Pharmacokinetics and X-ray Imaging of Long-acting Cabotegravir In Situ Forming Implant

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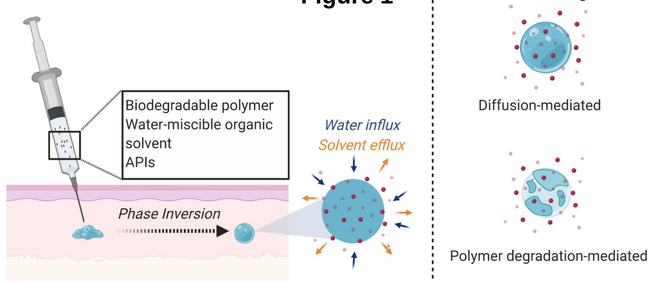
BACKGROUND

- Long-acting injectables (LAIs) for HIV PrEP can increase adherence and reduce stigma.
- Current LAIs are not removable, require physician assistance, and elicit a long pharmacokinetic (PK) tail.
- **To overcome these limitations, we developed a subcutaneous ultra-long-acting (ULA) biodegradable, injectable, and removable in-situ forming implant (ISFI) with cabotegravir (CAB).**

METHODS

- ISFIs are comprised of polymer (PLGA), solvent (NMP/DMSO), and cabotegravir (CAB; 500 mg/mL) to generate a homogenous and syringeable suspension **(Fig. 1).**
- Upon injection into the subcutaneous space, a phase inversion occurs generating a solid depot with CAB entrapped within the polymer matrix.

Figure 1



Mouse pharmacokinetics (PK) & X-ray study design

Injection volume: Mice were injected subcutaneously (s.c.) with 50 µL (1215 mg/kg), 100 µL (2430 mg/kg), or 2×50 µL (2430 mg/kg) of CAB ISFI.

Time to completion: Assessed time until CAB is depleted from CAB ISFI.

Tissue PK: Assessed CAB concentration in tissues (vagina, cervix, and rectum) for 180 days.

PK tail assessment: Removed ISFIs after 30-, 60-, 90-, and 180-days and assessed PK tail for 30 days post-removal.

Post-removal depot processing: Assessed retrievability, polymer degradation, and residual CAB after depot removal at 30-, 60-, 90-, and 180-days post injection.

Ultra-long-acting CAB ISFIs elicited plasma concentrations above 4× PA-IC90 for 11-12 months and can be visualized with x-ray imaging after a single subcutaneous injection in mice

X-ray imaging with barium sulfate ($BaSO_4$): CAB/$BaSO_4$ ISFIs and placebo/$BaSO_4$ ISFIs were injected into the right and left flanks of mice, respectively. Mice underwent full body X-ray imaging to assess implant visualization and migration post-injection.

RESULTS

- ULA CAB ISFIs elicited plasma concentrations above 4× PA-IC90 for 11-2 months **(Fig 2A)** and high tissue concentrations for 180 days **(Fig. 2B).**
- Significant decrease in CAB concentration in plasma was achieved post-depot removal with ~9-,13-,29-,and 11-fold decrease when removed at day 30, 60, 90, 180, respectively **(Fig. 2D-H)** . Depots were easily retrieved at day 180 **(Fig. 2I)**.

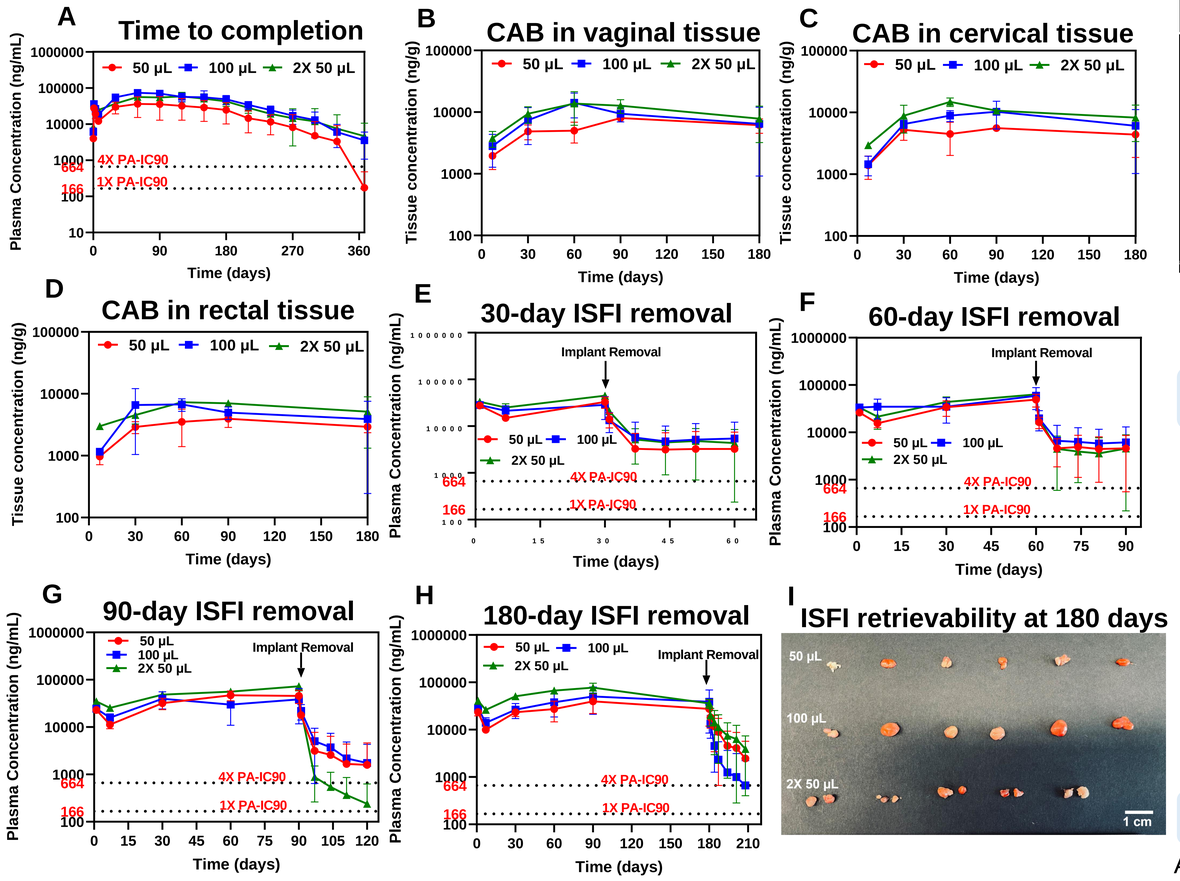


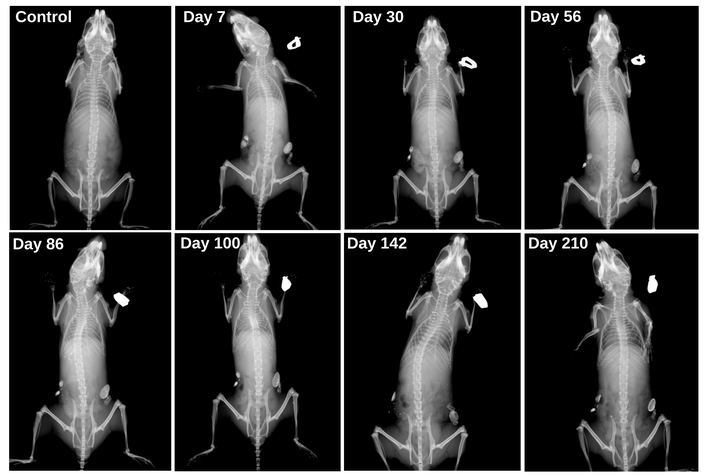
Figure 2. CAB time to completion, tissue PK and PK tail assessment

Injection Volume	% CAB Remaining			
	30 days	60 days	90 days	180 days
50 µL	93.2±4.5%	67.6±30.4%	61.7±6.5%	23.2±3.4%
100 µL	92.3±10.5%	59.5±13.6%	63.8±8.5%	34.6±7.4%
2×50 µL	90.4±3.6%	81.7±2.3%	60.1±8.5%	29.0±14.8%

Injection Volume	% PLGA molecular weight decrease			
	30 days	60 days	90 days	180 days
50 µL	11.6±5.6%	37.1±3.4%	49.7±5.4%	86.9±0.43%
100 µL	11.6±5.9%	36.3±0.7%	43.3±1.1%	85.8±0.83%
2×50 µL	9.1±1.3%	41.5±5.1%	49.1±3.7%	84.5±1.89%

After 180 days, there was ~25% CAB remaining and ~85% decrease in PLGA molecular weight for all injection volumes.

Figure 3. Full body X-ray imaging of CAB/$BaSO_4$ ISFIs (right flank) and placebo/$BaSO_4$ ISFIs (left flank)



ISFIs with $BaSO_4$ maintained visualization via X-ray imaging for 210 days after a single ISFI injection **(Fig. 3).**

CONCLUSIONS

- ULA CAB ISFI is the first s.c. injectable for HIV PrEP that is biodegradable and removeable (only if needed).
- ULA CAB ISFI elicited plasma concentrations above 4× PA-IC90 for 11-12 months and high tissue concentrations for 180 days after a single injection.
- Incomplete CAB elimination may be due to CAB accumulation in s.c. tissue.
- When co-formulated with $BaSO_4$, CAB ISFIs can be visualized for over 6 months with negligible migration.

ACKNOWLEDGMENTS & KEY INFORMATION

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