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

Abstract #875

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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
  - EC_{50} values for CVL antiviral activity calculated using a dose-response inhibition analysis

METHODS (Con't)

Figure 1. Schema, OL run-in

(≤45 days before V1)	V1 (overnight)		V2 (overnight)		V3	V4
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Screening	Enrollment →					Exit
	Dose 1 in clinic	Dose 2 in clinic	Dose 3 in clinic		Outpatient blood draw	

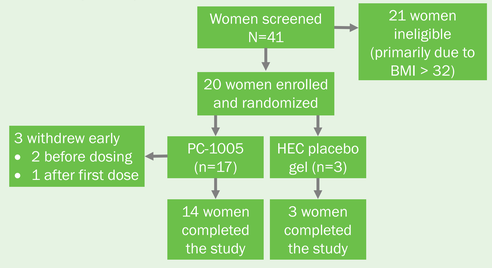
Figure 2. Schema, RCT

(≤60 days before V2)	V1 (≥7 days before V2)	V2	V3	V4	V5
Screening	Enrollment	Day 1	Day 8	Day 14/15*	Day 21
	Baseline biopsies	→			
		Dose 1 in clinic	Dose 8 in clinic	Dose 14 in clinic	Exit

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)	Main study 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)

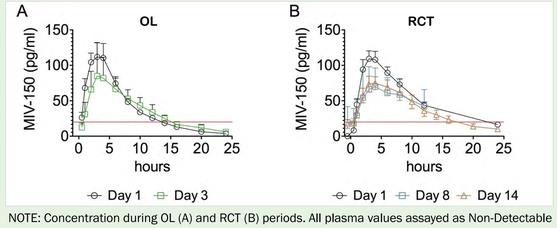
- MIV-150 was absorbed systemically at low levels with no accumulation detected.

TABLE 2. Summary of MIV-150 plasma pharmacokinetic parameters

Parameter statistics (Mean values)	Open label Day 1 (n=5)	Open label Day 3 (n=5)	RCT Day 1[a] (n=14)	RCT Day 8[a] (n=14)	RCT 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
$AUC_{0\text{-last}}$ (pg·h/mL)	885	834	839	601	826
$AUC_{0-\infty}$ (pg·h/mL)	906	ND	1173	ND	ND
$AUC_{0\text{-tau}}$ (pg·h/mL)	885	834	1126	847.3[c]	827
$AUC_{0\text{-}12}$ (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
$R_{AUC0\text{-}12}$	ND	0.858	ND	0.753	0.791
R_{Cmax}	ND	0.743	ND	0.702	0.648

Note: Values are geometric means; [a]Includes participants randomized to Time 1 and Time 2 on Day 14; [b]Only includes participants randomized to Time 2 on Day 14; [c]Data 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)

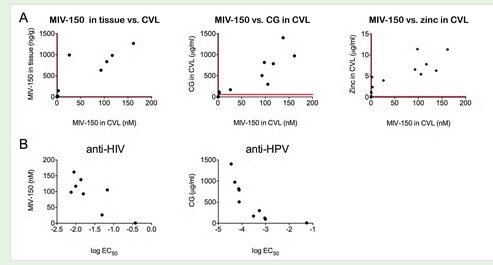
Exposure/Adherence (RCT)

- 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/compartment; 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 EC_{50} 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.

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