PBPK Modeling to Support PSG Revision for Cabotegravir Long-Acting Injectable Suspension

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Presentation Outline

- Cabotegravir LAI: Background, Pharmacokinetics, and BE Study Challenges
- In Vivo Behavior of LAI Crystalline Suspensions
- Cabotegravir PBPK Model Development and Validation
- Model Application to Assess Risk of Truncated BE Study

Cabotegravir LAI: Background, Pharmacokinetics, and BE Study Challenges

- Cabotegravir (Apretude®; NDA 215499) is HIV-1 integrase strand transfer inhibitor and indicated to reduce risk of sexually acquired HIV-1 infection
- Apretude® is an extended-release injectable suspension for IM use
  - It PK shows flip-flop kinetics
  - Has prolonged elimination half-life (5.6 - 11.5 weeks)
- Previous version of product-specific guidance (PSG) recommends single dose parallel bioequivalence (BE) study with PK endpoints
- Challenges with in vivo BE study:
  - Prolonged drug exposure necessitates an extended BE study duration
    - Measurable plasma concentrations persist for up to one year following a single IM injection
    - Following PK BE guidance of sampling for at least three half-lives, cabotegravir's half-life of ~11.5 weeks would necessitate a study duration of approximately 33 weeks
  - Long study duration creates practical challenges like high dropout rate, increased cost

PBPK Modeling Objectives

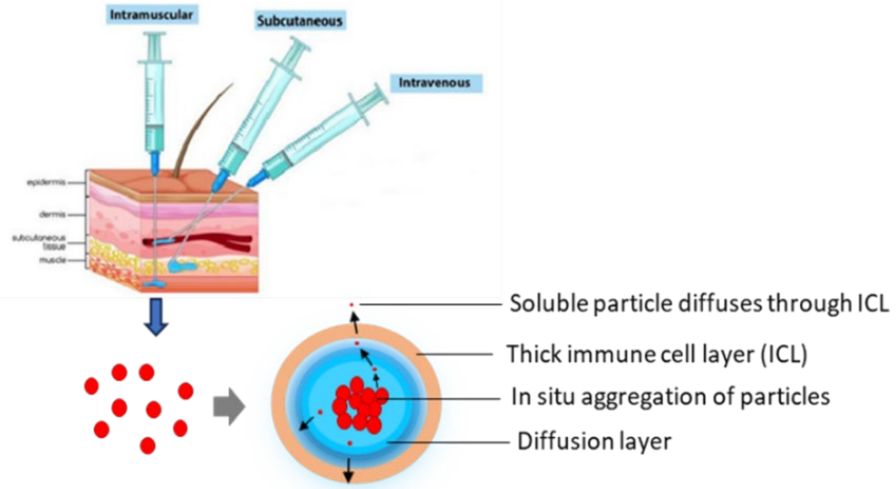
A mechanistic PBPK model was developed to assess study truncation risk and support PSG revision for cabotegravir long-acting injectable (LAI).

- Characterize the mechanistic factors governing absorption of cabotegravir LAI suspension
- Evaluate the feasibility of truncating the BE study duration
- Assess the ability of a truncated BE study to detect potential formulation differences and support PSG revision

In Vivo Behavior of LAI Crystalline Suspensions

Generally, LAI suspensions form a depot at the injection site, enabling sustained drug release often driven by low solubility of active pharmaceutical ingredient (API).

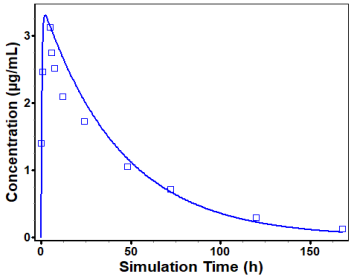
- In situ particle aggregation reduces effective surface area, slowing in vivo dissolution rates.
- Local immune reactions to solid particles drive fibrous capsule (ICL) formation around aggregates, further slowing absorption.
- The manufacturing process of cabotegravir LAI suspension utilizes a size reduction technique that produces nanosized crystalline particles. These particles are thermodynamically unstable and prone to aggregation.



Cabotegravir PBPK Model Development and Validation

Cabotegravir Oral Solution PBPK Model

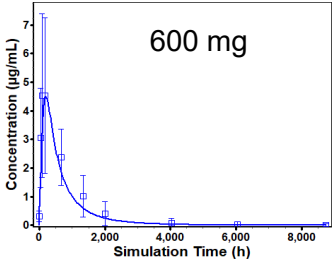
Objective: Characterize systemic disposition parameters (CL and Vd)



- Clearance (CL): captured through Km and Vmax values of UGT1A1 and 1A9, in the gut and liver
- Renal clearance: described by "fup × GFR"
- Volume of distribution (Vd): Estimated from tissue/plasma partition coefficients (Kp) to match observed data
- Absorption: Described by permeability parameter and in vitro dissolution data

Cabotegravir 600 mg IM suspension PBPK Model

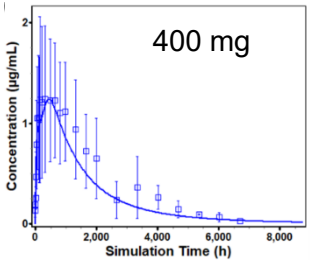
*Objective: Validate the model with PSG recommended dose (**600 mg**)*

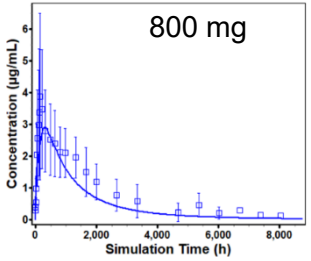


- Aqueous solubility: 48 µg/mL at pH 7.4
- In vitro particle size were scaled 160 – 400 folds to account for in vivo particle agglomeration
- Effective depot volume (based on injection volume administered)
- Local blood flow rates and tissue characteristics
- Local immune reactions leading to fibrous capsule formation around solid aggregates

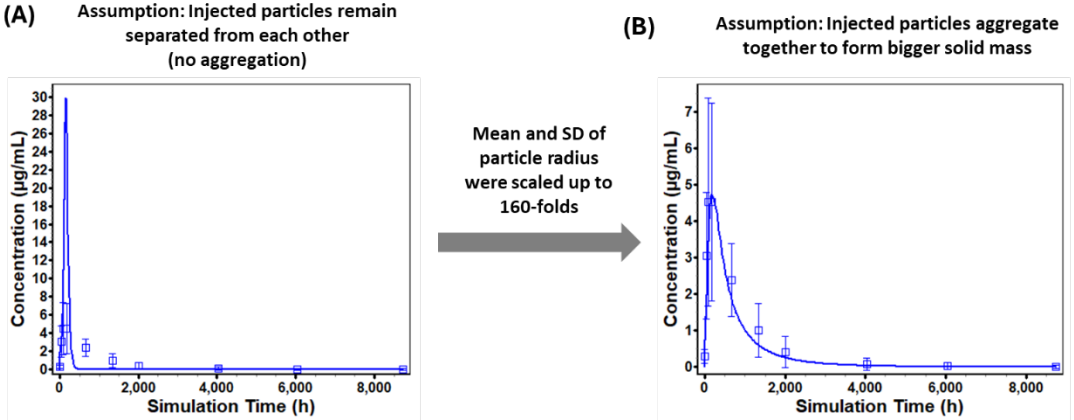
Cabotegravir 400 and 800 mg IM suspension PBPK Models

*Objective: Further validation of IM suspension model with **400 and 800 mg doses***





Scaling of In Vitro Particle Size to Account for In Vivo Particle Aggregation



Besides the in vivo effective particle size, there were a few additional sensitive model parameters that also impact the systemic exposures to some extent:

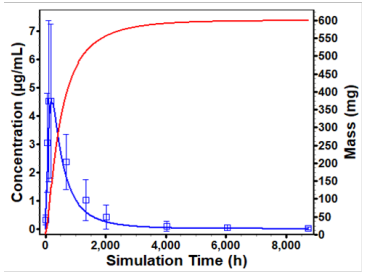
- Diffusion layer thickness
- Volume of injection
- ICL thickness
- Dynamic change in ICL thickness

However, none of these parameters' contribution compensate for the impact of in vivo particle aggregation.

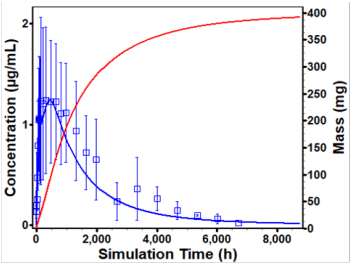
Model Application: Study Duration & Exposure Characterization

PBPK model predicted $AUC_{0-t}/AUC_{0-\infty}$ ratios and percentage of dose absorbed at different truncated timepoints.

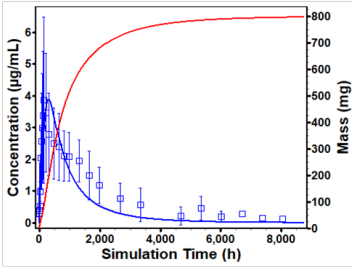
Cabotegravir 600 mg IM suspension



Cabotegravir 400 mg IM suspension



Cabotegravir 800 mg IM suspension



Simulated PK profile

Simulated absorption profile

PSG recommended dose for BE study

Dose	PBPK model predicted AUC_{0-t}/AUC_{0-inf} ratio					PBPK model predicted % of absorption completed at time t				
	Week 8	Week 12	Week 16	Week 20	Week 52	Week 8	Week 12	Week 16	Week 20	Week 52
600 mg	0.87	0.94	0.97	0.98	1.00	85.1	92.4	95.6	97.2	99.4
400 mg	0.63	0.76	0.84	0.88	0.98	57.5	71.3	79.8	85.3	97.6
800 mg	0.78	0.87	0.92	0.95	1.00	74.0	84.9	90.5	93.7	99.0

Model Application: Risk Assessment of Truncated BE Study

- Sensitivity analysis from PBPK model suggests that in vivo particle size (aggregated particles) is the most sensitive parameter for systemic exposure.
- A hypothetical Test (T) formulation was created that has two-fold higher propensity for in vivo particle agglomeration compared to reference (R) formulation.

Treatment	Dose	$AUC_{0\text{-}8\ week}$	$AUC_{0\text{-}12\ week}$	$AUC_{0\text{-}16\ week}$	$AUC_{0\text{-}20\ week}$	$AUC_{0\text{-}52\ week}$
With effective particle size used for model development (denoted as R)	600 mg	2797	3055	3167	3223	3298
	400 mg	1305	1639	1843	1974	2268
	800 mg	3223	3732	3991	4136	4380
With 2X higher effective particle size (denoted as T)	600 mg	2187	2597	2832	2976	3263
	400 mg	855	1157	1382	1552	2108
	800 mg	2316	2925	3321	3590	4259
T/R ratio for $AUC_{0\text{-}t}$	600 mg	0.78	0.85	0.89	0.92	0.99
	400 mg	0.66	0.71	0.75	0.79	0.93
	800 mg	0.72	0.78	0.83	0.87	0.97

$AUC_{0\text{-}t}$ values at 52 weeks were comparable between T and R (T/R ratios exceed 0.9 for all three cabotegravir doses)

As the truncation time decreases, the $AUC_{0\text{-}t}$ values diverge significantly between the formulations, and the T/R ratio becomes smaller.

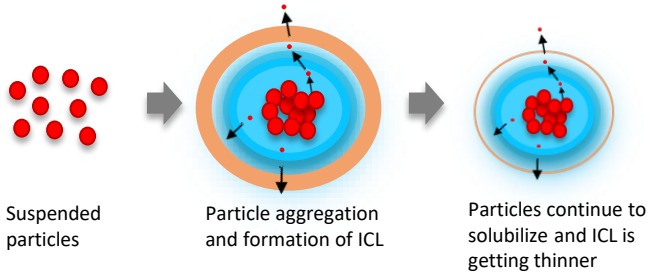
Critical Findings:

- Earlier truncation timepoints demonstrate superior discrimination compared to full-duration studies.
- The enhanced sensitivity at truncated timepoints provides regulatory confidence that meaningful formulation differences will not be overlooked in shorter duration studies.

Is the Release Mechanism Consistent Over Time?

A key regulatory consideration for study truncation is whether the release mechanism remains consistent throughout the absorption period.

- Cabotegravir LAI particles form an aggregated depot at the injection site, where drug release is driven by in vivo dissolution of aggregated particles — a mechanism that remains consistent over time.
- As particles gradually dissolve, the fibrous capsule (ICL) becomes progressively thinner. But the fundamental dissolution-driven release mechanism does not change at later timepoints.

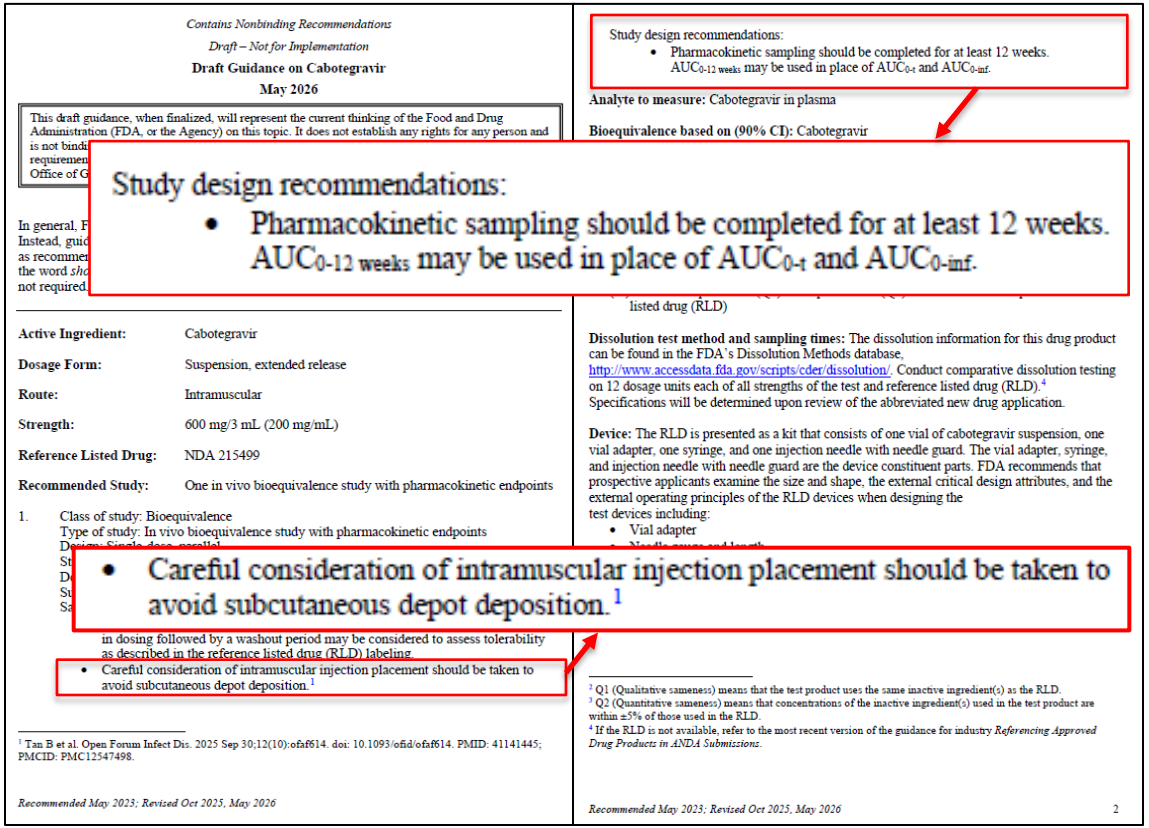


- Unlike rate controlling systems where release kinetics may shift due to structural changes in the carrier, cabotegravir LAI involves no rate-controlling matrix — eliminating a key source of time-dependent mechanistic variability.

These characteristics collectively support the feasibility of study truncation, as the early and late absorption phases are governed by the same underlying mechanism.

Revised PSG: Cabotegravir LAI Suspension

- **Truncated study duration accepted:** PK sampling for at least 12 weeks is now recommended, with $AUC_{0\text{-}12\ weeks}$ accepted in place of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ — a significant reduction from the previously required ~1-year study duration.
- **Study design retained:** Single-dose, parallel design with PK endpoints remains recommended, consistent with the prior PSG.
- **New safety recommendation added:** Careful consideration of IM injection placement is now explicitly recommended to avoid subcutaneous depot deposition, supported by clinical MRI data (Tan B et al., 2025).



Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Cabotegravir

May 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of G

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Study design recommendations:

- Pharmacokinetic sampling should be completed for at least 12 weeks. $AUC_{0\text{-}12\ weeks}$ may be used in place of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$.

Active Ingredient:	Cabotegravir
Dosage Form:	Suspension, extended release
Route:	Intramuscular
Strength:	600 mg/3 mL (200 mg/mL)
Reference Listed Drug:	NDA 215499
Recommended Study:	One in vivo bioequivalence study with pharmacokinetic endpoints

1. Class of study: Bioequivalence
Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, parallel
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in dosing followed by a washout period may be considered to assess tolerability as described in the reference listed drug (RLD) labeling.

- Careful consideration of intramuscular injection placement should be taken to avoid subcutaneous depot deposition.[1]

- Careful consideration of intramuscular injection placement should be taken to avoid subcutaneous depot deposition.[1]

[1] Tan B et al. Open Forum Infect Dis. 2025 Sep 30;12(10):ofaf614. doi: 10.1093/ofid/ofaf614. PMID: 41141445; PMCID: PMC12547498.

Recommended May 2023; Revised Oct 2025, May 2026

Study design recommendations:

- Pharmacokinetic sampling should be completed for at least 12 weeks. $AUC_{0\text{-}12\ weeks}$ may be used in place of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$.

Analyte to measure: Cabotegravir in plasma

Bioequivalence based on (90% CI): Cabotegravir

listed drug (RLD)

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference listed drug (RLD).[4] Specifications will be determined upon review of the abbreviated new drug application.

Device: The RLD is presented as a kit that consists of one vial of cabotegravir suspension, one vial adapter, one syringe, and one injection needle with needle guard. The vial adapter, syringe, and injection needle with needle guard are the device constituent parts. FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD devices when designing the test devices including:

- Vial adapter

[2] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD.
[4] If the RLD is not available, refer to the most recent version of the guidance for industry *Referencing Approved Drug Products in ANDA Submissions*.

Recommended May 2023; Revised Oct 2025, May 2026 2

Tan B et al., 2025. Open Forum Infect Dis. 2025 Sep 30;12(10):ofaf614

Key Takeaways: MIE Approach Supporting PSG Revision

PBPK modeling as a Model-Integrated Evidence (MIE) tool enabled a mechanistically justified revision of the cabotegravir LAI PSG.

- Mechanistic understanding informed regulatory decision-making: PBPK modeling revealed that in vivo particle aggregation is the primary driver of cabotegravir LAI absorption, providing a mechanistic basis for evaluating BE study design.
- Study truncation is scientifically supported: The PBPK model demonstrated that the dissolution-driven release mechanism remains consistent over time and that earlier truncation timepoints offer superior sensitivity in detecting formulation differences.
- MIE approach reduced study burden without compromising BE assessment: The revised PSG now recommends a 12-week PK sampling window with $AUC_{0\text{-}12\ week}$ as the primary endpoint — replacing the previously required ~1-year study duration.
- Broader implication: This case study demonstrates that mechanistic PBPK modeling can serve as a powerful MIE tool to address complex BE challenges for LAI suspensions and support evidence-based PSG revisions.

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