

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

Neliëtte van Niekerk¹, Jan Noukens², Jeremy Nuttall¹, Brid Devlin¹, Annalene Nel¹

¹International Partnership for Microbicides, Silver Spring, MD, USA; ²Venn Life Sciences, Breda, The Netherlands



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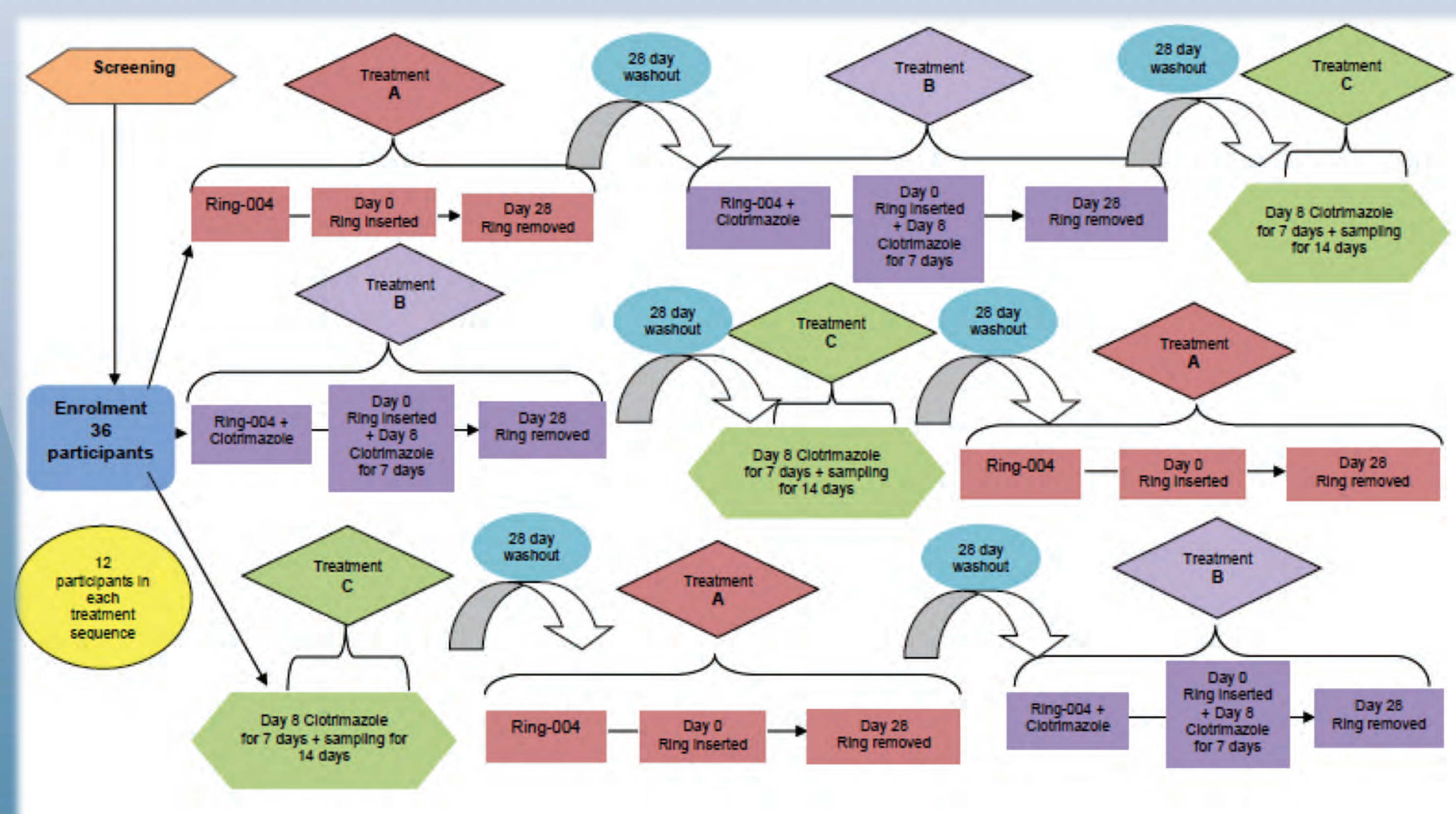
BACKGROUND

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 ($AUC_{7-14 \text{ days}}$) 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 3: Dapivirine Vaginal Fluid Concentrations - Cervix ($\mu\text{g/g}$)

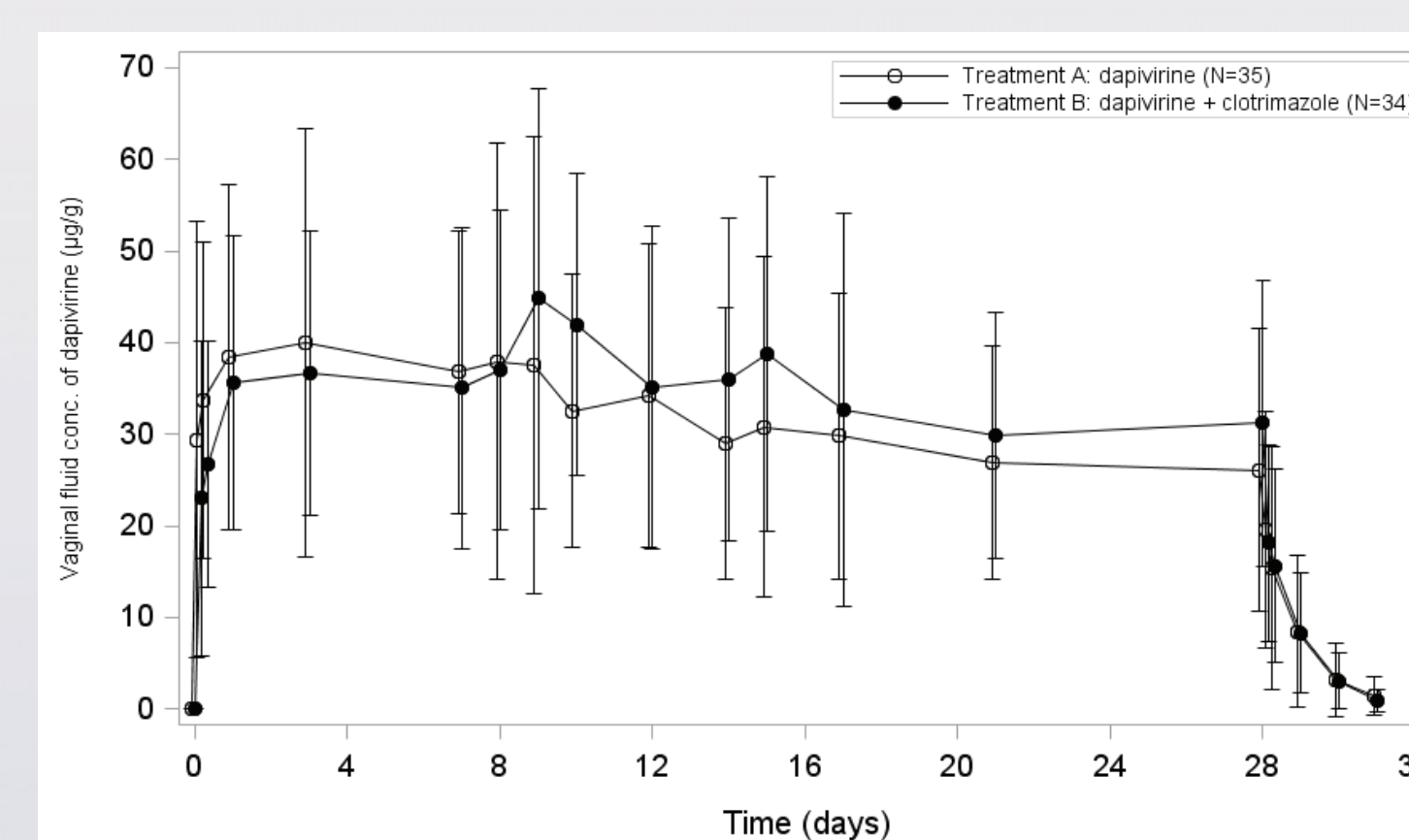


Figure 4: Clotrimazole Plasma Concentrations (ng/mL)

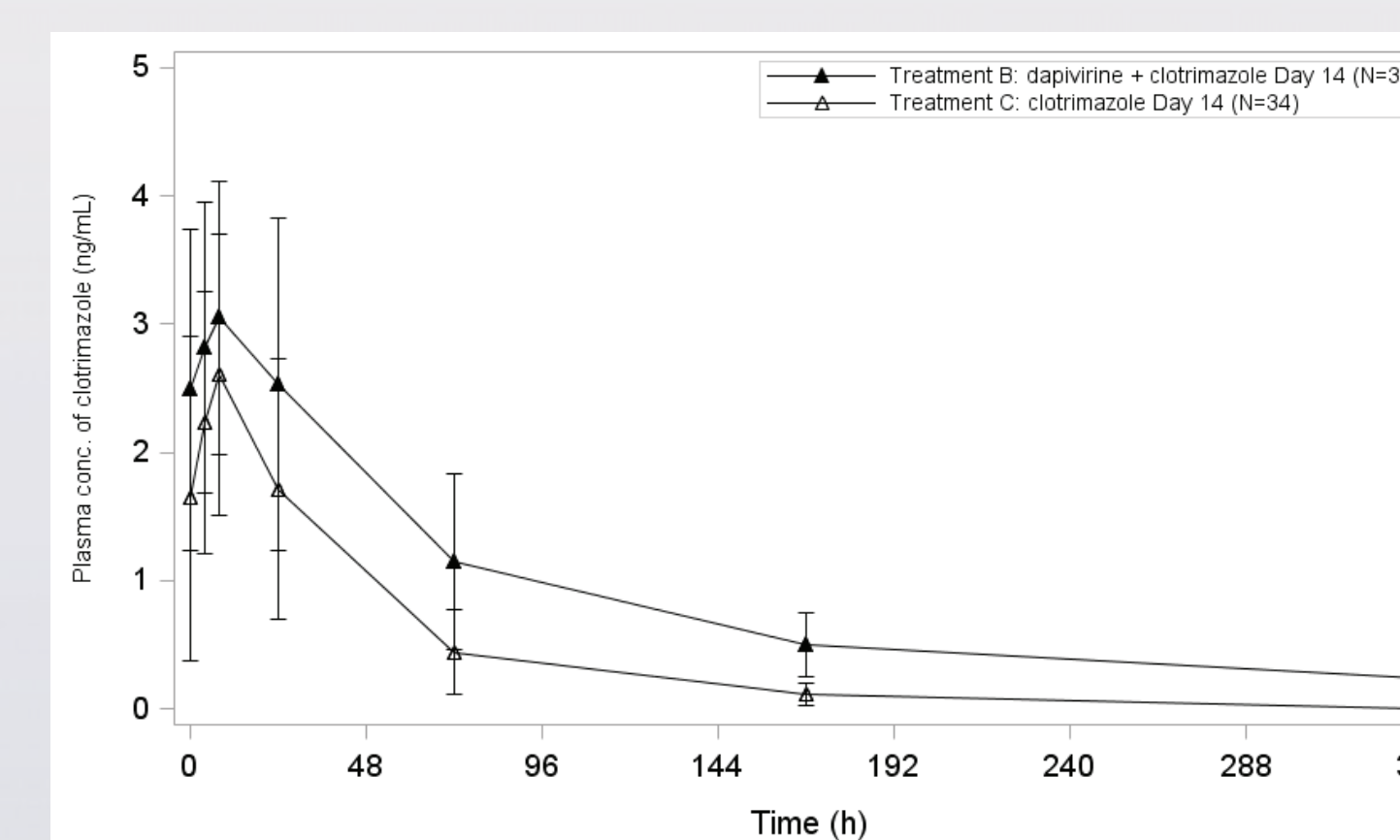


Figure 2: Dapivirine Plasma Concentrations (pg/mL)

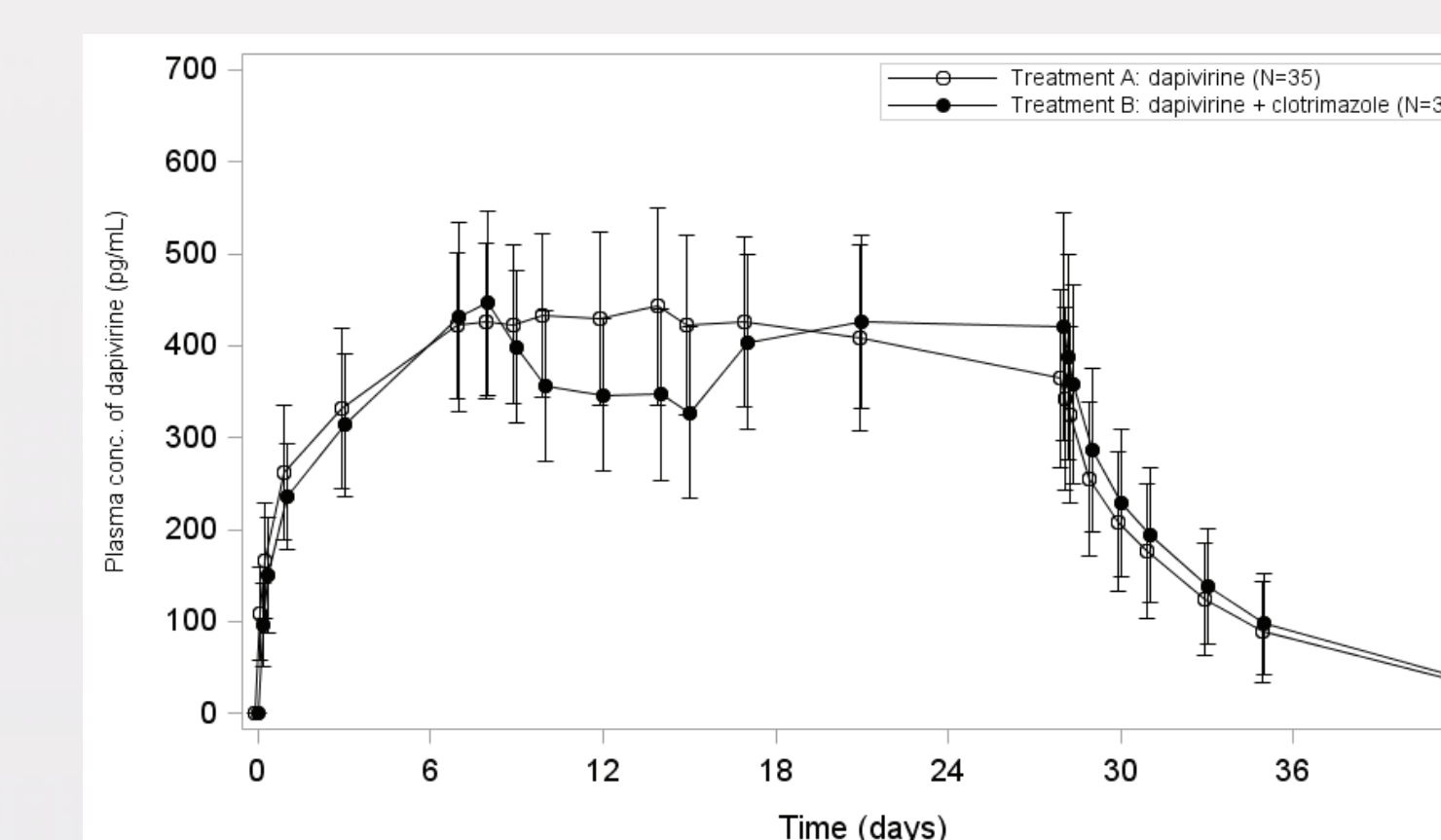
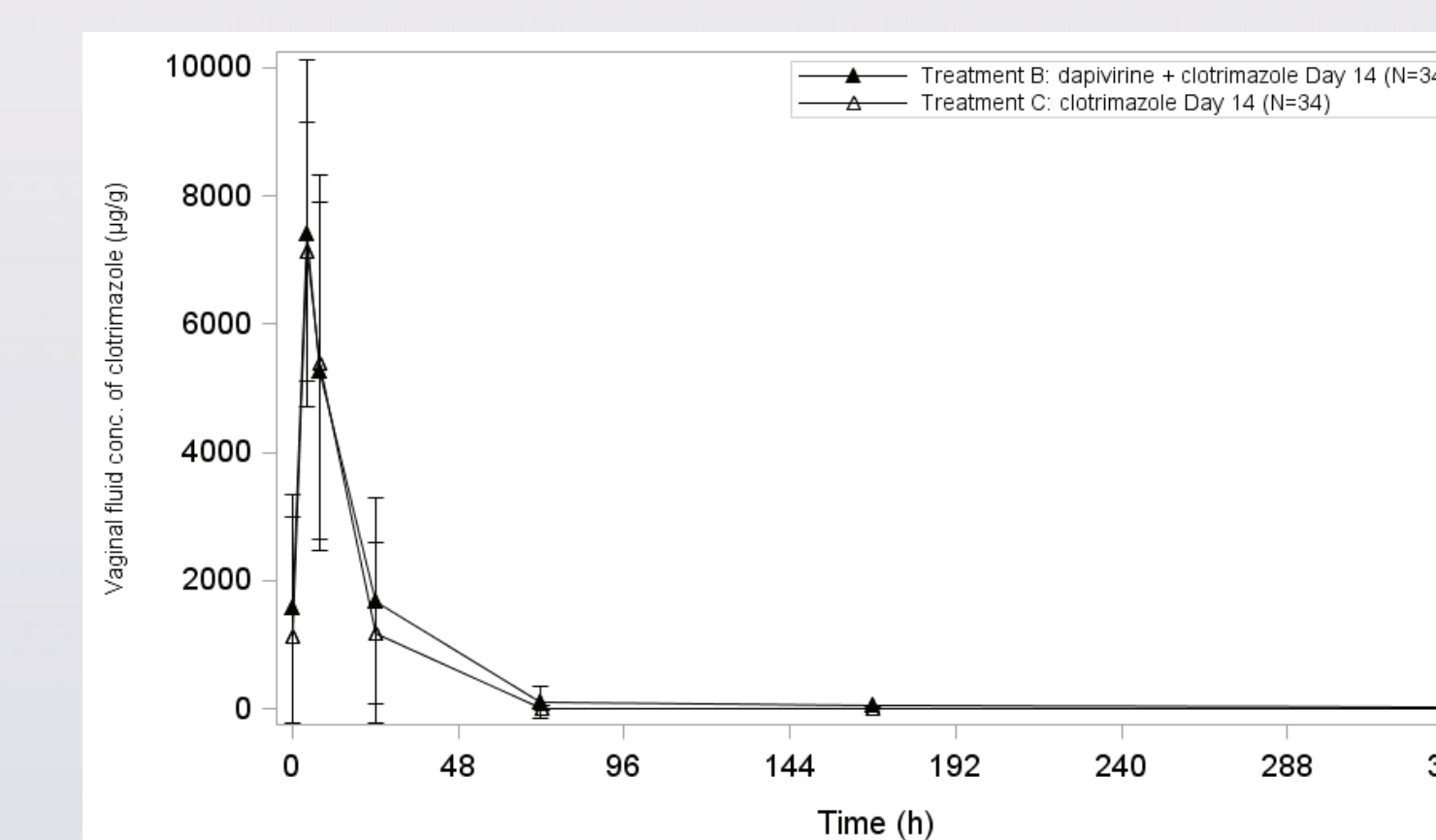


Figure 5: Clotrimazole Vaginal Fluid Concentrations - Cervix ($\mu\text{g/g}$)



RESULTS - CLOTRIMAZOLE

- After the first clotrimazole application, plasma C_{max} and AUC_{0-24h} were similar for clotrimazole with or without dapivirine.
- Repeated clotrimazole applications in the presence of dapivirine increased plasma clotrimazole C_{max} and AUC_{0-24h} 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.