

THE FIRST-IN-HUMAN TRIAL OF PC-1005 (MIV-150 AND ZINC ACETATE IN A CARRAGEENAN GEL)

Abstract #875

popcouncil.org

Barbara A. Friedland¹, Craig J. Hoesley², Marlena Plagianos³, Shimin Zhang³, Elena Hoskin³, Mohcine Alami⁴, Natalia Teleshova³, José A. Fernández-Romero³, Thomas M. Zydowsky³, George W. Creasy³

¹Population Council, New York, NY; ²University of Alabama, Birmingham, AL; ³Population Council, Center for Biomedical Research, New York, NY; ⁴Population Council, Washington, DC

BACKGROUND

PC-1005 is a promising multipurpose prevention technology (MPT) in development that is active against 3 non-curable STIs: HIV, herpes simplex virus (HSV), and human papillomavirus (HPV); and is designed for vaginal and rectal use.

PC-1005 is composed of: **MIV-150**, a potent NNRTI, not used for HIV therapy; **zinc acetate**, a selective antiviral agent generally recognized as safe (GRAS) by the US FDA; and **carrageenan (CG)**, a gelling agent derived from seaweed (also GRAS) with excellent antiviral activity against HPV.

Study Objectives:

- Primary:** to evaluate the safety of PC-1005 and to determine the pharmacokinetics (PK) of MIV-150 in plasma.
- Secondary:** to assess acceptability and adherence.
- Exploratory:** to determine the PK of zinc in plasma; to measure MIV-150 concentrations in cervical tissue; and to assess MIV-150, zinc and CG pharmacodynamics (PD) in cervicovaginal lavages (CVLs).

METHODS

Design: Randomized (4:1), placebo-controlled, double-blind trial (RCT); preceded by 3-day open-label (OL) run-in, PC-1005 only (Figures 1 and 2)

Population: Healthy, sexually abstinent women, aged 19–49 at one US site: University of Alabama, Birmingham (UAB)

Regimen: 4 mL PC-1005 (or HEC placebo) gel inserted vaginally once daily for 14 days; doses 1, 8 and 14 in the clinic

Endpoints and assessments:

- Safety:** Adverse events (AE), abnormal clinical or laboratory findings
- PK:** MIV-150 and zinc PK parameters calculated using non-compartmental techniques and actual sampling times
- Acceptability:** Self-administered questionnaire (Day 14); in-depth interview (Day 21)
- Adherence:** Self-report and applicator count (Days 8 and 14)
- PD:**
 - Antiviral activity against HIV, HSV-2 and HPV in CVL measured using cell-based assays
 - EC₅₀ values for CVL antiviral activity calculated using a dose-response inhibition analysis

METHODS (Con't)

Figure 1. Schema, OL run-in

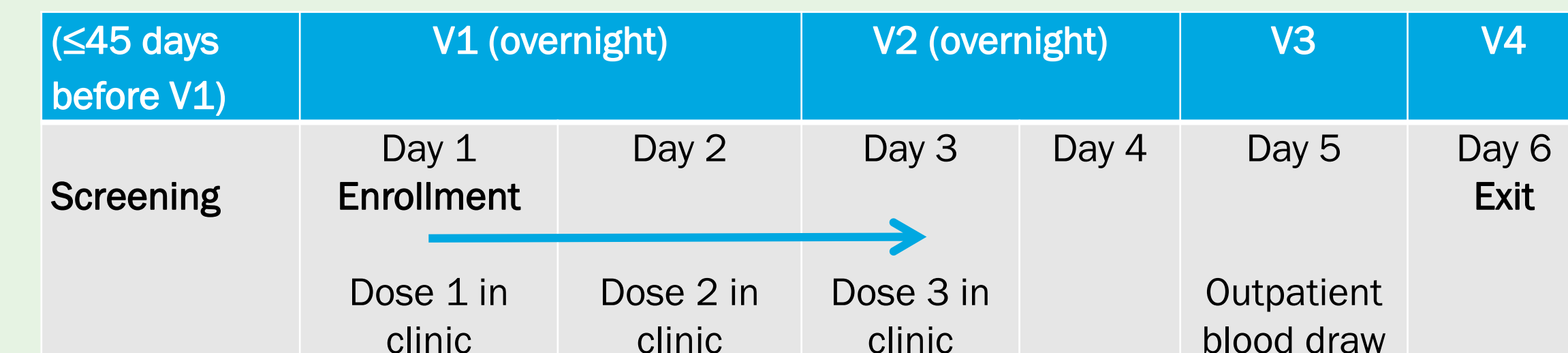
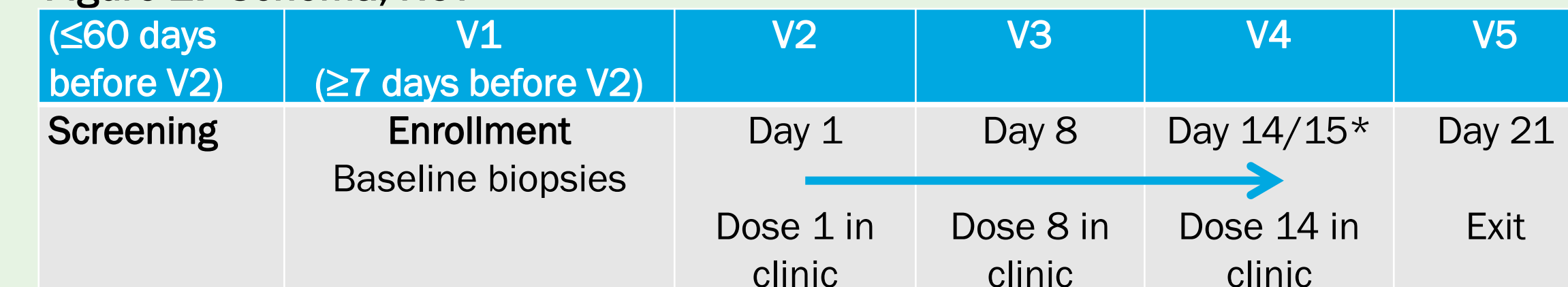


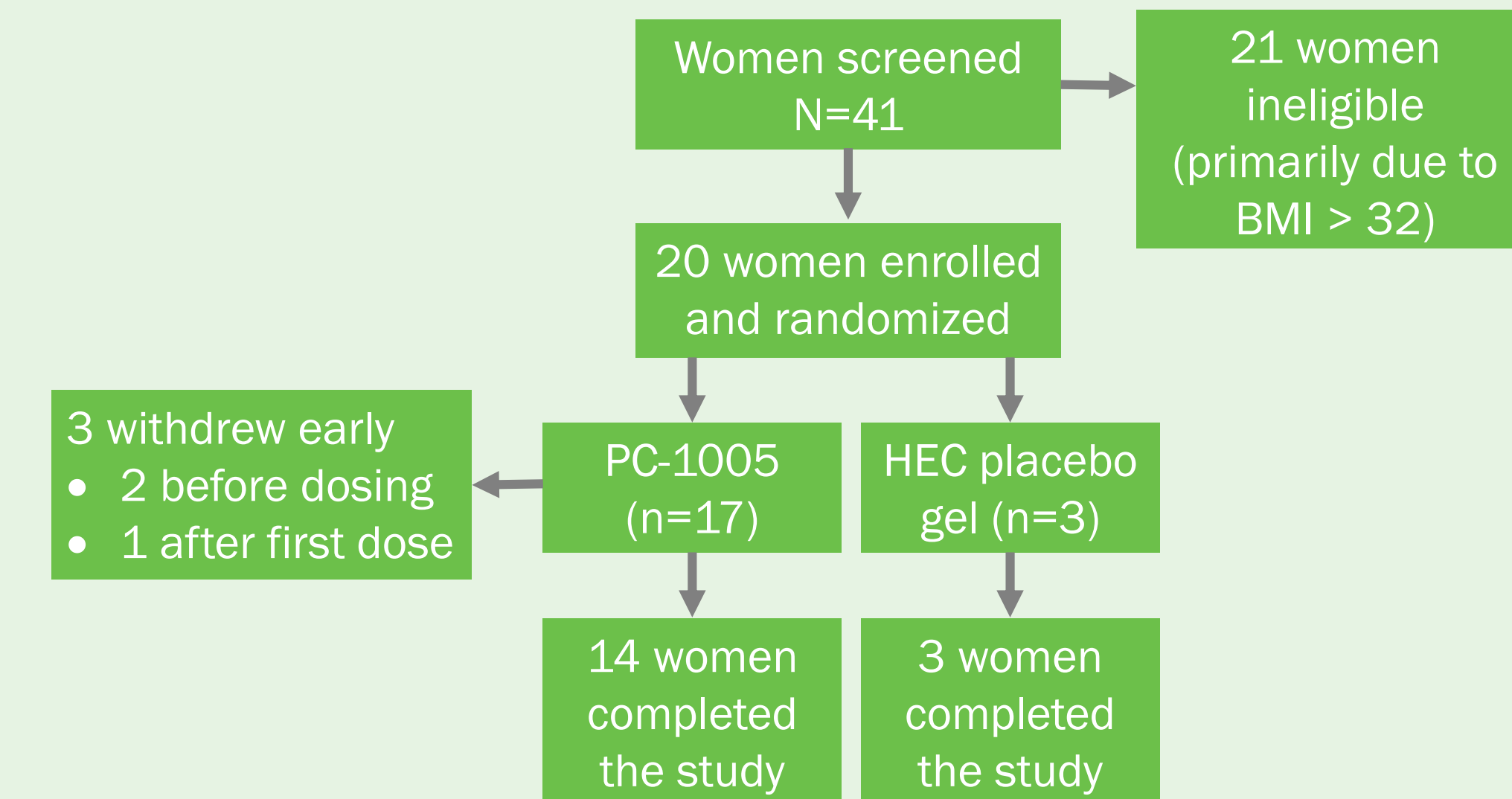
Figure 2. Schema, RCT



V=visit; *Half of participants randomized to final PK/PD assessment 4 hours after Dose 14 (Day 14); half randomized to final PK/PD assessment 24 hours after Dose 14 (Day 15).

RESULTS

Figure 3. Participant disposition, RCT



5/5 women completed the OL period and inserted all 3 doses.

TABLE 1. Demographics and other background characteristics (n=25)

	Open label PC-1005 (n=5)	Main study PC-1005 (n=17)	Placebo (n=3)
Age (years)			
Mean (range)	31.6 (29-38)	31.2 (19-44)	24.0 (21-29)
Race n (%)			
Black	2 (40%)	11 (64.7%)	0 (0%)
White	2 (40%)	5 (29.4%)	2 (66.7%)
Other	1 (20%)	1 (5.9%)	1 (33.3%)
Ethnicity			
Hispanic or Latino	0 (0%)	1 (5.9%)	0 (0%)
BMI			
Mean (range)	26.7 (22.1-31.6)	26.6 (18.9-31.3)	21.2 (19.6-23.1)
Partnership status			
Married	n/a	2 (11.8%)	2 (66.7%)
Single, never married	n/a	12 (70.6%)	1 (33.3%)
Divorced	n/a	3 (17.7%)	0 (0%)
Parity			
Mean (range)	1.2 (0-4)	1.2 (0-4)	1.3 (0-3)
Contraceptive method			
Hormonal*	4 (80%)	16 (94.1%)	2 (66.7%)
Non-hormonal**	1 (20%)	1 (5.9%)	1 (33.3%)

n/a = data not collected in OL phase; *Includes: combined oral contraceptives, Depo Provera, levonorgestrel-releasing intrauterine system (Mirena), implant, contraceptive patch; **Includes: Paragard, tubal ligation, vasectomy

RESULTS (Con't)

Primary Outcomes

Safety

- There were no SAEs or early discontinuations for AEs.
- Of the 18 AEs recorded, most were mild (n=13) and/or unrelated (n=9) and similar across groups (data not shown).
- No significant abnormalities were observed in clinical, lab or pathology results.

PK of MIV-150 (Table 2, Figure 4)

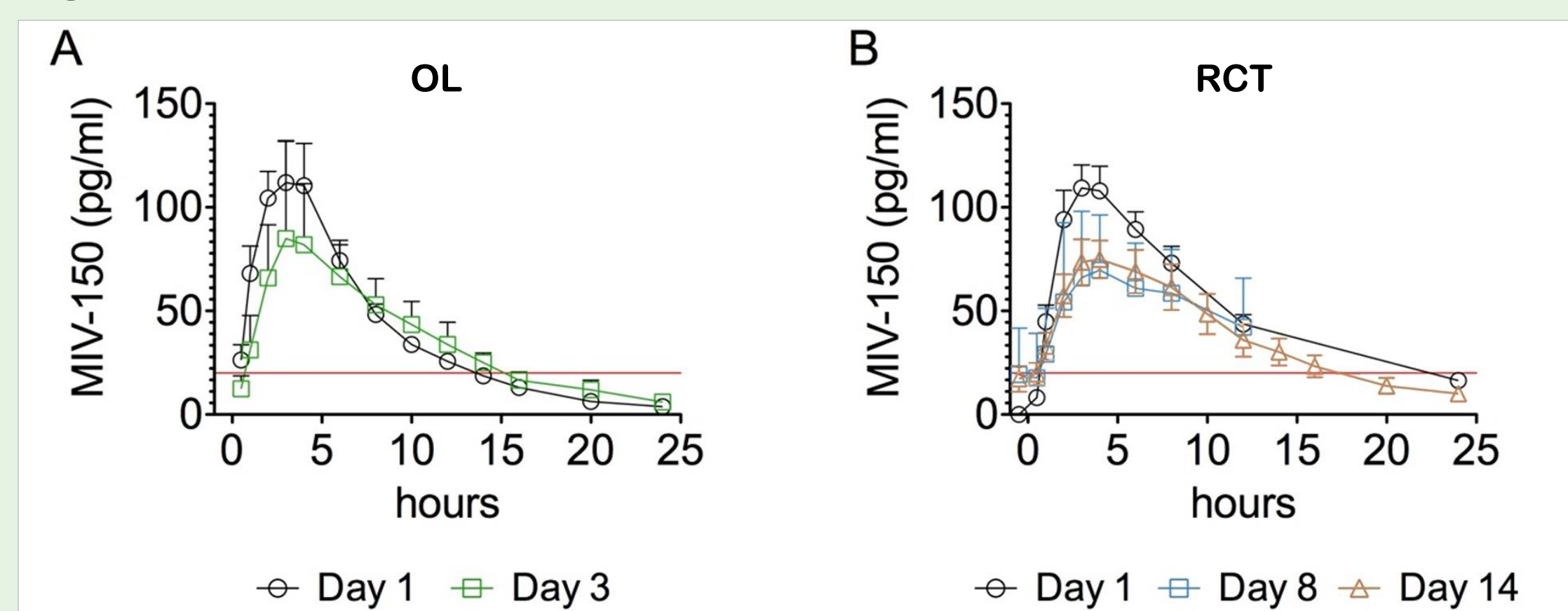
- MIV-150 was absorbed systemically at low levels with no accumulation detected.

TABLE 2. Summary of MIV-150 plasma pharmacokinetic parameters

Parameter statistics (Mean values)	Open label		RCT		
	Day 1 (n=5)	Day 3 (n=5)	Day 1 ^a (n=14)	Day 8 ^a (n=14)	Day 14 ^b (n=6)
C _{max} (pg/mL)	114	84.7	113	75.7	75.5
T _{max} (h)	3.92	3.92	2.95	3.98	4.96
C _{min} (pg/mL)	ND	3.52	ND	13.3	9.70
AUC _{0-last} (pg·h/mL)	885	834	839	601	826
AUC _{0-∞} (pg·h/mL)	906	ND	1173	ND	ND
AUC _{0-12h} (pg·h/mL)	885	834	1126	847.3 ^c	827
AUC _{0-12h} (pg·h/mL)	753	646	818	601	586
T _{1/2} (h)	3.89	4.82	4.44	4.20 ^c	5.51
Cl/F (L/h)	81.3	88.3	62.7	86.9 ^c	89.1
R _{AUC}	ND	0.942	ND	ND	0.837
R _{AUC0-12h}	ND	0.858	ND	0.753	0.791
R _{Cmax}	ND	0.743	ND	0.702	0.648

Note: Values are geometric means; ^aIncludes participants randomized to Time 1 and Time 2 on Day 14; ^bOnly includes participants randomized to Time 2 on Day 14; ^cData is from 1 participant; ND = Not determined

Figure 4. Mean MIV-150 plasma concentration-time profile, linear scale



NOTE: Concentration during OL (A) and RCT (B) periods. All plasma values assayed as Non-Detectable (ND) were assigned values of zero (0). All zero and non-zero plasma values were used in plasma PK parameter calculations. The red line horizontal to the X-axis is the Lower Limit of Quantitation (LLOQ) (20 pg/mL) for MIV-150 in plasma.

Secondary Outcomes

Acceptability

- 17/17 participants said the gel was easy to use.
- 11/17 reported liking the gel (somewhat or very much).
- 16/17 were willing to use the gel in the future if it was found to be effective and they felt they were at risk of HIV.
- 14/17 were not bothered by leakage, though 7/17 recommended reducing the volume.

RESULTS (Con't)

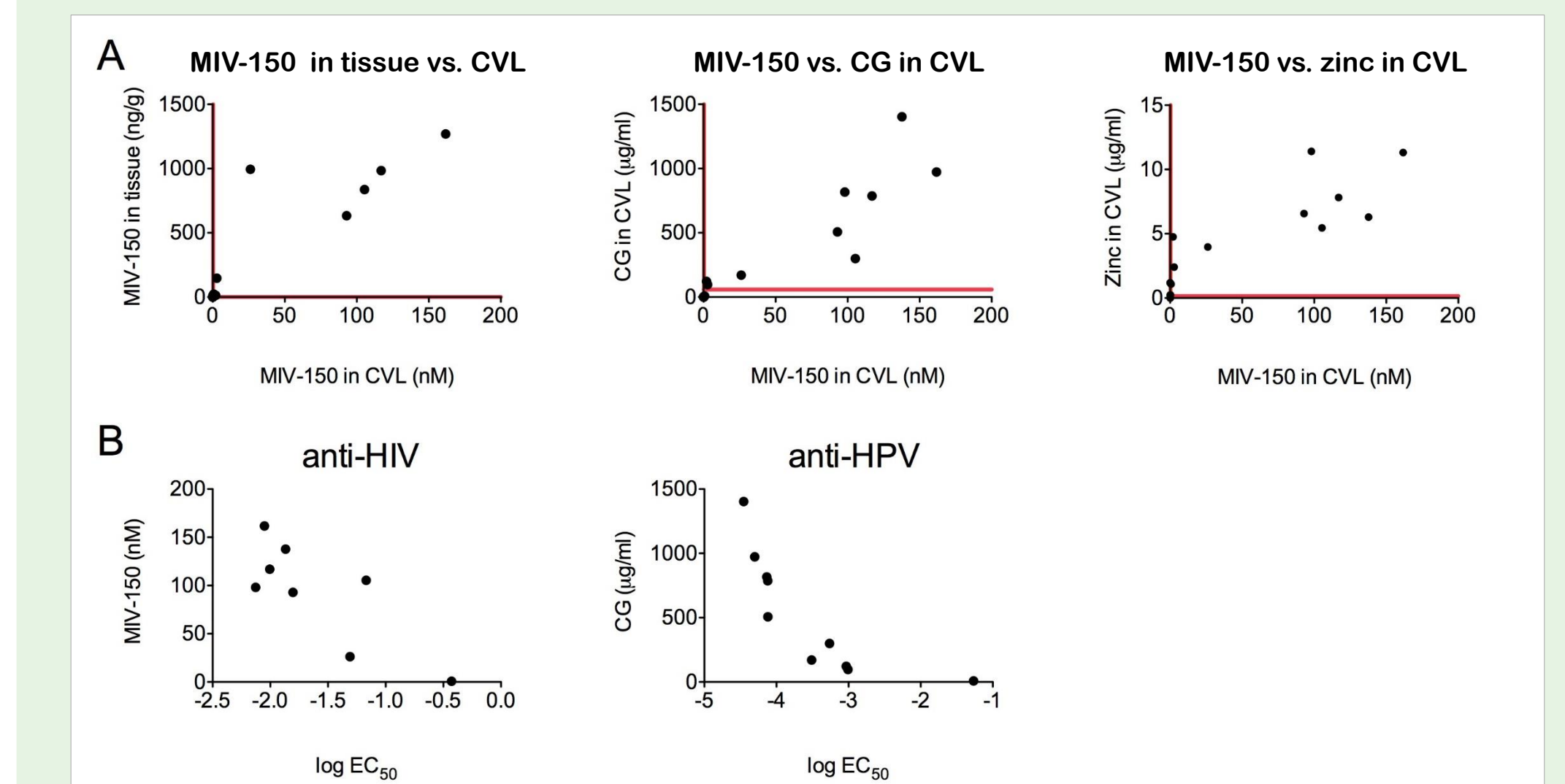
Exposure/Adherence (RCT)

- 13/17 participants inserted all 14 doses
- 16/17 participants used ≥ 93% of doses

Exploratory Outcomes

- Plasma zinc concentrations were unchanged from baseline (data not shown).
- 7/7 CVLs collected 4h post-dose demonstrated measurable anti-HIV and anti-HPV activity in cell-based assays (Figure 5).
- High antiviral activity in baseline CVLs precluded assessment of anti-HSV-2 activity in cell-based assays (see Abstract #876 for results of anti-HSV activity in explants).

Figure 5. Correlation of API levels with each other, in different compartments, and their respective antiviral activity



A) Concentrations of MIV-150 (plasma, CVL, tissue) were determined using LC-MS/MS; of zinc (plasma and CVL) using ICP-MS; and of CG (CVL) using ELISA. Red lines parallel to X and Y-axes are the LLOQ for each API/compartments; no red line indicates LLOQ of 0.
B) API concentrations were measured as described in A above; antiviral activity was determined using the TzM-bl and Luciferase assays for anti-HIV-1 and anti-HPV16 PsV activity respectively. The graphs show the log EC₅₀ values for each sample versus API concentration.

CONCLUSIONS

- PC-1005 gel used vaginally for 14 days was well-tolerated, with low systemic absorption of MIV-150 and measurable HIV and HPV antiviral activity in CVL.
- These results warrant continued development of PC-1005 as a viable MPT for vaginal or rectal prevention of HIV/STIs.

FOR MORE INFORMATION

For more information please contact **Barbara Friedland** at bfriedland@popcouncil.org.

This work was made possible by the generous support of the American people through the United States Agency for International Development (USAID) Cooperative agreement GPO-A-00-04-00019-00. These contents are the responsibility of the Population Council and do not necessarily reflect the views of USAID or the United States Government.

