIGURE 1: TRIAL DESIGN



RESULTS - DAPIVIRINE

- In the presence of clotrimazole, dapivirine plasma and vaginal fluid concentrations were similar compared to dapivirine alone.
- Clotrimazole had no clinically relevant effect on plasma dapivirine C_{max} and AUCs.
- Dapivirine vaginal fluid exposure ($AUC7_{-14\ days}$) was 20% higher during co-administration with clotrimazole, but similar across the 28-day ring use period for both treatments.
- Dapivirine residual levels in used rings were 19.8 mg and 20.3 mg for dapivirine + clotrimazole and dapivirine alone, respectively.

Figure 2: Dapivirine Plasma Concentrations (pg/mL)

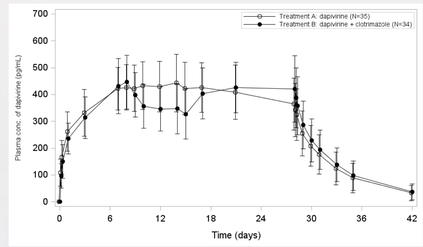


Figure 3: Dapivirine Vaginal Fluid Concentrations - Cervix (µg/g)

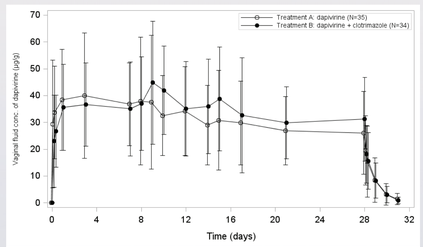


Figure 4: Clotrimazole Plasma Concentrations (ng/mL)

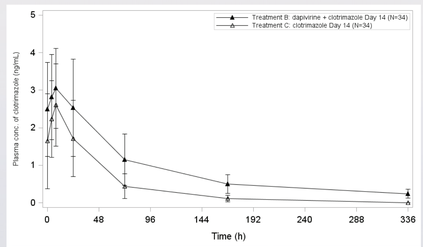
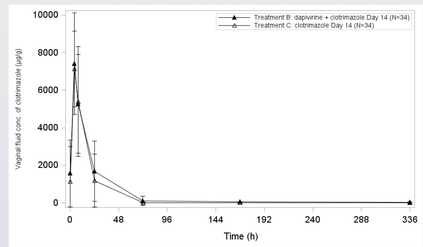


Figure 5: Clotrimazole Vaginal Fluid Concentrations - Cervix (µg/g)



RESULTS - CLOTRIMAZOLE

- After the first clotrimazole application, plasma C_{max} and AUC0-24h were similar for clotrimazole with or without dapivirine.
- Repeated clotrimazole applications in the presence of dapivirine increased plasma clotrimazole C_{max} and $AUC_{0\text{-}24h}$ by 23% and 33%, respectively.
- Vaginal fluid exposure parameters were comparable. Clotrimazole elimination after the last dose was slower in the presence of dapivirine.

RESULTS - SAFETY

- No clinically relevant safety differences were observed between treatments.
- No product-related SAEs were reported.
- One product-related adverse event (Grade 1 vulvovaginal pruritus) was reported in the dapivirine + clotrimazole arm.

CONCLUSION

Local and systemic dapivirine exposure was similar in the presence and absence of vaginal clotrimazole. A modest increase in systemic clotrimazole exposure (33%) in the presence of dapivirine was observed but was not considered clinically relevant. Dapivirine Vaginal Ring was well tolerated and safety findings were similar to those observed in earlier trials.

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

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