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A Phase I Trial of a Rectally Administered Gel Formulated with the NNRTI IQP-0528

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Introduction

- A microbicide gel with lubricating properties applied at vaginal and rectal sites of sexual HIV exposure may provide a behaviorally congruent and discreet strategy to improve adherence and reduce the risk of HIV infection.
- IQP-0528 is a potent pyrimidinedione non-nucleoside reverse transcriptase inhibitor (NNRTI) with a second inhibitory mechanism preventing viral entry into target cells.
- DuoGel™ is a topical IQP-0528-containing gel formulated for both rectal and vaginal use.
- Vaginal application of DuoGel™ to SHIV-positive Rhesus macaques yielded detectable concentrations in the rectum 4 h post-dosing.

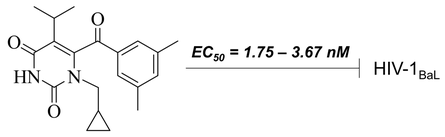
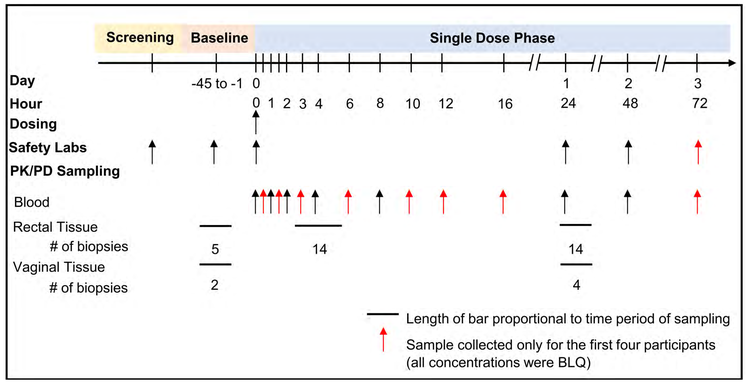


Figure 1. *In Vitro* Efficacy of IQP-0528.
IQP-0528 structure and EC_{50} values alone and in the presence of simulated seminal and vaginal fluids.

Study Objectives and Schema

Our study is a first-in-human evaluation of the safety and single-dose pharmacokinetics and pharmacodynamics of 10 mL *rectally administered* DuoGel™ containing IQP-0528.

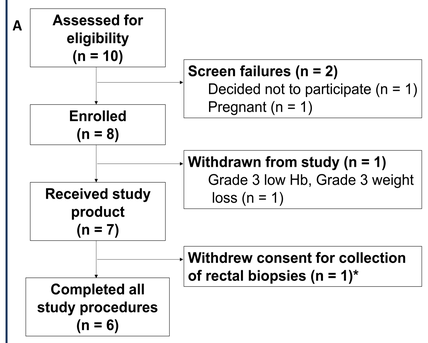
- Unprotected receptive anal intercourse carries the highest risk of HIV transmission per sex act, relative to oral sex and receptive vaginal intercourse.
- Evaluating rectal dosing allows for greater diversity in our population.



- IQP-0528 concentrations were measured using a validated LC-MS/MS assay consistent with FDA, Bioanalytical Method Validation, Guidance for Industry recommendations.
- Biopsies were placed in tissue culture media and challenged with HIV for 2 h. Supernatants for p24 assay were collected on days 4, 7, 10, and 14. Cumulative, biopsy weight-adjusted, p24 values over 14 days was the pharmacodynamic unit of analysis.

Results

Participants



B

	Value
Number (n)	8
Age, years (median [range])	34 [31, 53]
Sex (no.)	
Male	5
Female	3
Race (no.)	
African-American	5
White	2
White/American Indian	1
BMI, kg/m^2 (median [range])	27.3 [22.8, 41.2]

Figure 2. Participant Status and Baseline Demographics
A. CONSORT diagram detailing movement of participants through study procedures. *This participant completed all other study procedures and was excluded only from PK, PD, and histological analysis of colorectal tissue. **B**. Baseline demographics of study participants (n = 8).

Safety

Table 1. Number of adverse events reported by severity and relationship to study product.

Relationship to Study Product	Grade 1	Grade 2	Grade 3
Related	1[a]	0	0
Unrelated	1	2	2[b]

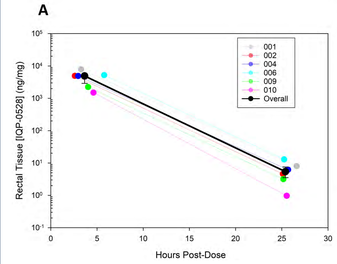
[a]Headache; resolved shortly after onset
[b]Clinically significant low hemoglobin and weight loss. Occurred prior to study product exposure

Table 2. Histological scoring of rectal biopsies. Values reported as median [range].

Parameter	Baseline	3-5 h Post-Dose	24-26 h Post-Dose
Surface Denudation[a]	1 [0, 2]	1 [0, 3]	1 [0, 3]
Lamina Propria Hemorrhage[a]	1 [1, 1]	1 [0, 1]	1 [0, 2]
Apoptotic Bodies[b]	0.0 [0.0, 0.8]	0.0 [0.0, 1.3]	0.0 [0.0, 0.3]

No significant differences in parameters were observed across visits by Friedman ANOVA ($p > 0.05$).
[a]Reported using semi-quantitative scoring system: 0, no surface involved; 1, less than 1/3 surface involved; 2, 1/3 to 2/3 surface involved; 3, greater than 2/3 surface involved.
[b]Reported as the decimal equivalent of the average number of bodies per multiple x20 fields.

Pharmacokinetics



Matrix	IQP-0528 Concentration (ng/mg)		Half-Life (h)
	3-5 h Post-Dose	24-26 h Post-Dose	
Plasma*	BLQ	BLQ	ND
Rectal Tissue	4914 [1682, 5135]	5.4 [3.5, 11.2]	2.2 [2.2, 2.3]
Vaginal Tissue	BLQ	BLQ	ND

Values reported as median [IQR]
IQR: interquartile range. BLQ: below limit of quantitation; < 3 ng/mL (plasma); < 0.250 ng/sample (rectal and vaginal tissue). ND: not determined.
*IQP-0528 was undetectable in all plasma samples across participants.

Figure 3. Systemic and Local IQP-0528 Pharmacokinetics
A. Plot of IQP-0528 concentration (ng/mg) over time in rectal tissue. **B**. IQP-0528 concentrations (ng/mg) over time and half-lives (h) in physiologic matrices. Values reported as median [IQR].

Pharmacodynamics

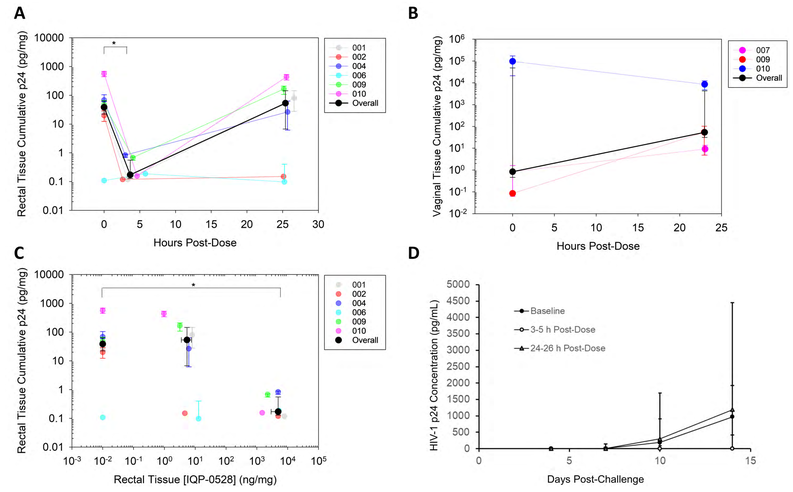


Figure 4. IQP-0528 PD and PK/PD Correlation
Median (IQR) weight-adjusted cumulative p24 measured from *ex vivo* challenge assays versus time in rectal (**A**) and vaginal (**B**) tissue. Values at time 0 indicate baseline. **C**. Median (IQR) weight-adjusted cumulative p24 versus IQP-0528 concentration in rectal tissue. Error bars represent IQR. Pre-dose IQP-0528 concentration are imputed as 0.01 pg/mL due to log-scale. Cumulative p24 values below the lower limit of quantitation (LLOQ) were set as the median biopsy weight-adjusted LLOQ/2. * indicates $p < 0.05$ by Wilcoxon Signed Rank test. **D**. Median (IQR) p24 value for individual rectal biopsy supernatant collection time (4, 7, 10, and 14 days).

Conclusions

- The IQP-0528-containing gel was found to be safe and did not impact colon tissue histology.
- Concentrations remained well above the *in vitro* EC_{50} of 1 ng/mL within 3-5 h post-dosing. However, this was not sustained due to the short half-life.
- Cumulative p24 reductions are significantly associated with greater IQP-0528 concentrations.
- No IQP-0528 was detected in the vagina following rectal dosing. This suggests that both locations must be dosed to achieve protection.