

# Model System Characterizing Subcutaneous Long-Acting Injectable Depots

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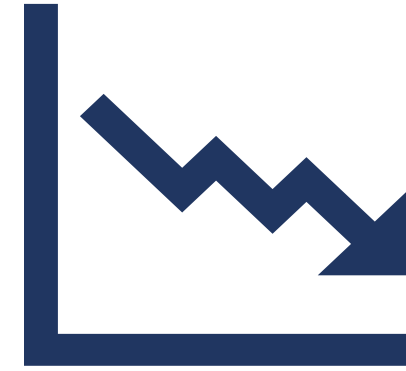


## **Disclosures:**

**Authors are employees of Gilead Sciences, Inc. and contracted work was completed by MED Institute Incorporated at the request of Gilead Sciences.**



# Antiretroviral therapies have progressed to a one pill regimen, but treatment persistence remains an issue



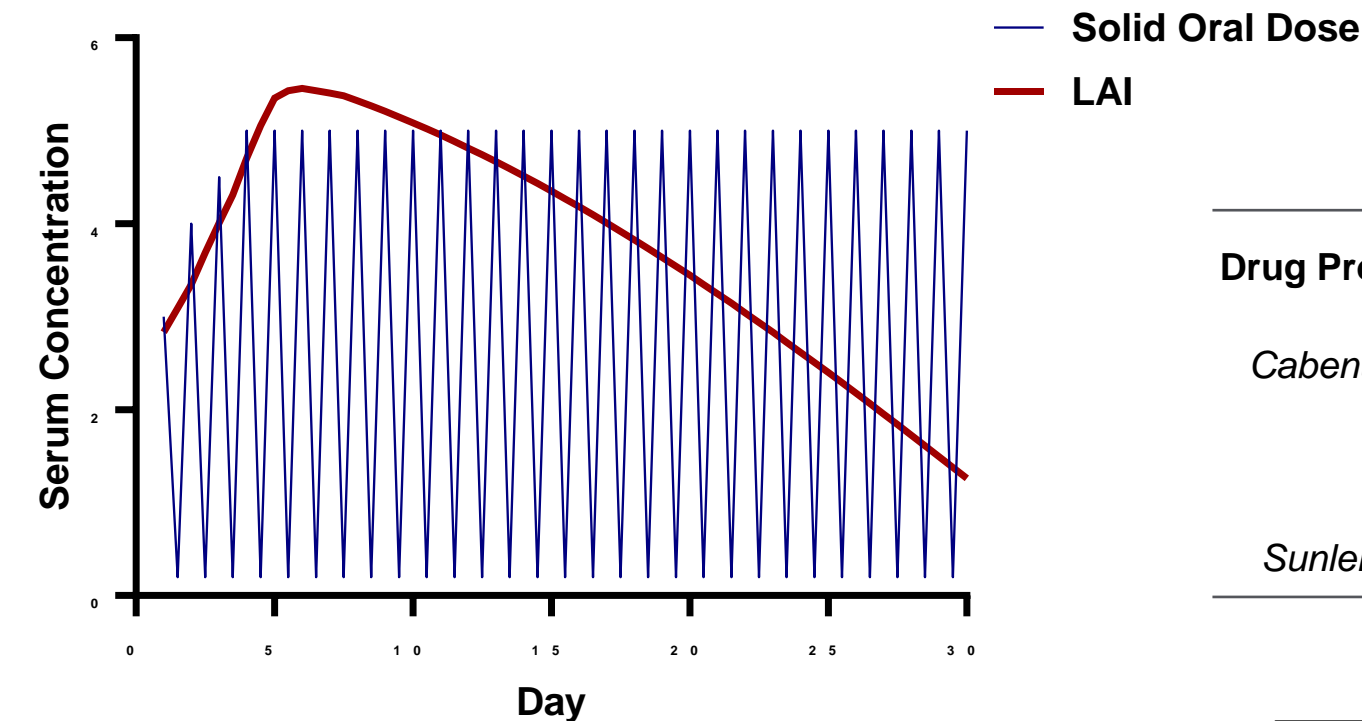
**After 1 Year**

**40%-50%** of chronic therapy patients stopped taking their medication (persistence)

**35%** drop in patients who correctly dosed each day (adherence)

Coy, K *JIAS* (2019)

# Long Acting Injectable (LAI) formulations are a solution to limit pill burden and maintain treatment persistence



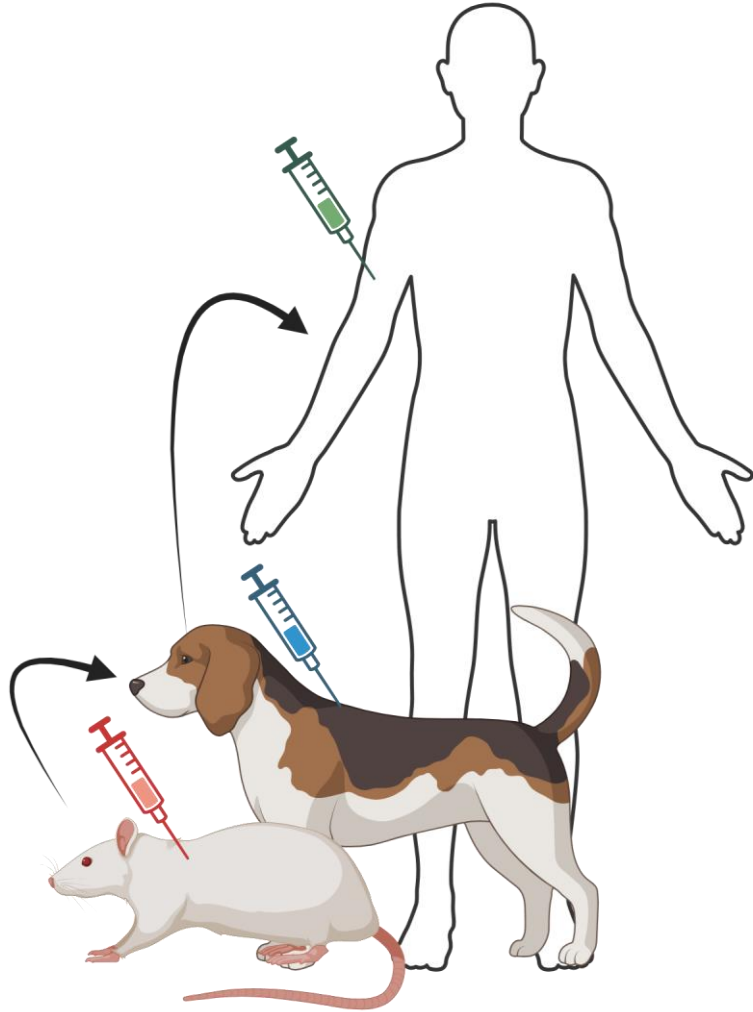
Drug Product	API Name	Compartment	Format
<i>Cabenuva</i>	Cabotegravir Rilpivirine	Intramuscular	Suspension
<i>Sunlenca</i>	Lenacapavir	Subcutaneous	Solution

Multiple daily doses consolidated into 1 injection

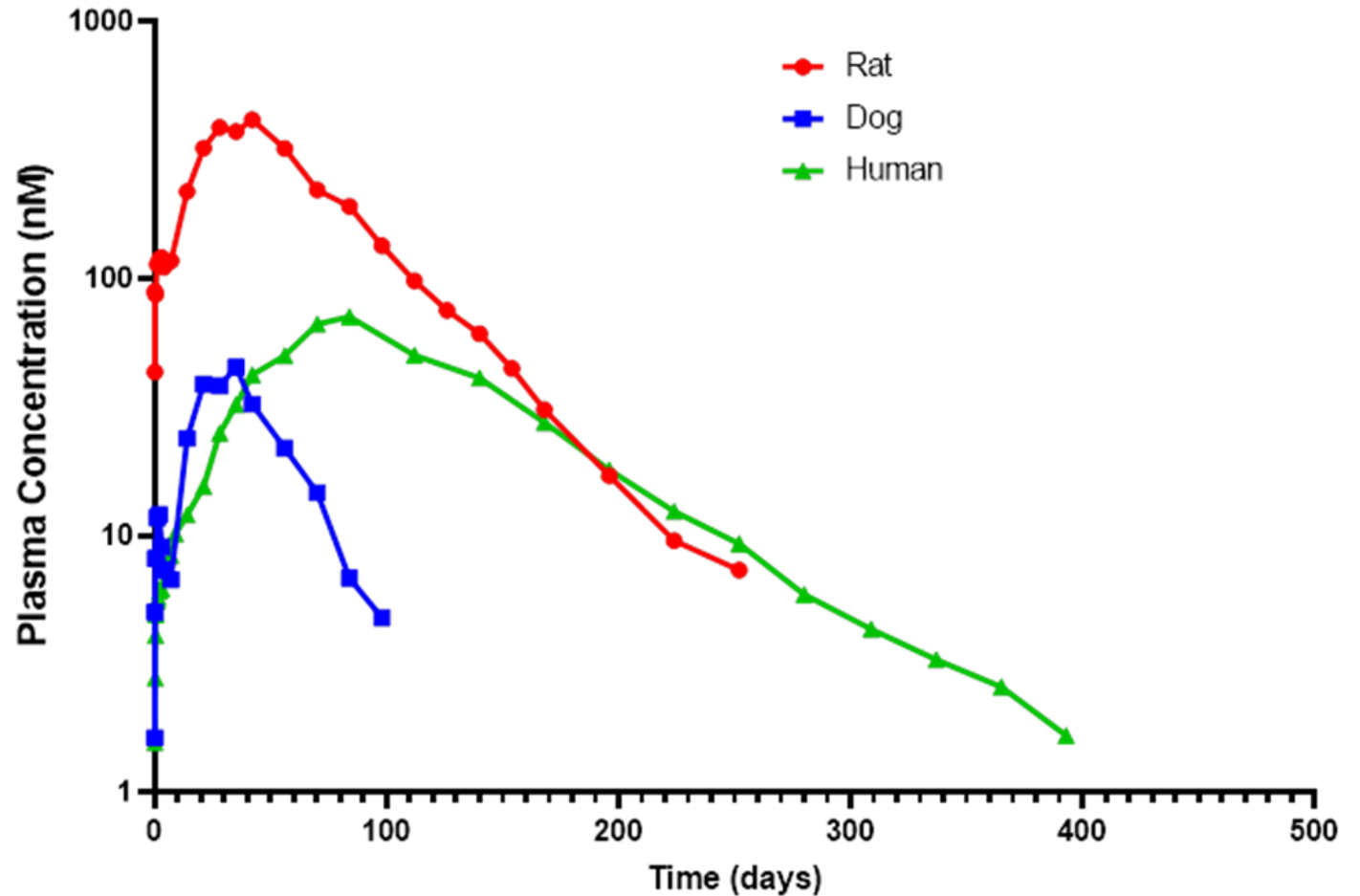
Examples of LAI antivirals on the market



# Preclinical models for LAI development are time intensive and are not adequately predictive



Biorender

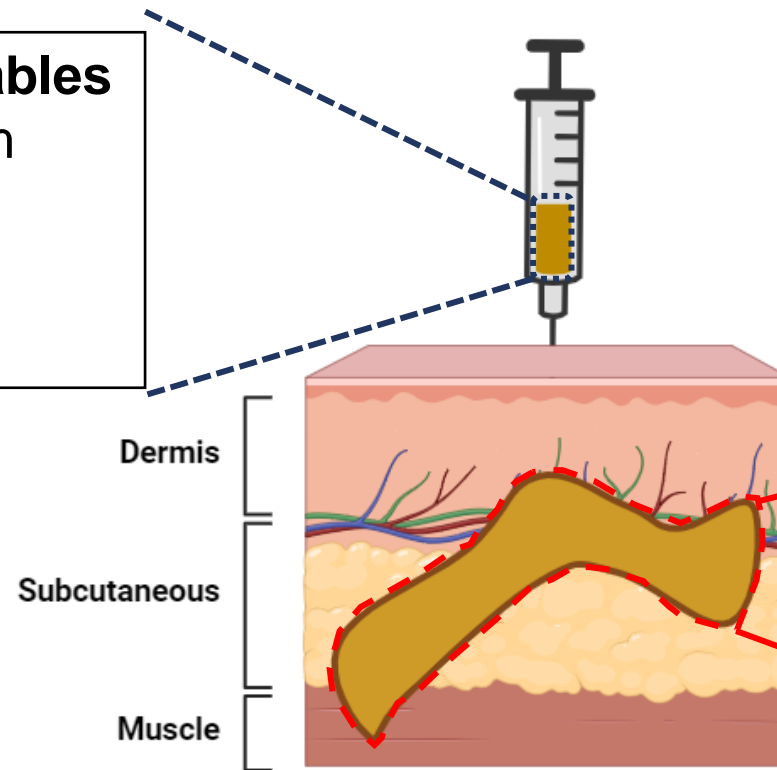


Example serum data from antiviral LAI

# Altering formulation variables can affect release through depot characteristics

## Formulation Variables

- Compound Form
- pH
- Excipients
- Viscosity

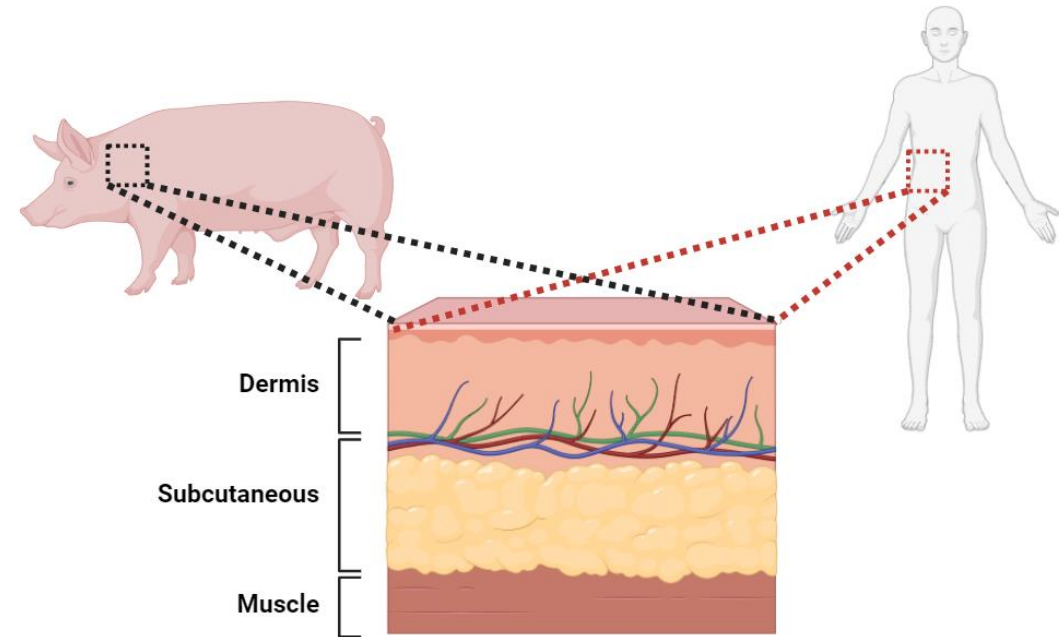


## Morphology Characteristics

- Surface area to volume ratio
- Porosity
- Tissue compartment

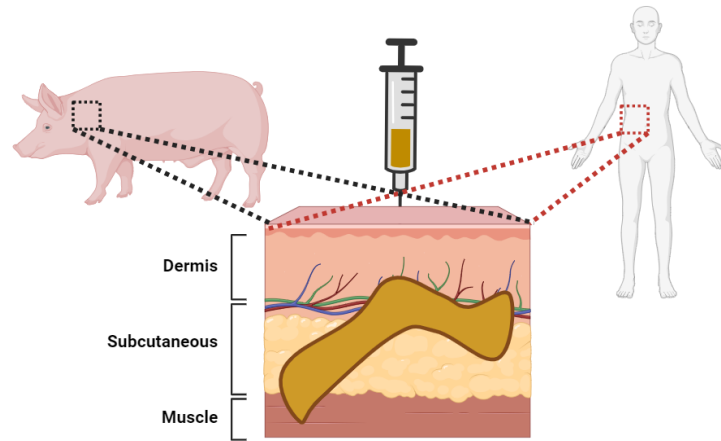
# Porcine subcutaneous tissue is physiologically and anatomically similar to human

- Porcine epidermis, dermis, and subcutaneous tissue organization is anatomically like human
- Porcine models are extensively used in biomedical research
- Pigs offer substantial amounts of tissue for extensive studies for long acting injectables





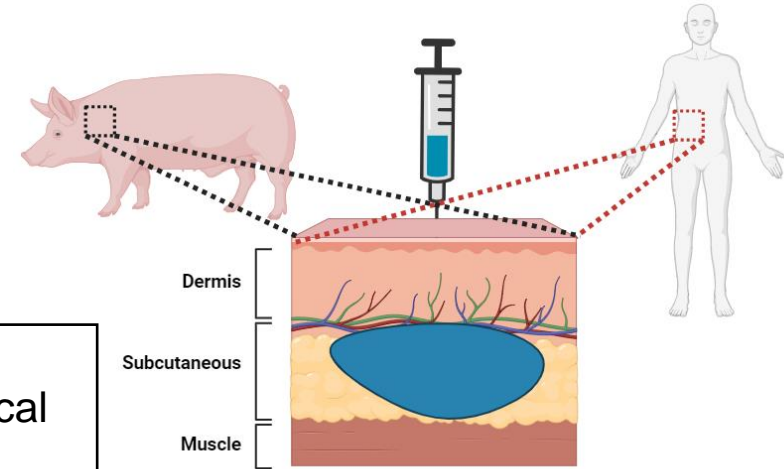
# Goal: Assess differences between *ex vivo* and *in vivo* LAI depot morphology via $\mu$ CT



**Formulation A**  
Compound 1  
Crystalline form A

## Formulation Parameters

- Same active pharmaceutical compound
- Analogous excipients
- Similar physical characteristics
- **Different crystalline form**



**Formulation B**  
Compound 1  
Crystalline form B

There remains an unmet need for preclinical models to bridge the differences of preclinical animal studies and clinical findings.

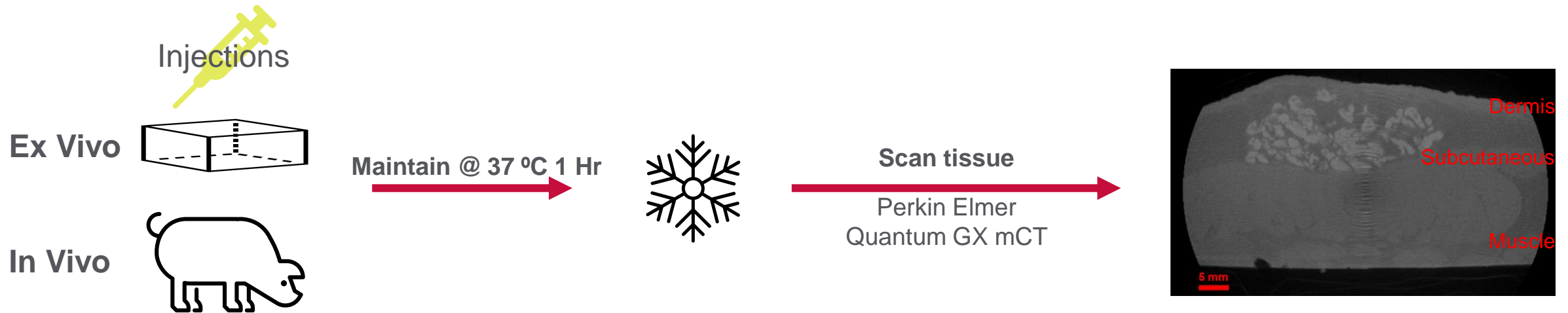


# Experimental process flow (Change)

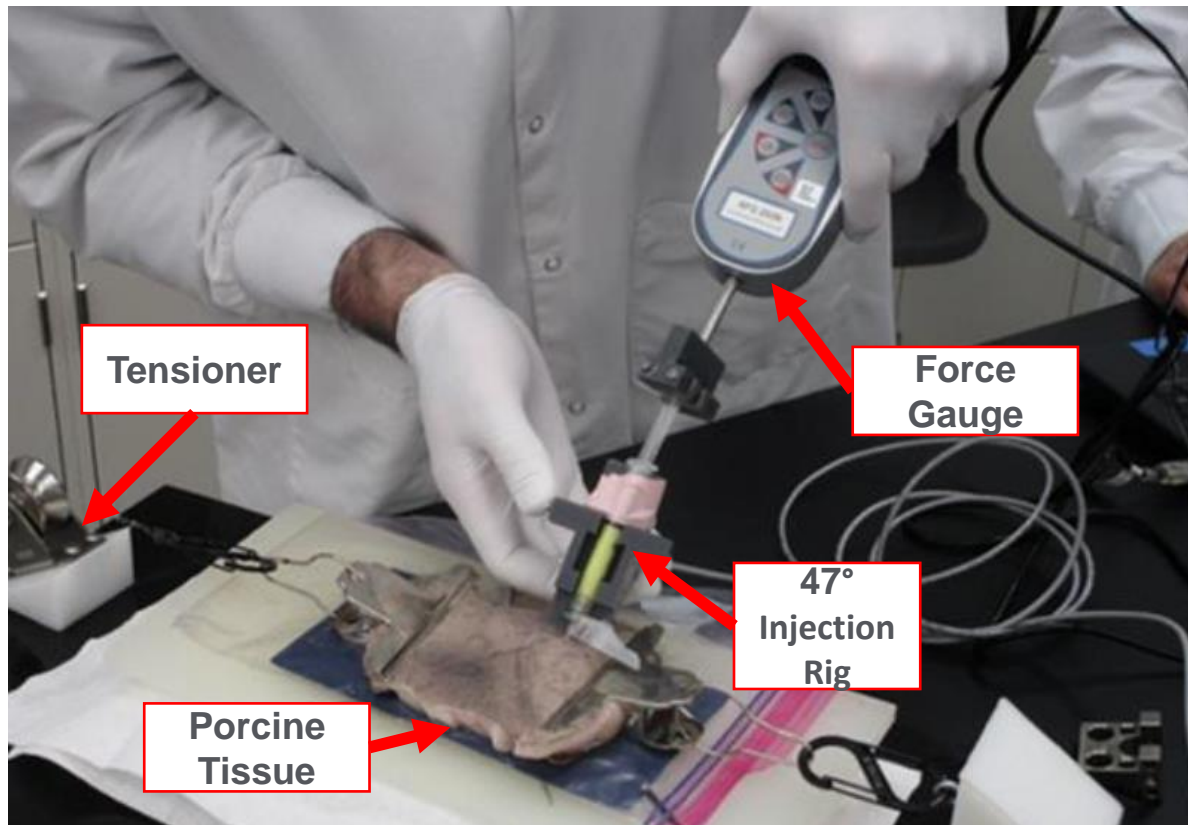
Collect Injection Force  
Data over 30 s

Freeze @ -80 °C

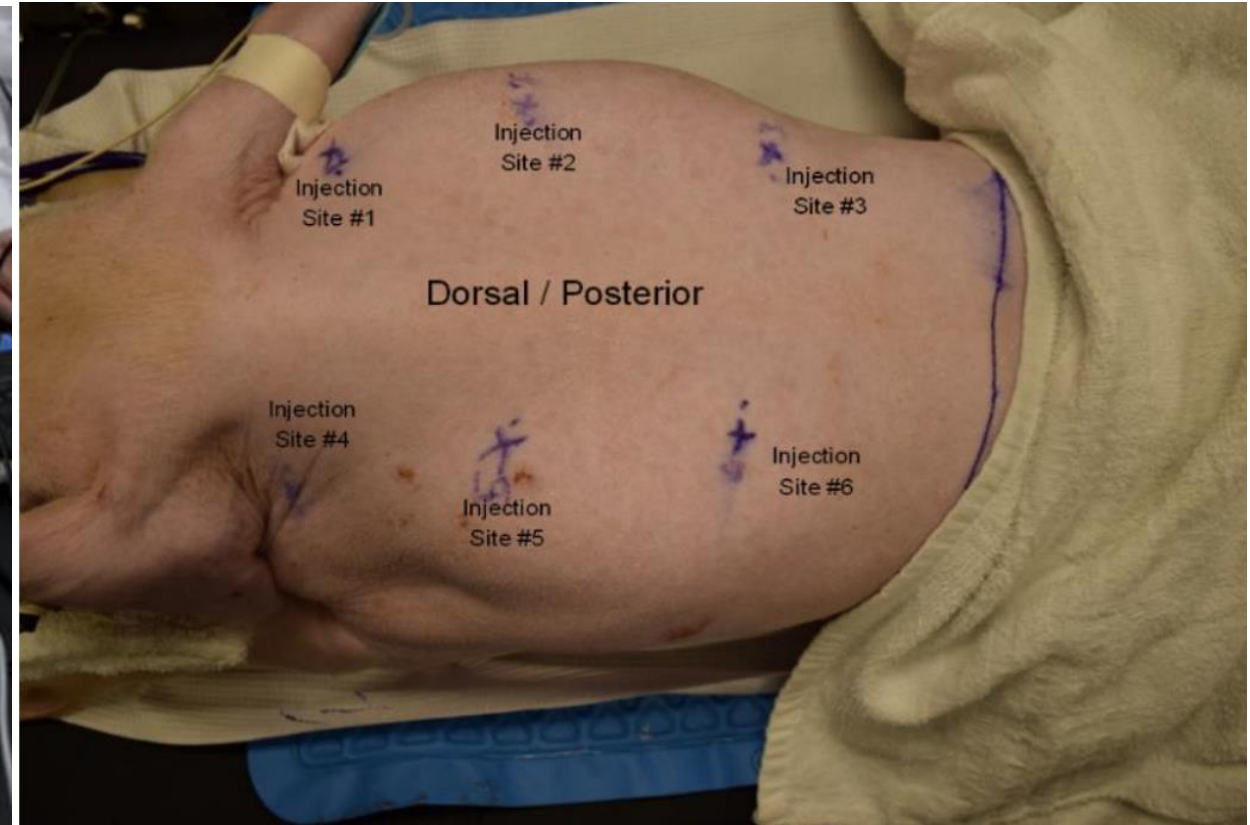
Scan and reconstruct depots,  
quantify morphology



# Experimental setup for *ex vivo* and *in vivo* study



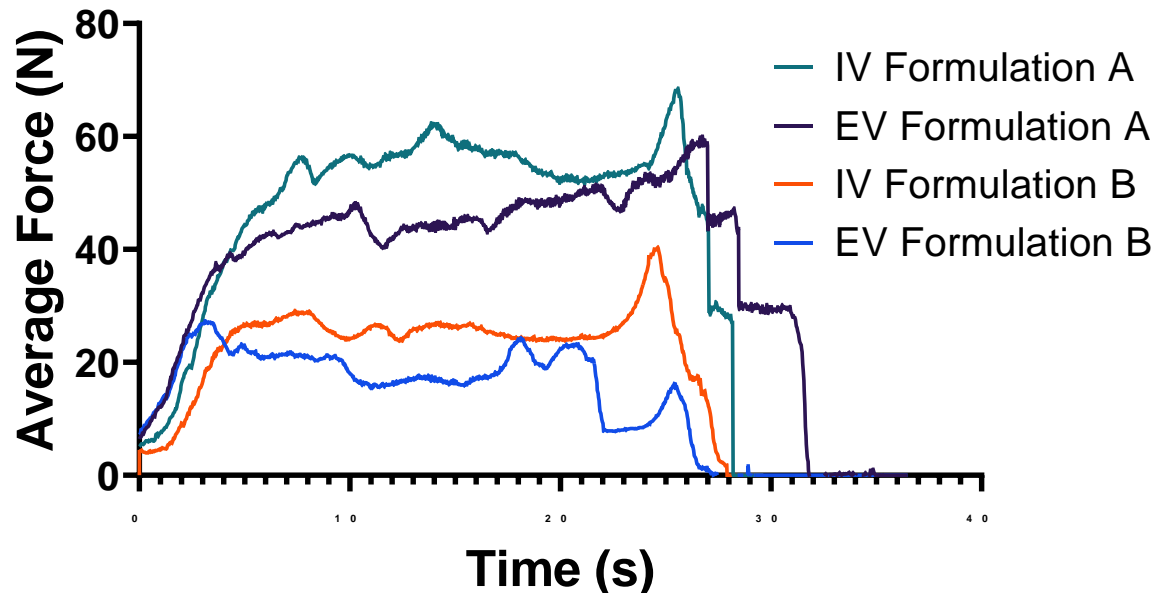
*Ex vivo* porcine injection setup



*In vivo* injection on anesthetized animal

# Formulation A injection forces are higher and *in vivo* injections require higher force than *ex vivo*

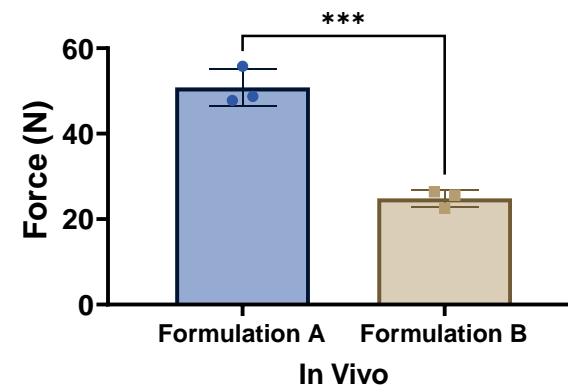
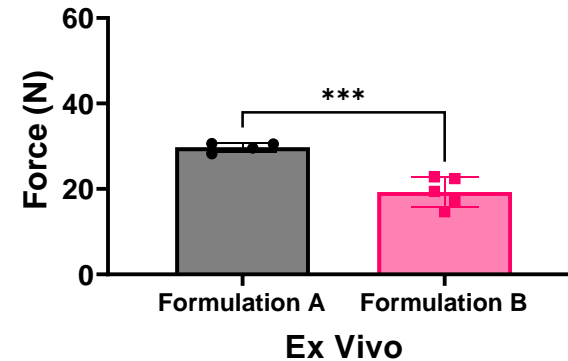
Average force trace across formulations



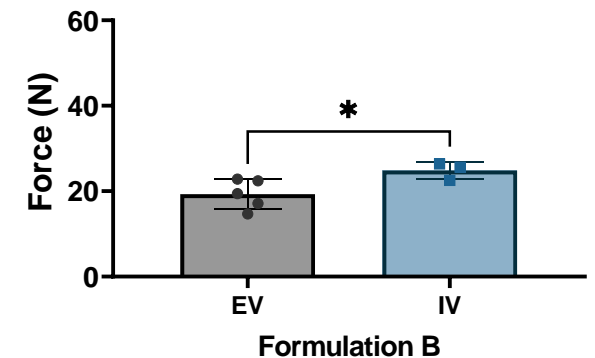
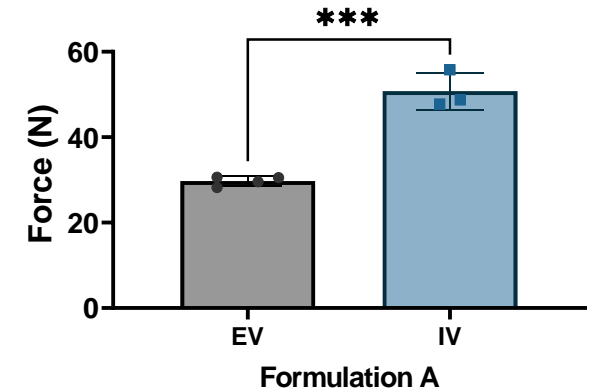
## Formulation Parameters

- Same active pharmaceutical compound
- Analogous excipients
- Similar physical characteristics
- Different crystalline form

Formulation A = Higher force

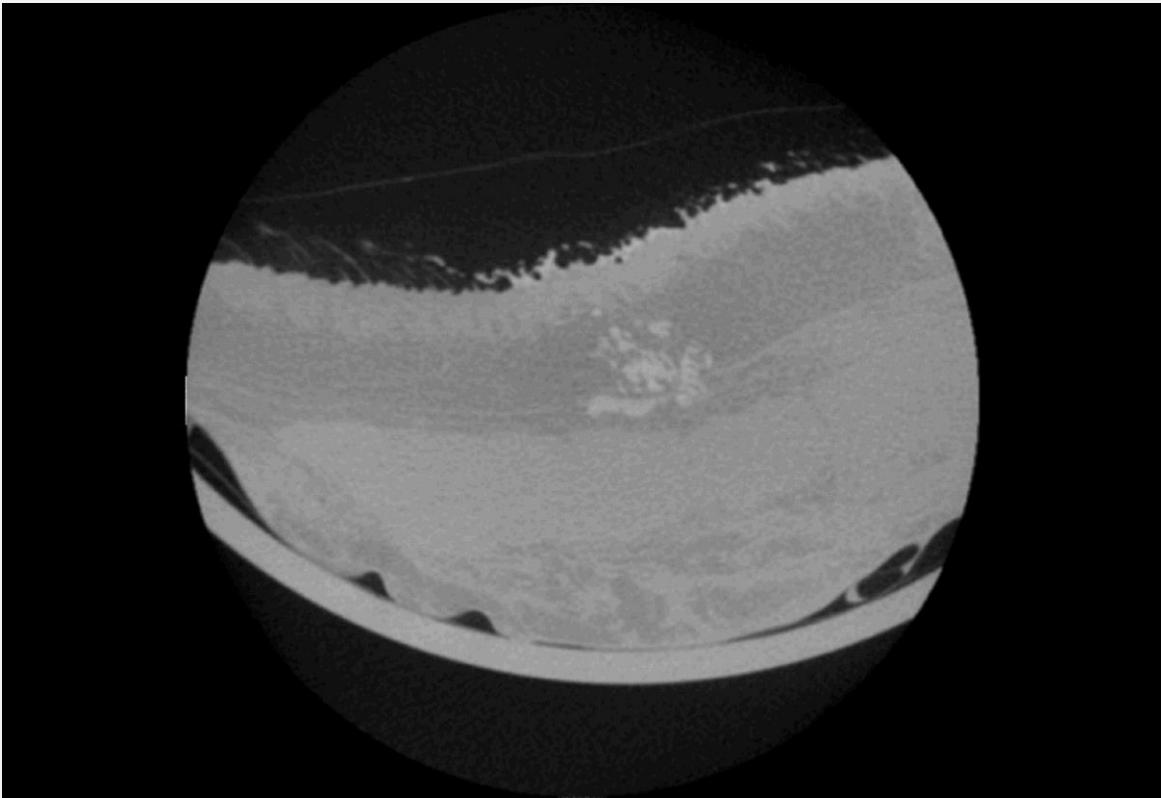


*In vivo* = Higher force



# Depot reconstruction provides sufficient resolution to compare morphology between formulations

Stepping through  $\mu$ CT projects in the x-direction

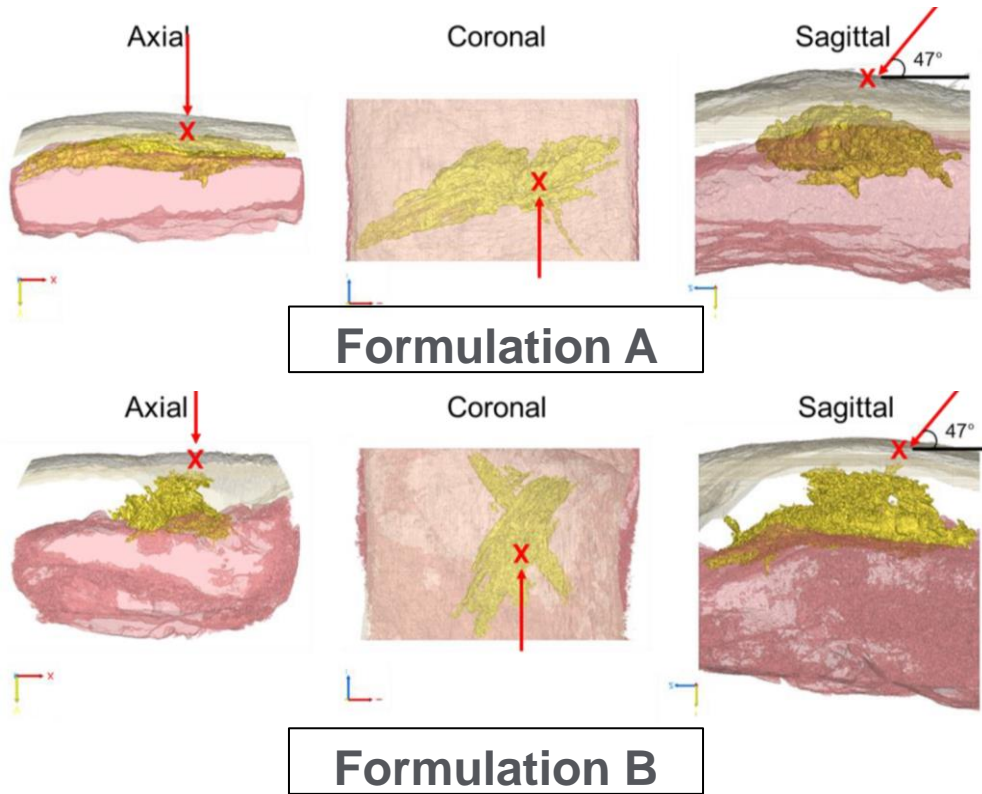


Reconstructed subcutaneous LAI depot

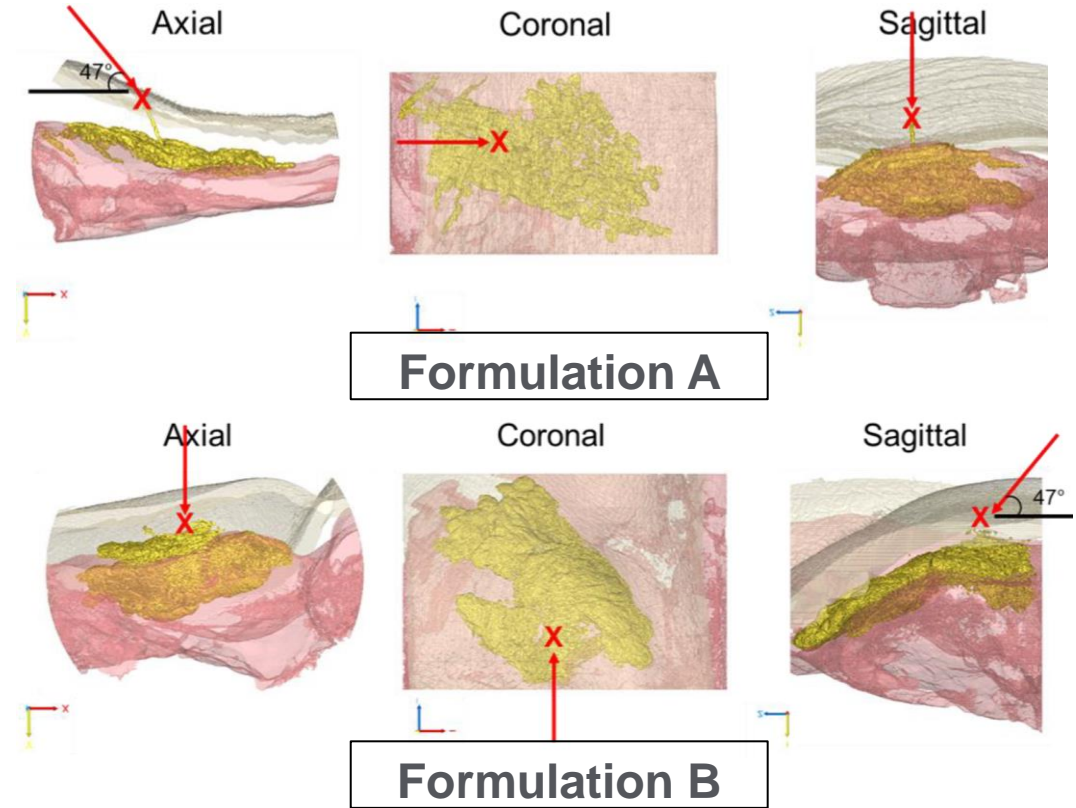


# Formulations were successfully reconstructed from *ex vivo* and *in vivo* depots with $\mu$ CT

## *Ex Vivo*



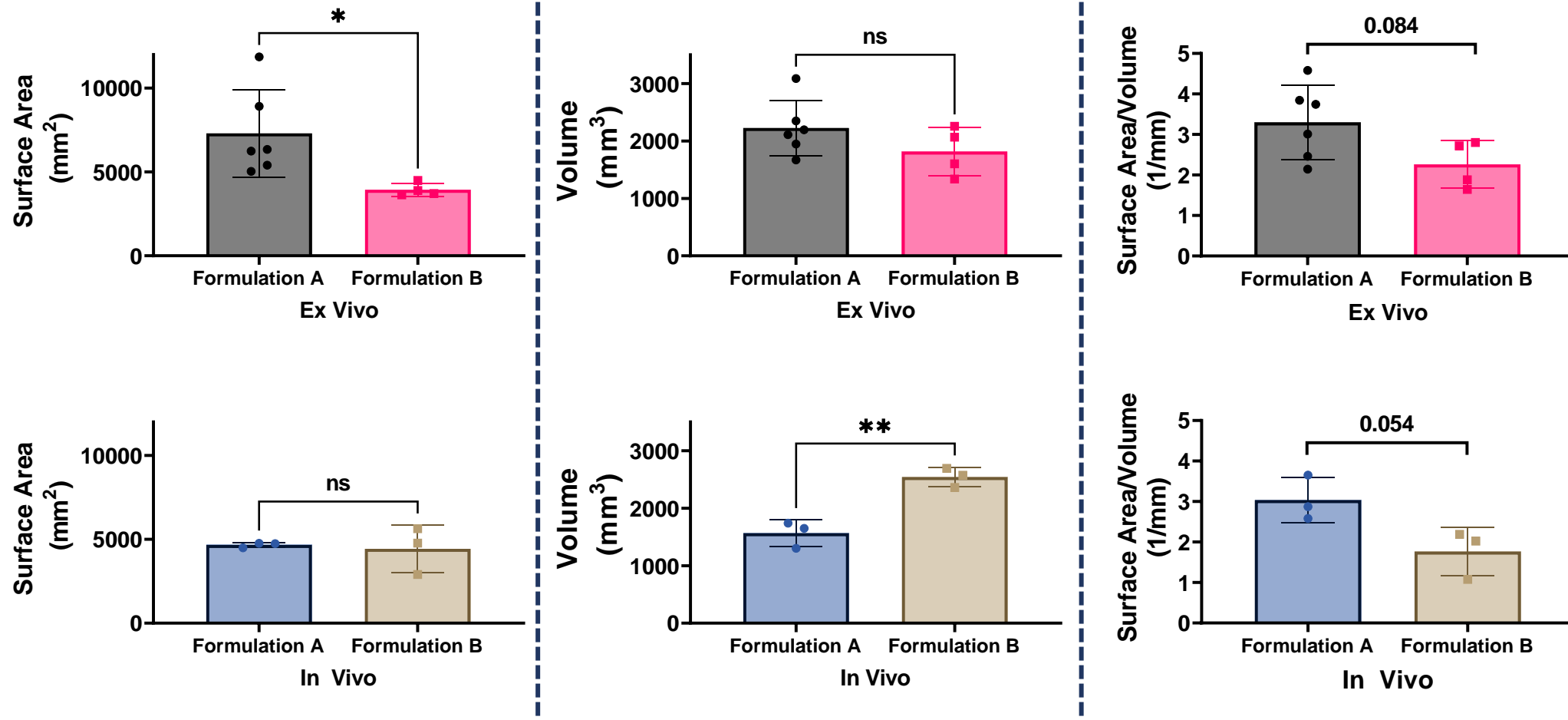
## *In Vivo*



1 Hour Post Injection

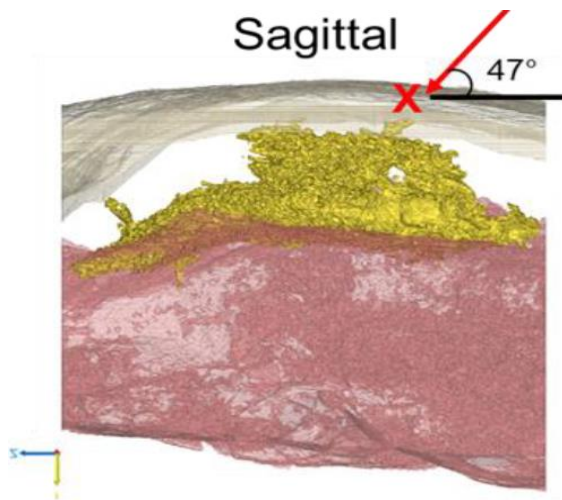


# Surface area and volume trends differ between *ex vivo* and *in vivo* models

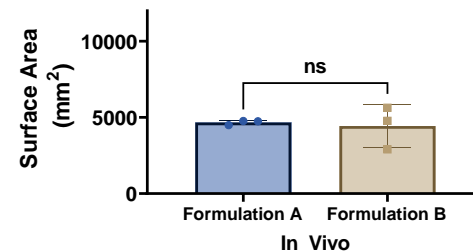
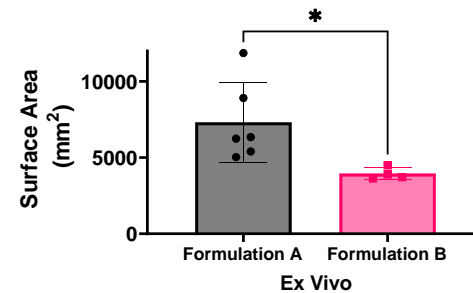


# Conclusions

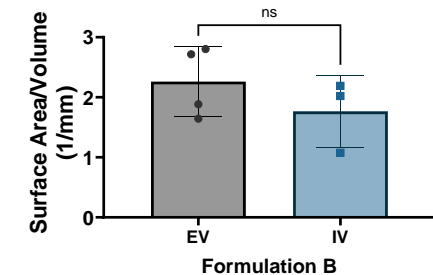
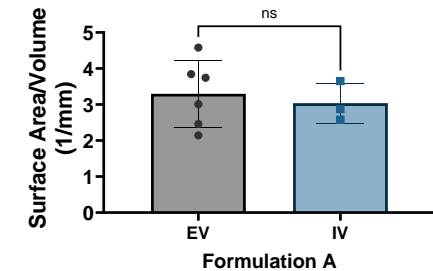
- LAI depots can be reconstructed and quantified *ex vivo* and *in vivo* using  $\mu$ CT



- There are morphology differences within the same formulation between models



- Surface area to volume ratios between depots are different between formulations but this alone does not explain the pharmacokinetic profile





# Acknowledgments

## **Gilead Sciences, Inc.**

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- Tyler Novak, PhD
- Ethan Stroh
- Vel Cunningham
- William Rowe, PhD
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- Raju Subramanian, PhD

## **MED Institute, Inc.**

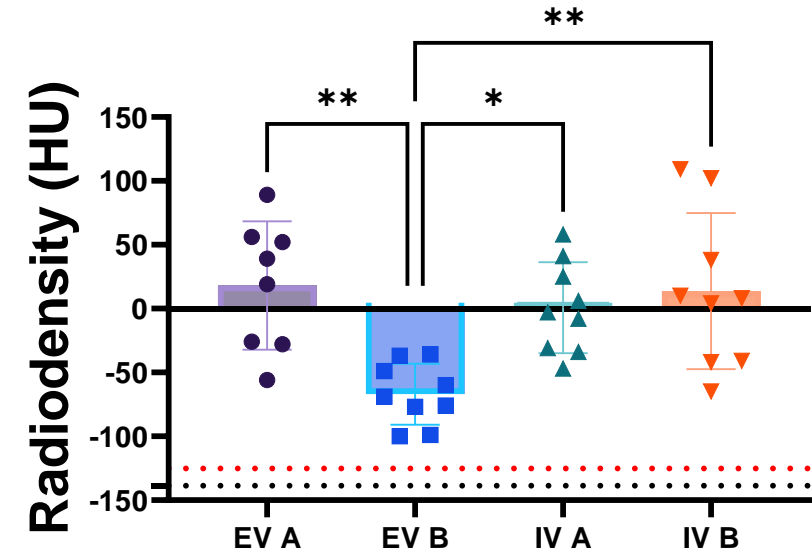
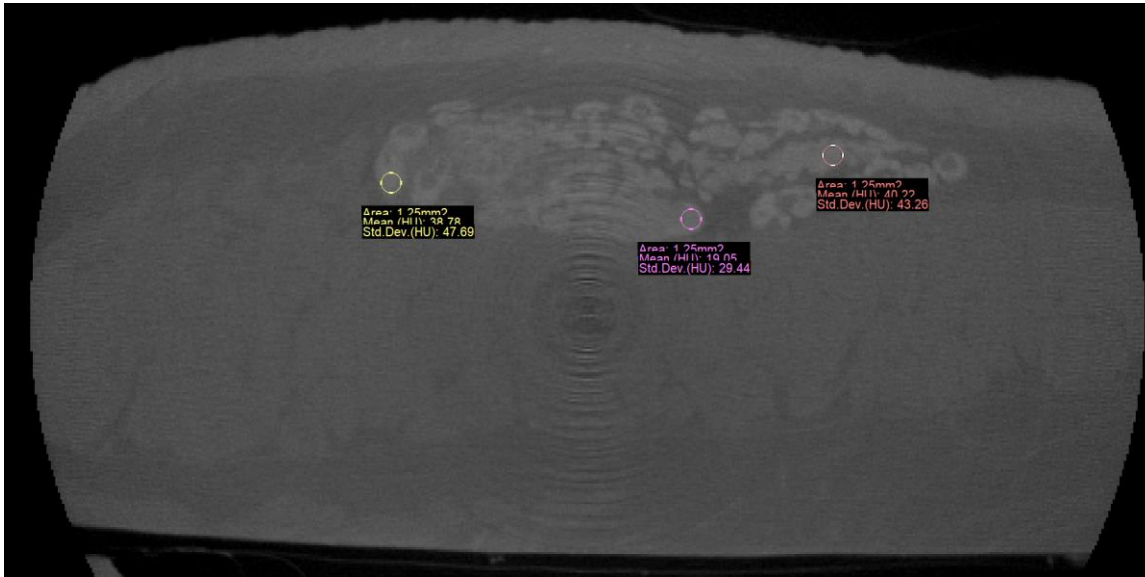
- Eric Anttila, PhD
- Joe Obermiller





Thank You

# Radiodensity is increased in formulations including API when compared to vehicle alone



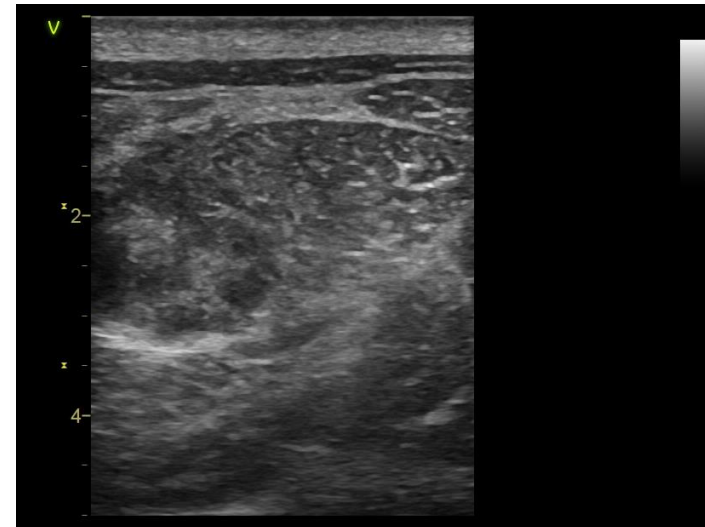
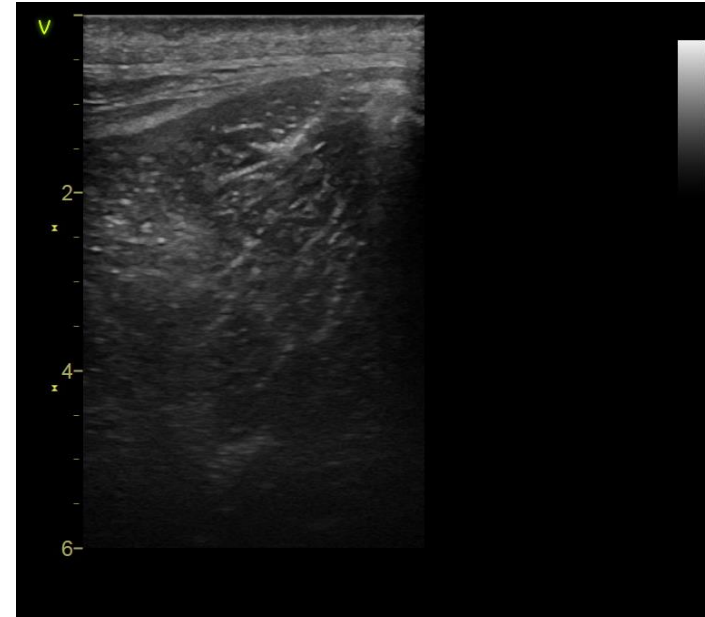
# μComputed Tomography (μCT) setup and reconstruction

- **Equipment Model:** Perkin Elmer Quantum GX MicroCT
- **Voltage and current:** 90 kVp tube voltage, 88 mA tube current
- **Filter:** Al 0.05 mm + Cu 0.06 mm
- **Acquisition time:** 14 minutes
- **#Slices and slice thickness:** 427 slices
- **Dicom pixel dimensions:** 512x512
- **Resolution:** 90-micron voxel resolution
- **Reconstruction Approach:** Ring artifact reduction, IM, Dermis Reconstruction, Mimics Medical v26.0





# Macro images and ultrasound of the subcutaneous space



# Surface area to volume ratio of formulations are similar between models but does not fully capture model differences

