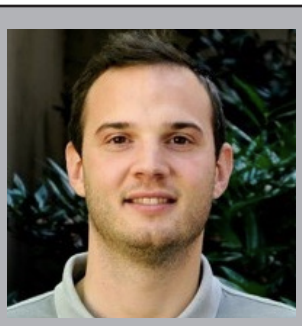


Simone Perazzolo Senior Scientist, TLC-ART Program at University of Washington

"Role of modeling and simulation as a tool for assessment of BE of LAI formulations"

Challenges of modeling BE for LAI products

- Extremely long duration.
- Complicated and resource intensive BE study designs.
  - ◊ Parallel design requires a very large sample size.
- Single vs multiple dosing issue – steady-state PK is important.
  - ◊ ER formulation accumulations at the end hinder SS.
  - ◊ SS can be achieved in years?
  - ◊ Is SD AUC approximately 90% of RLD?
- Depot formulations can generate variable PK (i.e., Release-controlled).
  - ◊ Is the AUC/Cmax 80-125% range too stringent?
  - ◊ What about other noncompartmental parameters (Ctau, Cmin, pAUC)? Computation requires a complex, resource intensive sampling schedule.
- What happens if APIs have a nonlinear PK?

Our experience with TLC-ART 101

Sought FDA approval via NDA 505(b)(2) pathway.

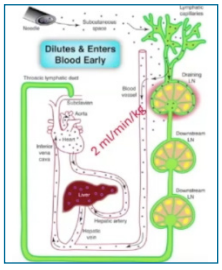
- Modification of existing products.
  - ◊ New route of administration from oral to injectable LPV/r+TFV DcNP formulation.
- Information required for approval.
  - ◊ Safety and efficacy.
    - * Relied in part on data we did not generate + new P1 study for additional PK data.
  - ◊ Evidence on how the formulation works, where it goes, and how long it stays.
    - * Mechanistic (PBPK) modeling to predict release kinetics, regional effects, and scaling.
- BE studies were not required.

Using PBPK modeling to bridge mechanistic unknowns.

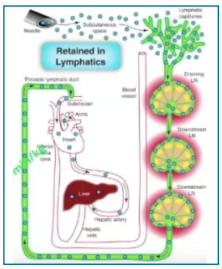
- The key is the release. Understanding the factors that control the release kinetics may better predict critical PK parameters.
  - ◊ Tmax (First peak is important for OLI).
  - ◊ AUC (Scaling).
  - ◊ Tail (Varies across LAIs).
- Focus on the injection site (Where, how, how long).
  - ◊ What happens immediately after you inject a LA-producing product?

Scenario 1
LA in solution. (Free ARV, depot, implant, etc.)
Small molecules are better suited for blood uptake. Drug dilutes in interstitial space and enters the blood early where the rate of fluid flow is more rapid (2 mL/min/kg).
How the formulation is designed to release the drug determines release kinetics for LA
Simple calculation of blood flow can yield Tmax not more than ½ hour after injection.
BE biowaiver is possible.[1]

[1] If release kinetics can be understood in vitro, there is potential to better understand PK in vivo.

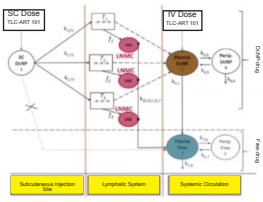


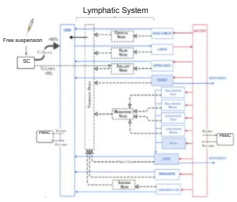
Scenario 2
Large particle or high stability formulation. (DcNP, mAbs, d-interferons, IgM)
Depot moves to lymphatics with delayed blood entry. Drug is retained in the lymphatics where the rate of fluid flow is much slower (0.02 mL/min/kg).
Leveraging this slower route can achieve LA.
From Tmax, there will be extreme slow release that will direct half-life and peaks.
Modeling to bridge mechanistic unknowns.



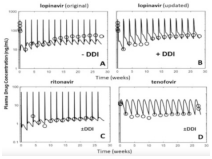
Modeling approach for TLC-ART 101 leveraging NHPs.

- Models to predict Tmax, AUC, and Tails. Incorporated data from higher mammals, tissues, cells, & IV administration (BA) in the modeling & validated.
  - ◊ Theoretical compartmental modeling to understand lymphatic transport via LMNCs.
  - ◊ Physiologically based modeling (i.e., using physiological flow volumes) to attempt realistic scale up or down by factors (From NHPs to humans and adults to pediatrics).





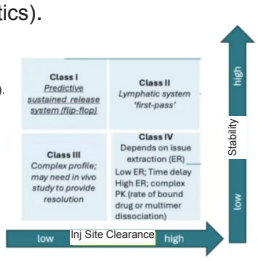
- DDI and SS modeling. We trained the model to achieve SS in NHPs and include DDIs, which provided strong evidence of behavior in humans.
  - ◊ After validation, our formulation was able to advance.
  - ◊ 6-month study of Q2w TLC-ART 101 in NHPs.
    - * TFV achieved SS with first dose
    - * LPV/r required >5w to achieve SS.
    - * DDI disturbed SS achievement.
  - ◊ **What better tool than PBPK modeling to predict SS and DDI findings and validate with a representative species for humans.**



A possible redefinition of the BCS

LA BCS based on Formulation stability and Injection site clearance (Key determinants of release kinetics).

- Class 1. Depot formulation.
  - ◊ High formulation stability.
  - ◊ Not cleared from the injection site (PK tail releases drug).
  - ◊ Potential for biowaiver.
- Class 2. DcNP formulation or bNAb.
  - ◊ High stability to exploit the lymphatic system route.
  - ◊ High injection site clearance.
  - ◊ TLC-ART 101: No depot found at the injection site, but high drug concentrations in LMNCs (Depot moved to the lymphatic system).



Summary

- Not all LAIs are the same pharmacologically speaking. (Class 1, Class 2, or Hybrid).
- Need strong mechanistic understanding and modeling.
  - ◊ Focus on understanding the release dynamics to explain Tmax, Cmax, and AUC.
  - ◊ Get to SS predictions.
  - ◊ Understand DDI and time-varying effects.
- Key parameters.
  - ◊ Formulation stability.
  - ◊ Where does the API go?
  - ◊ Where does the API stay?
  - ◊ How long does the API take?

"[Leveraging] this school of thought, we can better predict where noncompartmental parameters will fall and when the steady state will be and cut down time"