Ultra-long-acting Injectable, Biodegradable, and Removable In-situ Forming Implant with Cabotegravir for HIV Prevention

Thy Le

CONTROLLED RELEASE SOCIETY
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INTEGRATING
Delivery Science
ACROSS DISCIPLINES

Introduction

39 million people are currently living with HIV with **~1.3 million new infections every year (UNAIDS)**

Advances in HIV Prevention: **Pre-exposure Prophylaxis (PrEP)**

Unmet need: **Ultra long-acting formulation for reduced dosing frequency and enhanced compliance**

Current Solutions for Pre-exposure prophylaxis (PrEP)

Daily Oral Pill
(Truvada, Descovy)

365
Doses/Year

Low patient compliance

Long-acting Injectable
(Apretude)

6
Doses/Year

Non-removable with a Long Pharmacokinetic Tail

New Era of PrEP

Daily Oral Pill
(Truvada, Descovy)

- Frequent dosing required
- Low user compliance
- Reduced efficacy with low adherence

Long-acting Injectable
(Apretude)

- Long-acting
- Reduced dosing frequency
- Non-removable
- Long pharmacokinetic tail from last injection

OUR SOLUTION

In-situ forming Implants
(ISFI technology)

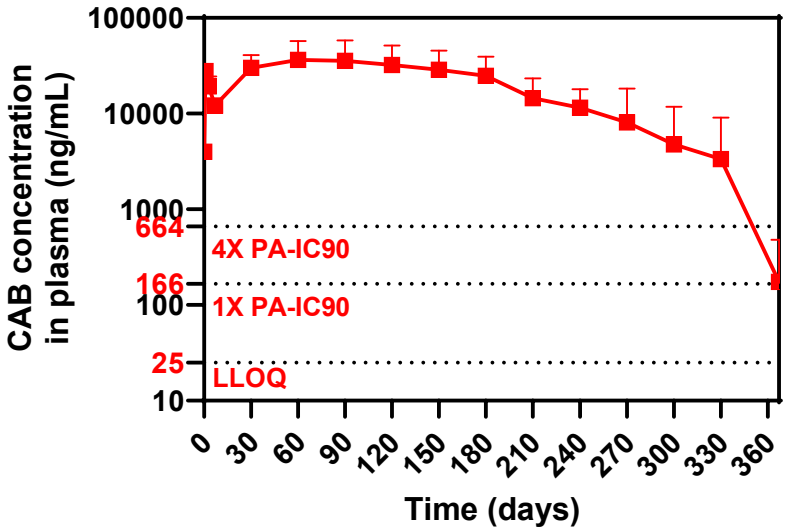
- Ultra-long-acting (≥6 months)
- Reduced dosing frequency (1-2x/year)
- Biodegradable and removable if necessary
- Possible self administration (SC injection)

Formulation development and optimization → In vitro testing → In vivo testing

Cabotegravir (CAB)

CAB is a **highly potent antiretroviral drug** (IC-90, 166 ng/mL) efficacious for HIV treatment (Cabenuva) and prevention (Apretude) in the form of long-acting injectables

We previously developed an **ultra-long-acting** treatment with CAB for PrEP



Formulation development and optimization → In vitro testing → In vivo testing

In situ Forming Implant (ISFI) formulation

Biodegradable polymer

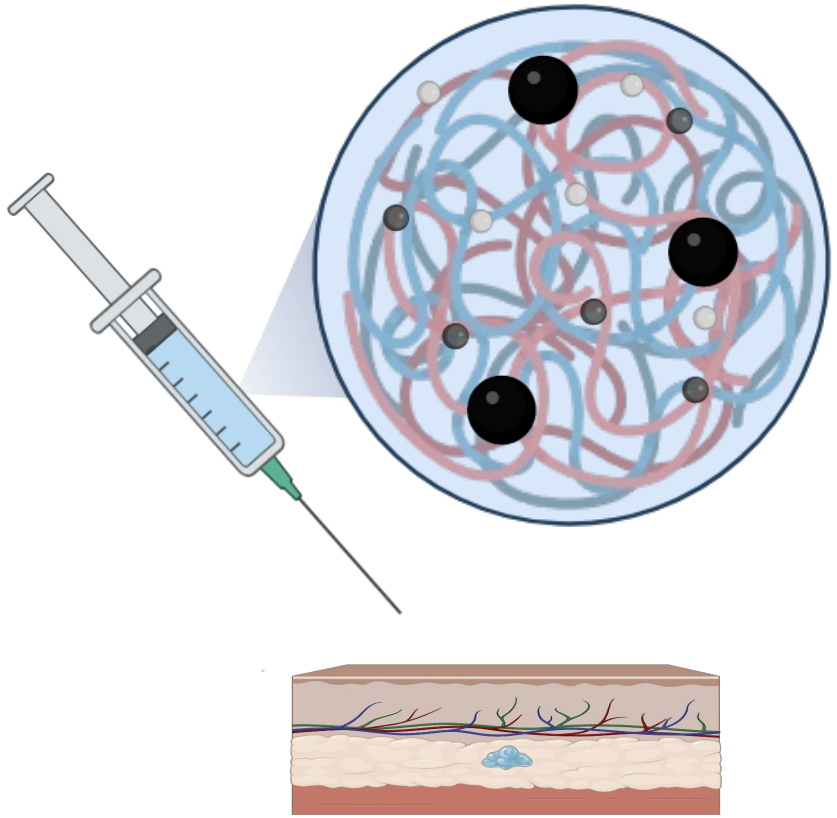
Water-miscible organic solvent(s)

Active pharmaceutical ingredient(s)

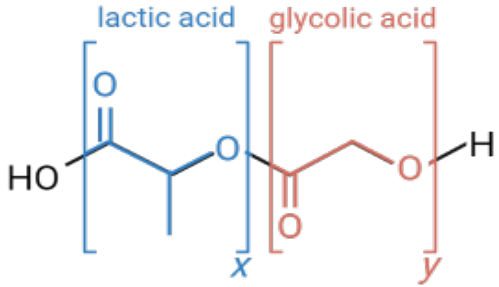
Formulation development and optimization → In vitro testing → In vivo testing

CAB (ISFI) formulation

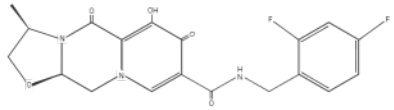
- **Polylactic-co-glycolic acid (PLGA)**
- Dimethyl sulfoxide (DMSO)
- *N*-methyl-2-pyrrolidone (NMP)
- **Cabotegravir (CAB)**



Polylactic-co-glycolic acid (PLGA)



Cabotegravir (CAB)



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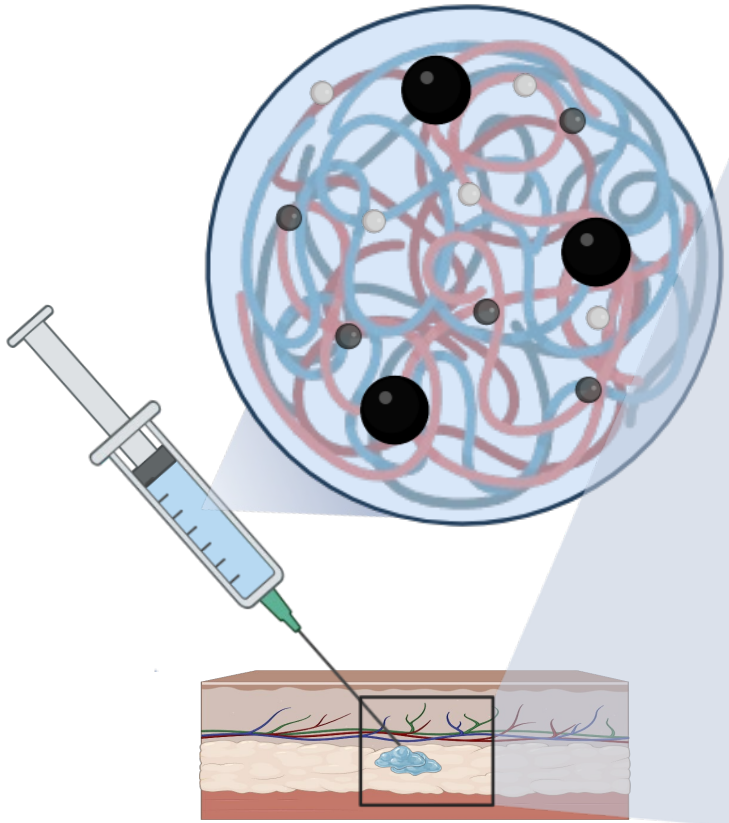

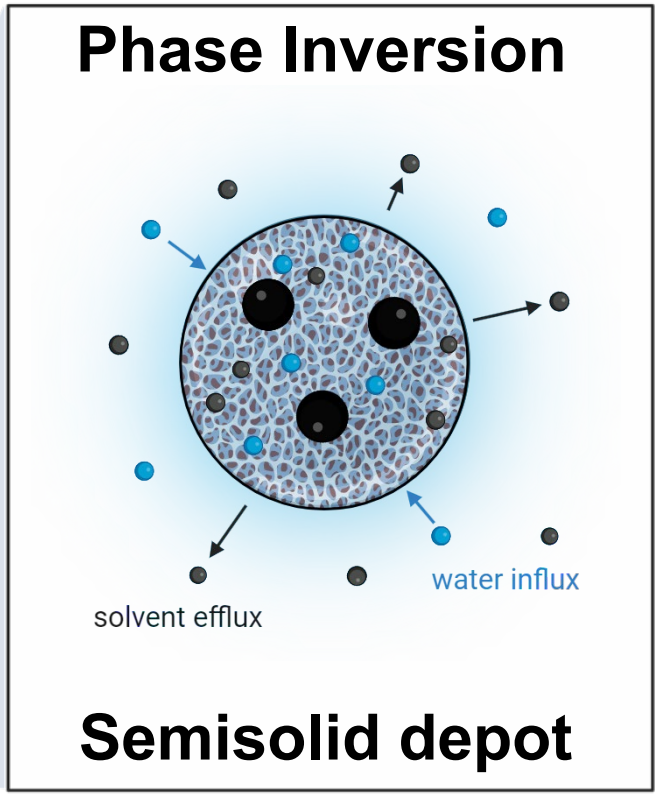

Formulation development and optimization → In vitro testing → In vivo testing

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- Dimethyl sulfoxide (DMSO)
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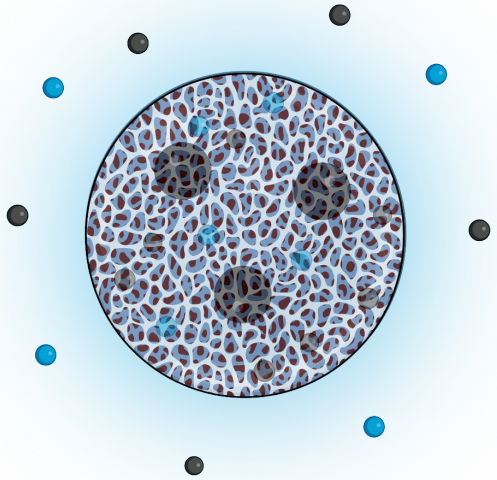
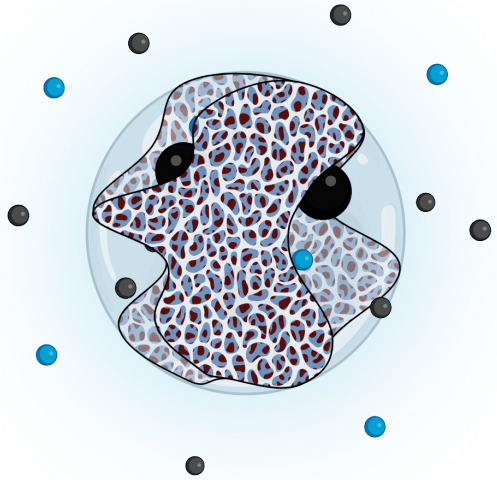
- Cabotegravir (CAB)

Mechanisms of Drug Release



Diffusion-mediated

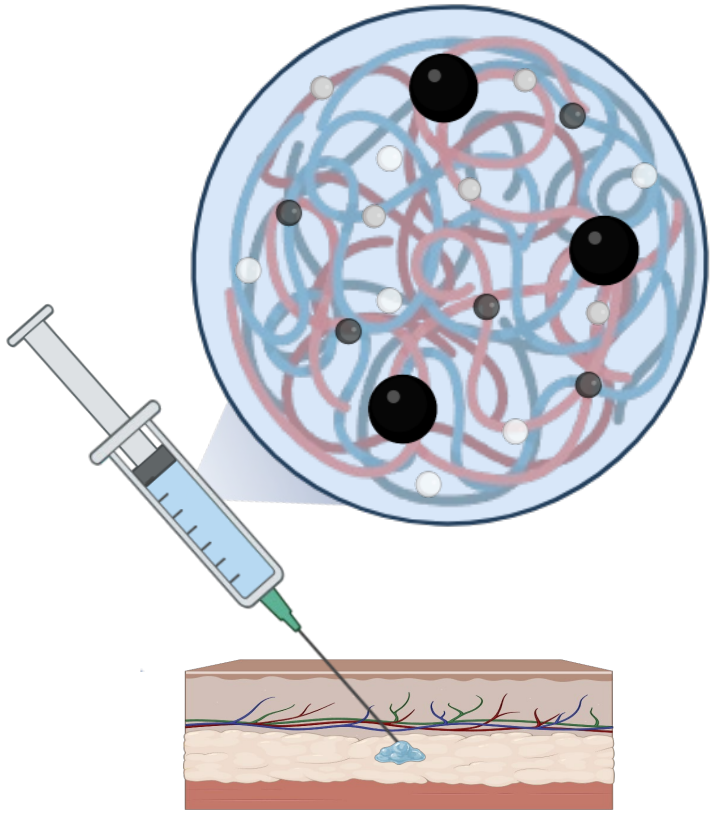


Polymer degradation-mediated

Formulation development and optimization → In vitro testing → In vivo testing

CAB/$BaSO_4$ (ISFI) formulation

- **Polylactic-co-glycolic acid (PLGA)**
- Dimethyl sulfoxide (DMSO)
- *N*-methyl-2-pyrrolidone (NMP)
- **Cabotegravir (CAB)**
- **Barium Sulfate ($BaSO_4$)**

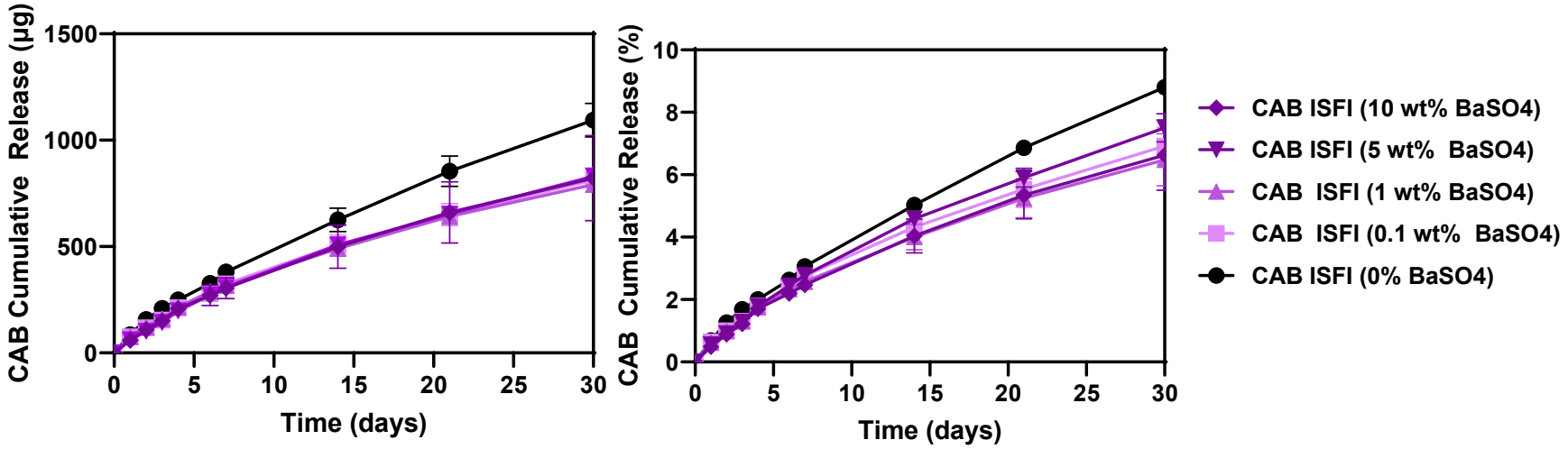


CAB ISFI Technology

- Long-acting
- Reduced dosing frequency
- **<u>Biodegradable and removable</u>**
- Possible self administration

Goal: Create a formulation with barium sulfate to enhance **ease of retrievability** and assess possible **implant migration**

Formulation development and optimization → **In vitro testing** → In vivo testing



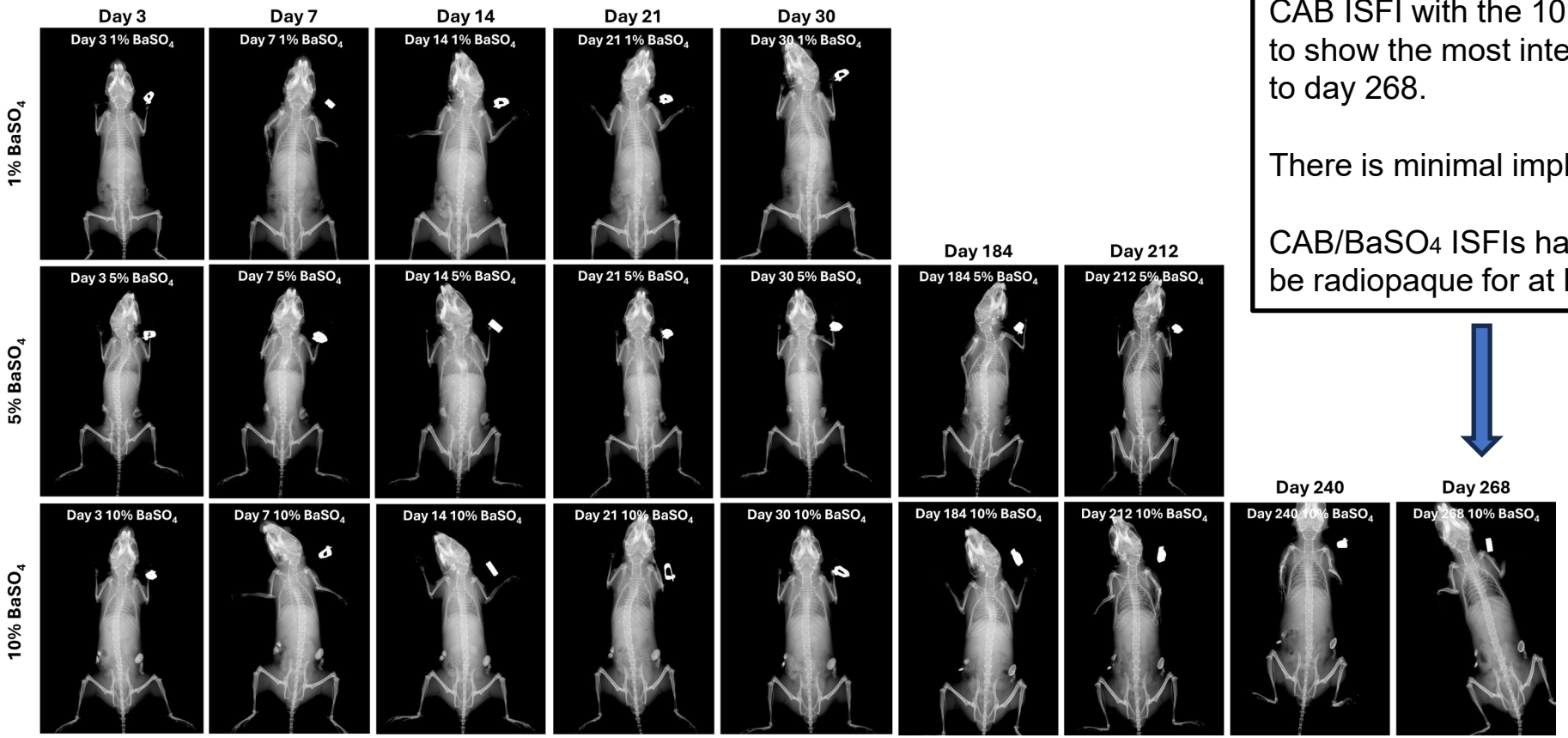
The addition of barium sulfate at different concentrations did not significantly affect the release of the CAB ISFI formulation.

CAB/$BaSO_4$ formulations have the potential to release for more than 180 days.

500 mg/mL CAB + % BaSO4	CAB Analytical Concentration (mg/mL)	Burst Release (24h) (µg)	Burst Release (24h) (%)	Cumulative Release at 30 days (%)	Release rate (µg/day)
0 wt%	504.4±26.6	85.5±9.4	0.69±0.04	8.80±0.18	35.47
0.1 wt%	510.3±4.7	75.4±10.0	0.64±0.07	6.92±0.60	26.38
1 wt%	501.8±17.2	76.3±5.03	0.62±0.07	6.48±0.84	25.53
5 wt%	500.0±12.1	62.0±8.6	0.56±0.05	7.50±0.45	27.30
10 wt%	505.9±4.2	59.6±7.53	0.49±0.04	6.63±1.13	26.99

Pilot X-ray Studies

X-ray signal of mice taken to assess radiopacity of $CAB/BaSO_4$ ISFI for up to 268 days (n=3 per group per timepoint)



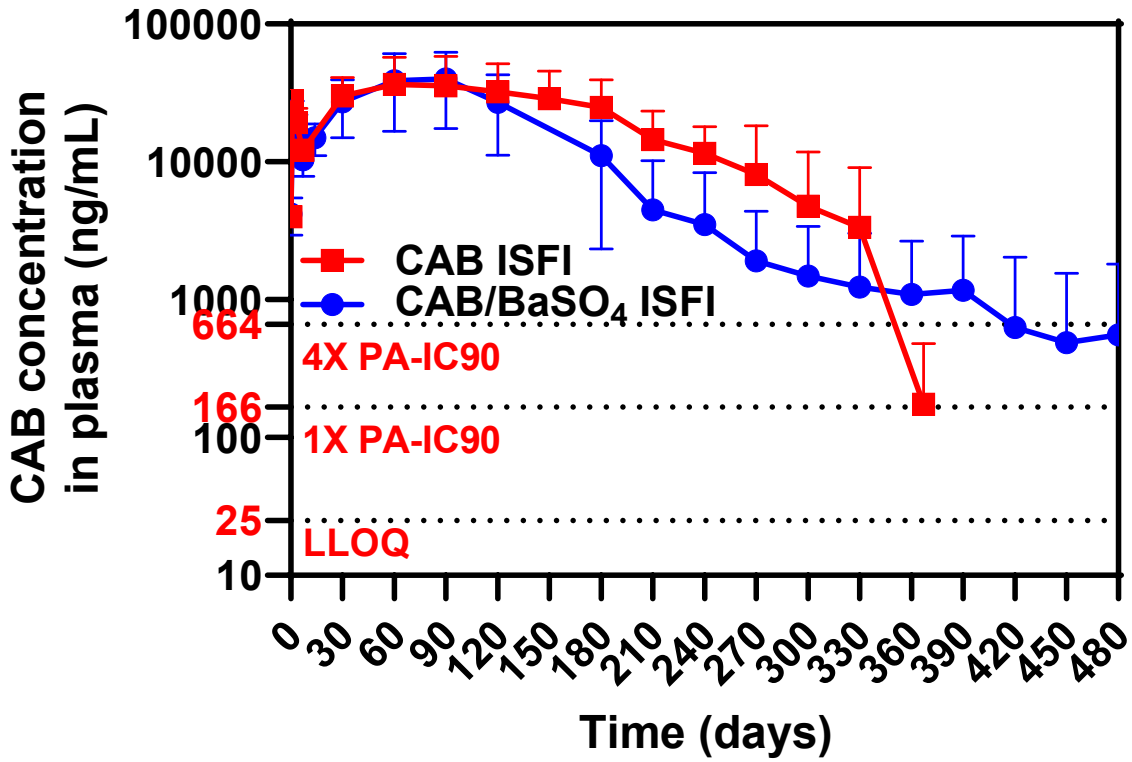
CAB ISFI with the 10% $BaSO_4$ was able to show the most intense x-ray signal up to day 268.

There is minimal implant migration.

$CAB/BaSO_4$ ISFIs have the potential to be radiopaque for at least 268 days.

Pharmacokinetics (PK) Time-to-completion

CAB plasma concentration quantified to assess pharmacokinetic profile of $CAB/BaSO_4$ ISFI for up to 480 days (n=6 per group per timepoint)



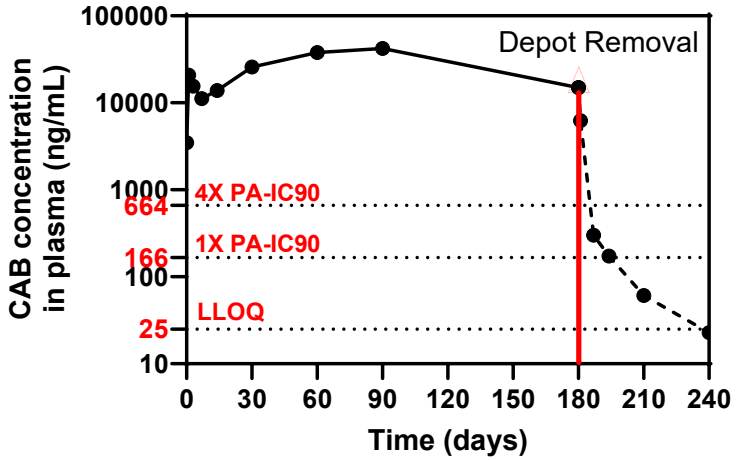
Target plasma PK is 4× PA- IC90

CAB/BaSO4 ISFI is well above the human efficiency benchmark for up to 390 days

There is no significance between CAB only and CAB/BaSO4 release.

Pharmacokinetics (PK) tail post-implant removal

CAB plasma concentration quantified to assess PK tail post-implant removal 180 days after injection (n=6 per group per timepoint) and implants collected to quantify polymer degradation with GPC and residual drug with HPLC



Time post-depot removal (day)	Fold decrease
1	2.41×
7	49.8×
14	86.2×
30	246.4×

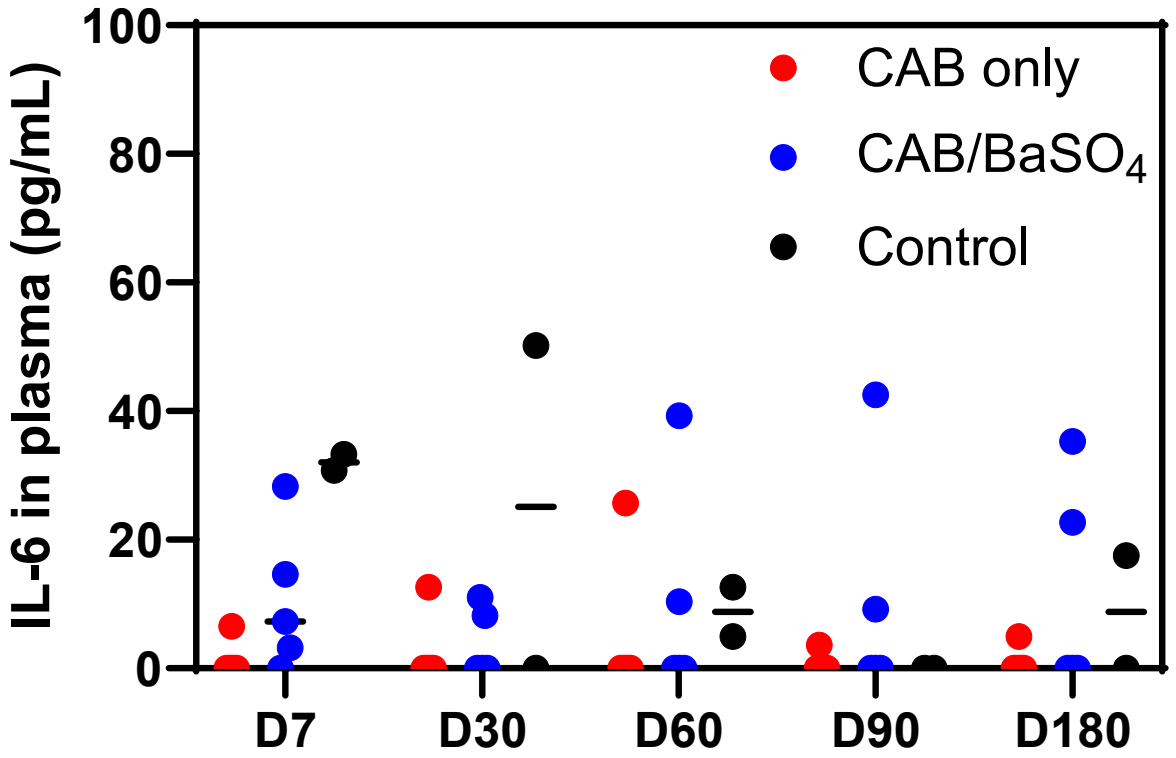
PK tail drops at/below 1x PA-IC90 threshold 14 days post-removal

CAB/$BaSO_4$ ISFI can be safely removed if required

Formulation 500 mg/mL CAB (1:4 PLGA (10kDa, 50:50): NMP/DMSO + 10% $BaSO_4$	% Mass Loss	% PLGA Degradation	% CAB Remaining
Day 180	68.1±23.7	82.2±0.8	42.1±11.9

In vivo safety; systemic inflammation

Utilize enzyme-linked immunosorbent assay (ELISA) to detect **TNF-α and IL-6** (major pro-inflammatory cytokines responsible for immune response activation) at 7, 30, 60, 90, 180-days post-injection (n=2-5 per group per timepoint)

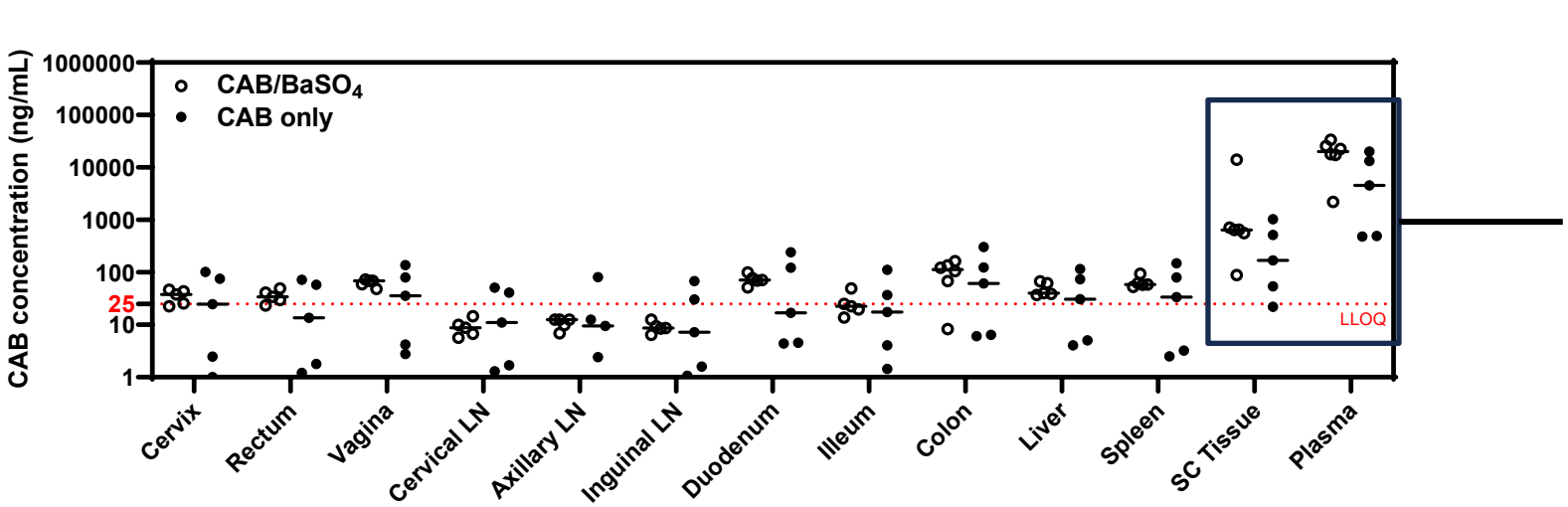


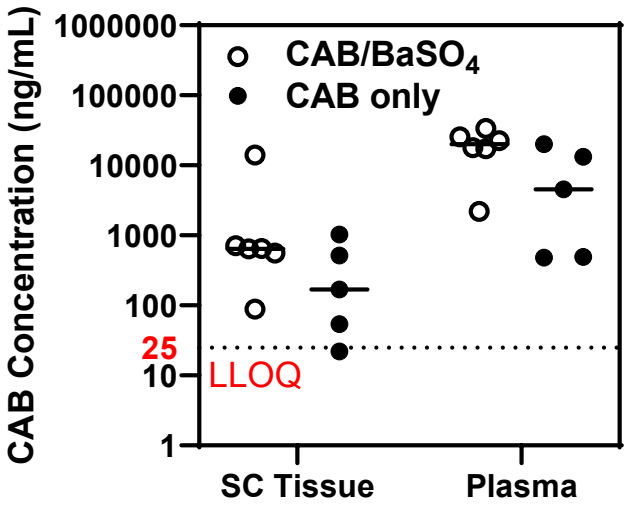
Median inflammatory cytokine levels are low (undetectable), with outliers being due to variability between mice.

CAB/$BaSO_4$ ISFI does not cause systemic inflammation.

In vivo organ

CAB plasma and tissue concentration quantified to assess biodistribution of CAB at 180 days post-injection (n=5-6 per group)





At day 180, CAB is distributed mainly in plasma and subcutaneous tissue for both formulations

Conclusion

- Successfully developed CAB/$BaSO_4$ ISFI at translational concentration (500 mg/mL)
- Demonstrated sustained release of CAB in vitro and in vivo at target release rates up to 1 year
- Implants can be visualized via X-ray with minimal migration
- Implants can be safely removed to potentially shorten PK tail
- Implants are well tolerated in vivo
- CAB accumulation occurs in the subcutaneous tissue

Future Work

- Characterize degradation of CAB and CAB/$BaSO_4$ ISFI
- Assess Stability of CAB/$BaSO_4$ ISFI
- Assess long-term safety: local inflammation (H&E)
- Assess CAB/$BaSO_4$ ISFI for safety, PK, and efficacy
- Formulation for PK in non-human primates

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