Safety and Pharmacokinetics of Dapivirine Vaginal Rings in Postmenopausal U.S. Women

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Background

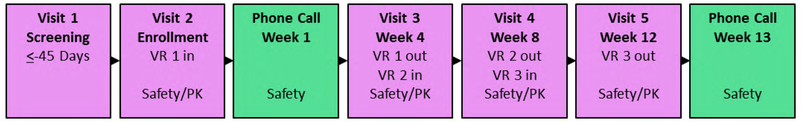
- Postmenopausal women may be at higher biological risk for HIV than premenopausal women due to increased CCR5 expression and decreased HIV-1 innate activity (1, 2)
- Microbicide vaginal rings (VR) hold promise for sustained drug release and increased adherence; no prior studies in postmenopausal women
- VRs containing dapivirine (DPV), an NNRTI, are currently in phase 3 effectiveness trials

Objective

- To evaluate safety and pharmacokinetics (PK) of a VR containing DPV compared to placebo in postmenopausal women

Methods

- MTN-024/IPM 031: Phase 2a, double-blind, randomized (3 DPV : 1 Placebo) trial
- Study sites: Birmingham (AL), Cleveland (OH), and Pittsburgh (PA)
- Monthly VRs contained 25 mg DPV or placebo for 12 weeks followed by 1 week off-product



- Healthy, post-menopausal, age 45-65, no menses ≥12 mos, FSH ≥40 mIU/ML, HIV negative
- Safety: related Grade 2 or higher genital, genitourinary, or reproductive system adverse events (AEs) and Grade 3 or higher AEs, compared to placebo using Fisher's exact test
- PK assessments for DPV levels: plasma at Weeks 4, 8 and 12 (n=96); vaginal fluid (VF) at Weeks 4, 8 and 12 (n=45); cervical tissue biopsies at Week 12 (n=15)
- DPV concentrations at Weeks 4, 8 and 12 were analyzed using repeated measures ANOVA
- Used rings were analyzed for residual drug levels

Results

Table 1. Demographics (N=96)

	DPV	Placebo	All Arms
Mean Age in Years (SD)	57.2 (4.3)	55.3 (3.0)	56.8 (4.1)
45-49 Years (n,%)	1 (1%)	0 (0%)	1 (1%)
50-54 Years (n,%)	21 (29%)	12 (50%)	33 (34%)
55-59 Years (n,%)	26 (36%)	11 (46%)	37 (39%)	
60-65 Years (n,%)	24 (33%)	1 (4%)	25 (26%)
Race			
Black or African American (n,%)	22 (31%)	8 (33%)	30 (31%)
White (n,%)	48 (67%)	15 (63%)	63 (66%)
Other (n,%)	2 (3%)	1 (4%)	3 (3%)
Mean Age of Menopause (SD)*	49.4 (4.1)	49.5 (5.2)	49.5 (4.3)

* n = 81 (menopausal age not evaluable for some women due to hysterectomy or ablation)

Table 2. Adverse Events

	DPV		Placebo		All Arms	
	Not related	Related	Not related	Related	Not related	Related
Grade 1	35 (41.2%)	**50 (58.8%)**	8 (40.0%)	**12 (60.0%)**	43 (41.0%)	**62 (59.0%)**
Grade 2	22 (78.6%)	**6 (21.4%)**	11 (73.3%)	**4 (26.7%)**	33 (76.7%)	**10 (23.3%)**
Grade 3	3 (75.0%)	**1 (25.0%)**	0	**0**	3 (75.0%)	**1 (25.0%)**
Grade 4	0	**0**	0	**0**	0	**0**
Death	0	**0**	0	**0**	0	**0**
Total	60 (51.3%)	**57 (48.7%)**	19 (54.3%)	**16 (45.7%)**	79 (52.0%)	**73 (48.0%)**

- Study retention was 97%
- No difference in related Grade 2 or higher genital, genitourinary, or reproductive system AEs in DPV vs. placebo (6/72 (8%) vs. 3/24 (13%), *P*=.69)
- No difference in Grade 3 or higher AEs in DPV vs. placebo (4/72 (6%) vs. 0/24 (0%), *P*=.57)
- 6 protocol-required product holds for 5 women, all due to AEs that resolved
- Two women in DPV arm declined to restart study product
- Majority of AEs were grade 1; only half were deemed related

Table 3. Pharmacokinetics

Plasma DPV (pg/mL)	Median (IQR)	Mean (95% CI)
Week 4 (n=69)	268 (213, 325)	273 (250, 297)
Week 8 (n=70)	288 (217, 325)	289 (259, 318)
Week 12 (n=69)	262 (227, 351)	298 (264, 333)

Vaginal Fluid DPV (ng/mg)	Median (IQR)	Mean (95% CI)
Week 4 (n=33)	34 (26, 61)	64 (41, 88)
Week 8 (n=34)	45 (32, 78)	79 (46, 111)
Week 12 (n=33)	41 (22, 81)	72 (44, 101)

- No change in median DPV in plasma and VF over 12 weeks
- DPV detectable in cervical tissue in only 5/10 women; median biopsy weights were 36% lower when DPV undetectable
- Residual VR DPV content in returned rings
  - Across all visits, median 21.1 mg (IQR 20.7, 21.5)
  - Consistent with adherence to VR use
  - No difference in residual DPV between women with detectable vs. undetectable cervical tissue DPV levels

Conclusions

- DPV VR safe & well tolerated in postmenopausal women
- Only 2/96 (2.1%) chose not to continue VR use due to AEs
- Plasma & VF DPV concentrations constant over 12 weeks
- Undetectable DPV in cervical tissue may be due to small biopsies
- Postmenopausal women plasma DPV similar to reproductive age women (median plasma DPV levels of 217.5 to 260 pg/mL at 28 days [3, 4])
- Further studies needed to assess biological differences in the postmenopausal genital tract

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