

Use of Integrated PK-Viral Dynamic Model to Support Dose Selection of S/GSK1349572 in Phase IIB

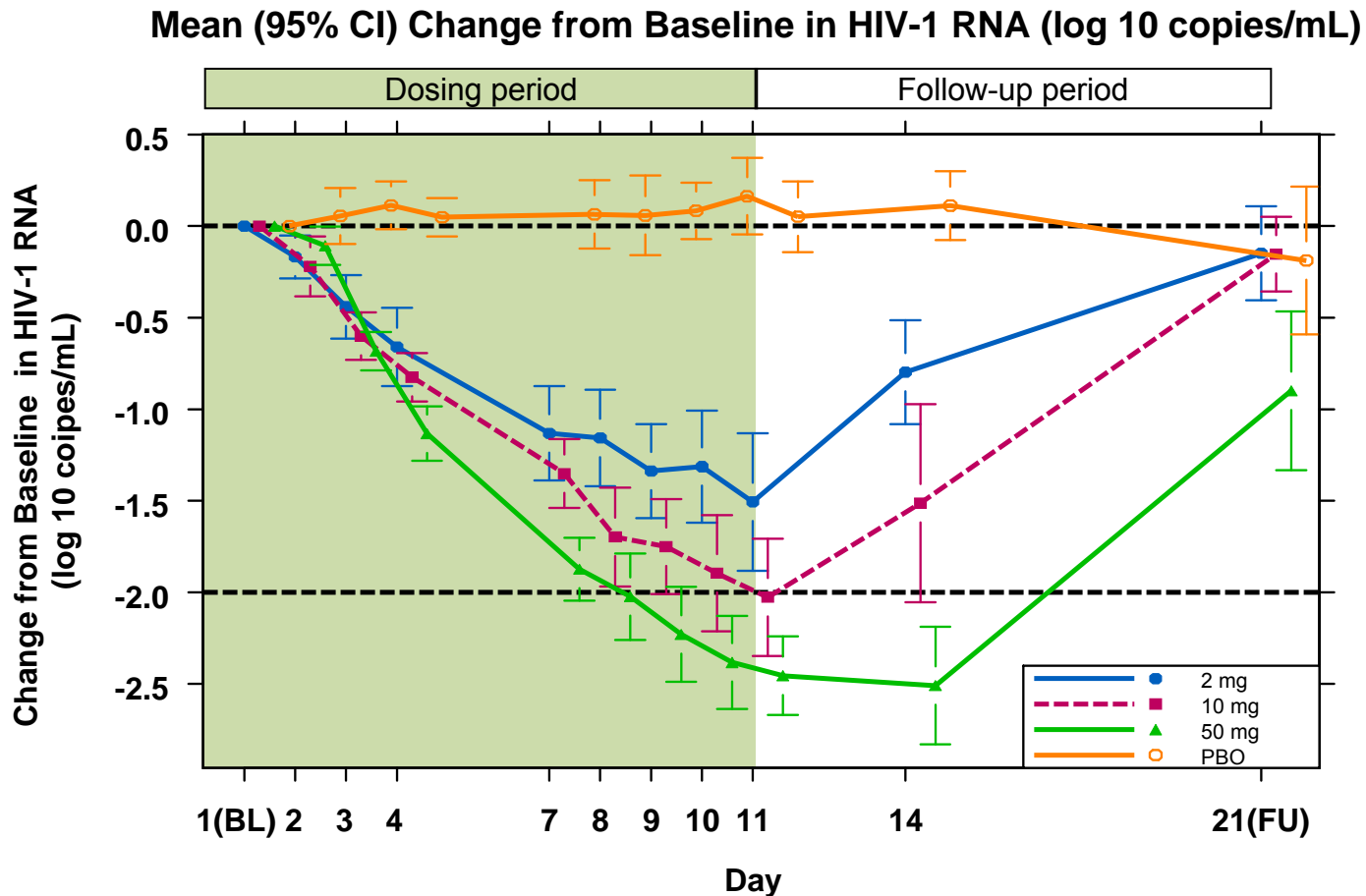
I. Song

Clinical Pharmacology Modeling Simulation

GlaxoSmithKline



POC Results: Potent Antiviral Activity with Clear PK/PD Relationship in Monotherapy

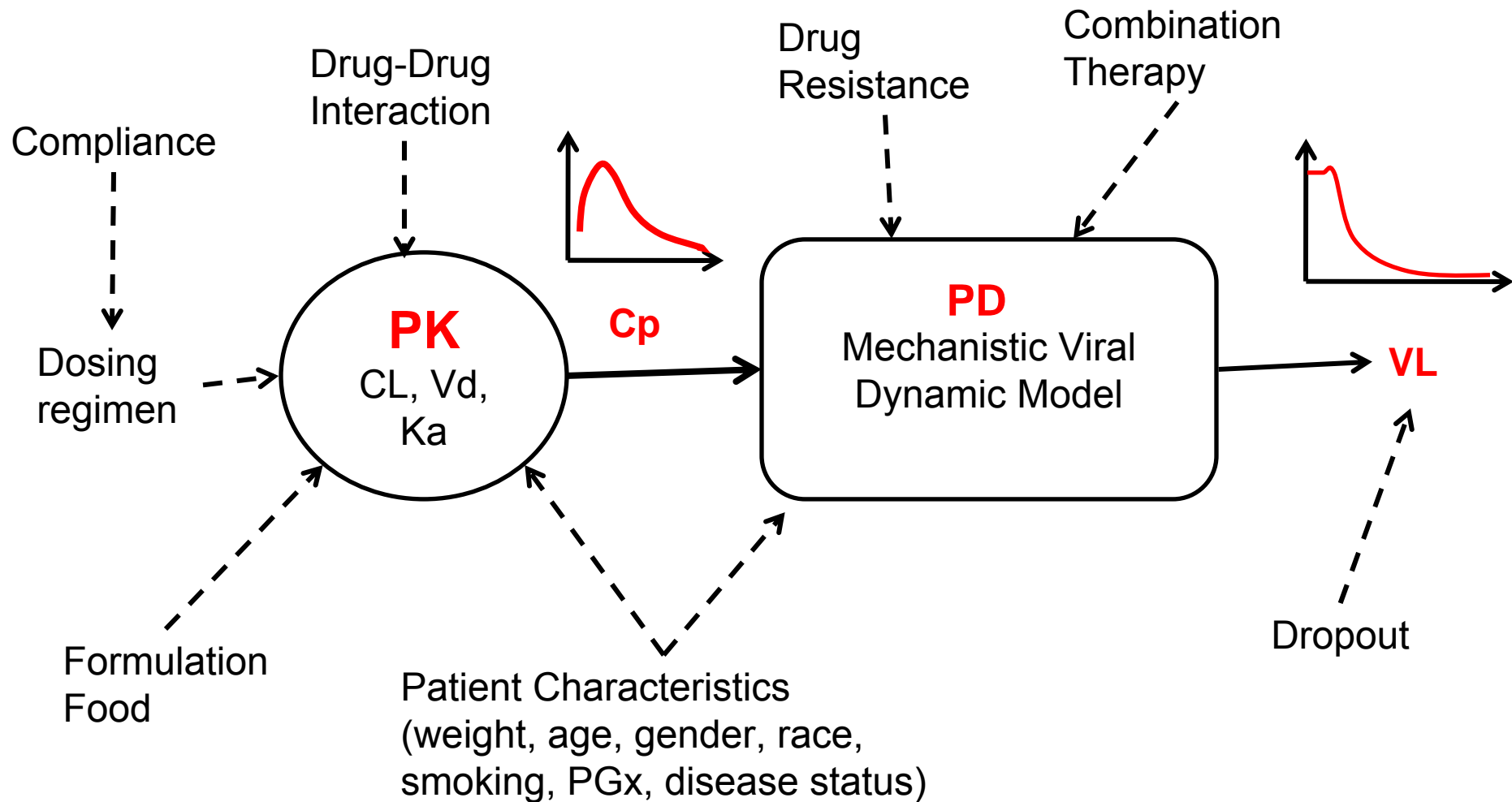


Treatments: 2, 10, and 50mg QD vs placebo x 10 days in INI-naïve HIV patients.
Ref: Min S. 5th IAS 2009, Cape Town, abstract 2120.

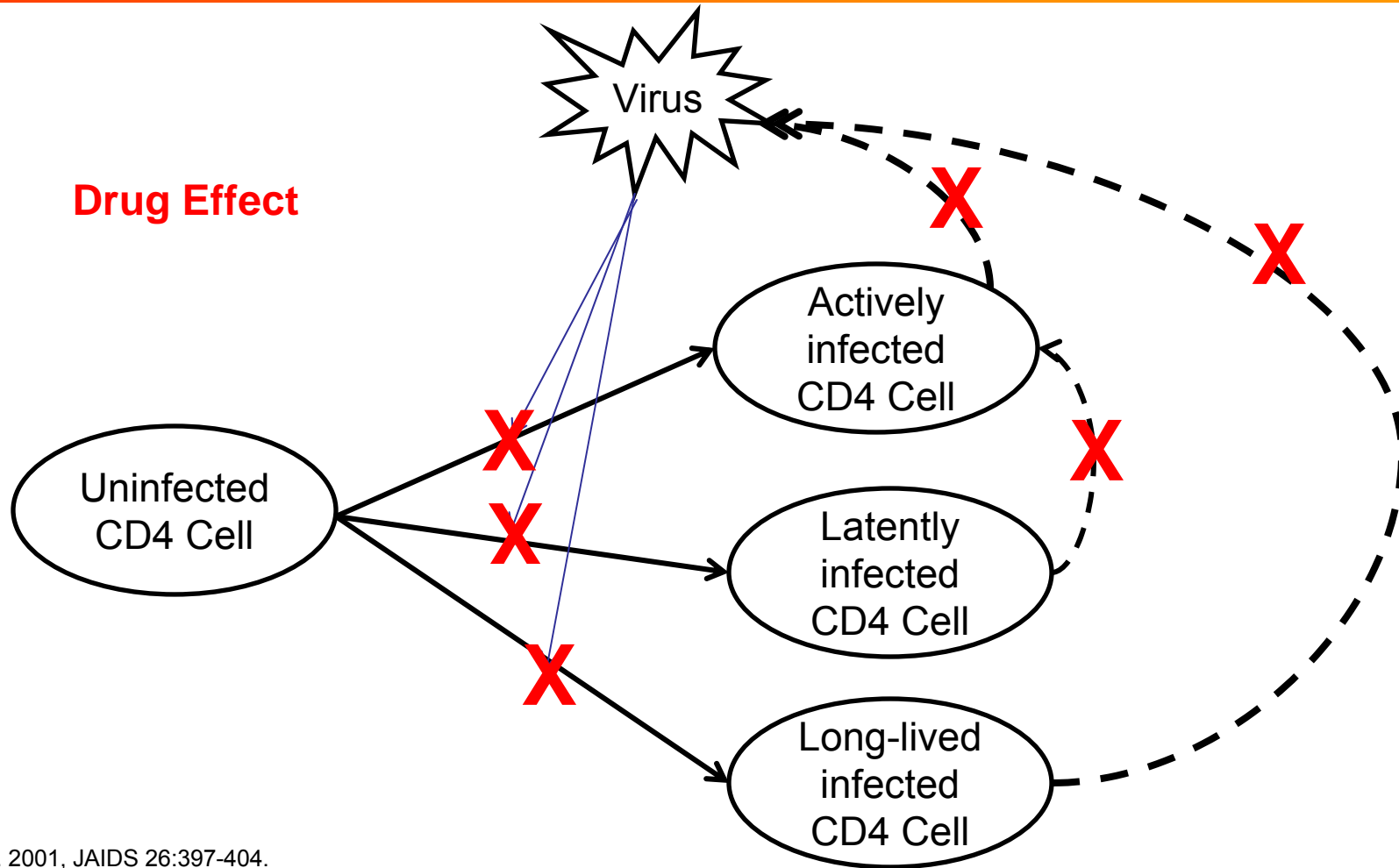
Objectives and Challenges for Phase IIb/III

- **Objectives: dose selection and study design for Phase IIb/III**
- **Challenge: using short-term (10-day) monotherapy antiviral activity data to predict long-term efficacy in combination therapy in different patient populations**
 - Treatment-naïve population
 - Treatment-experienced population/INI naïve
 - Treatment-experienced population/INI resistant
- **Approach: apply integrated PK-viral dynamic modeling**

Integrated Drug-Disease Modeling



Mechanistic Viral Dynamic Model



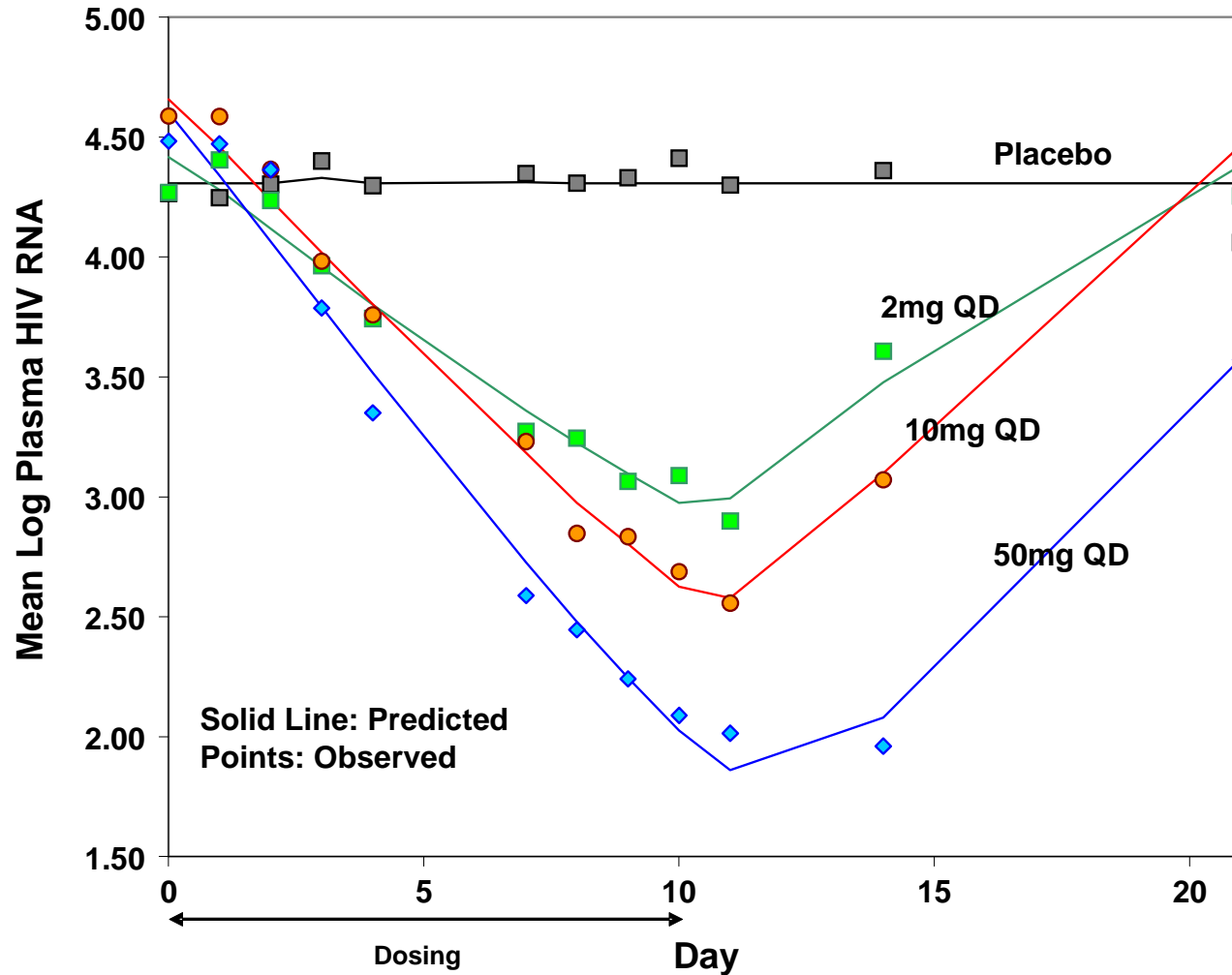
1. Funk G.A. et al. 2001, JAIDS 26:397-404.

2. Nowak MA and May RM 2000, *Virus Dynamics*. New York, Oxford U. Press.

PK-Viral Dynamic Modeling

- **572 plasma concentration and VL data from Phase2a**
- **PK: equivalent constant concentration (ECC) [Poland, 2008 ASCPT]**
- **Simplified viral dynamic model (JP's presentation)**
- **Model validation by visual predictive check (VPC) and goodness of fit**

Good Prediction of Phase2a Data Gave Confidence for Predicting Long-Term Antiviral Activity Using Integrated Model

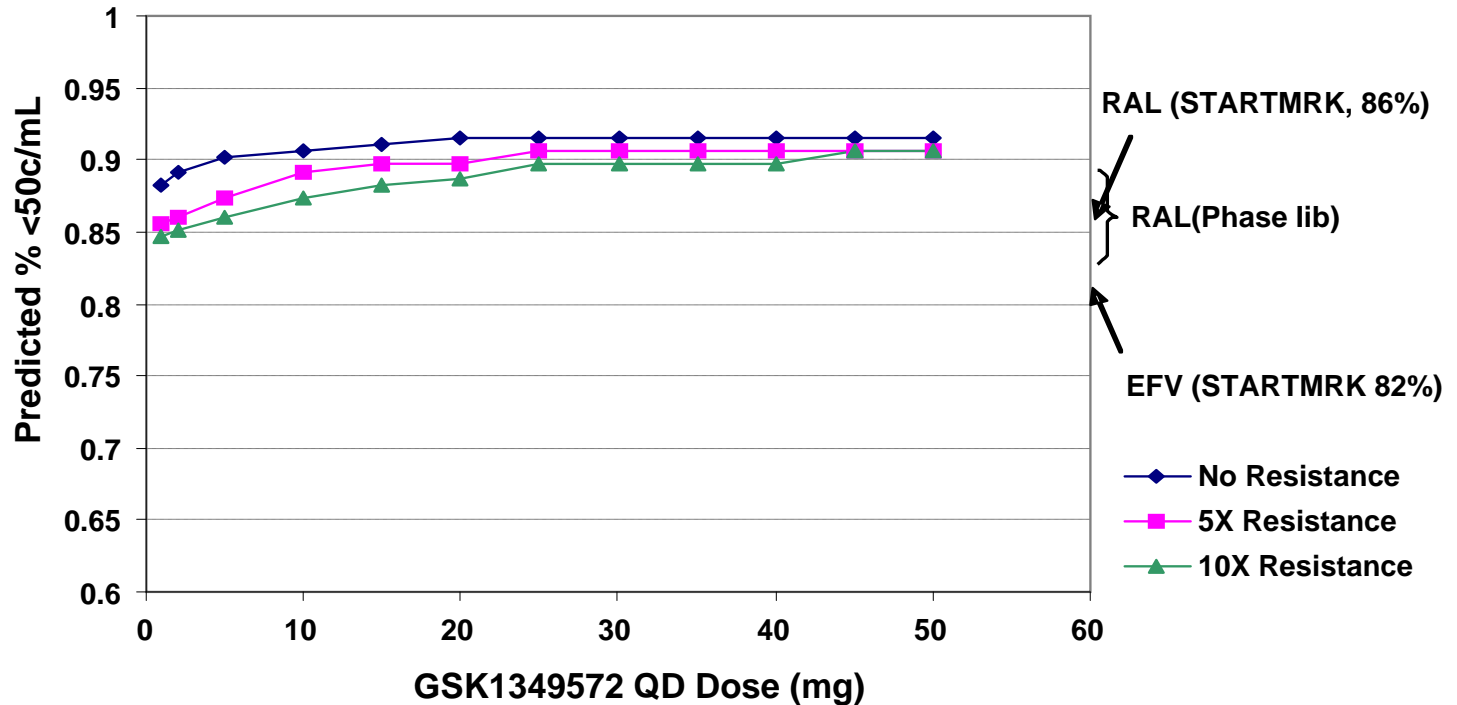


Clinical Trial Simulation

- **Trial Simulator© (Pharsight)**
- **Assumptions**
 - **Baseline VL (log): 4.5-4.8**
 - **90% compliance**
 - **Raltegravir-like non-virologic failure early dropout rate**
- **Endpoints (response rate):**
 - **Treatment-naïve and –experienced/INI-naive: % <50c/mL at up to 96 weeks**
 - **INI-resistant: log VL change from baseline after 10 days functional monotherapy**
- **Simulation scenarios:**
 - **Dose (1-50mg QD)**
 - **Emergence of resistant virus to 572 (INI-naïve)**
 - **Efficacy of optimized background therapy (treatment-experienced/INI-naive)**
 - **Baseline resistance to 572 (INI-resistant)**

Simulation Result: Treatment-Naïve Population

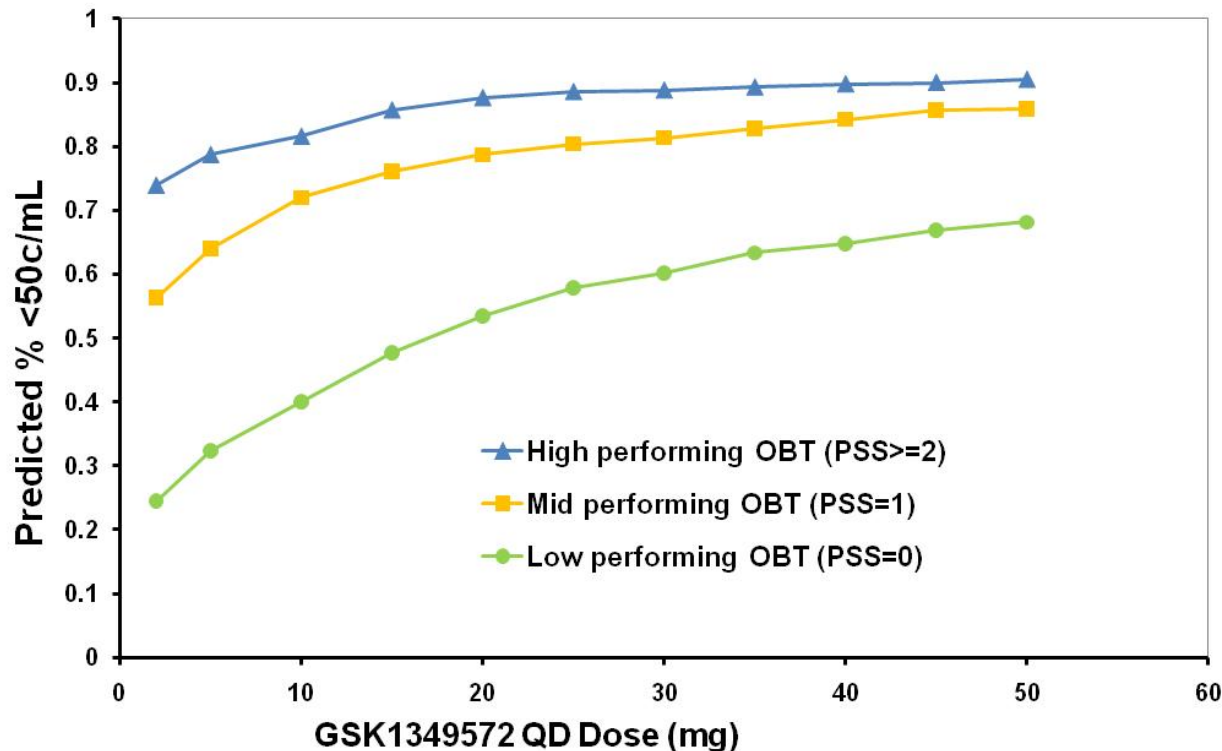
Predicted % Subject with VL <50c/mL at 48 week with Truvada in Naive Pop, n=200/scenario, RAL-like Viral Dynamic BLVL mean(sd): 4.8(0.5), RAL-like Dropout (8% at 48wk)



- Similar antiviral efficacy expected at dose ≥ 10 mg;
- Differentiation among doses will be driven by safety/tolerability;
- Likely to demonstrate at least non-inferiority to RAL with possibility to show superiority;
- 10, 25, and 50mg QD were progressed in Phase IIb

Simulation Results: Treatment-Experienced /INI Naïve

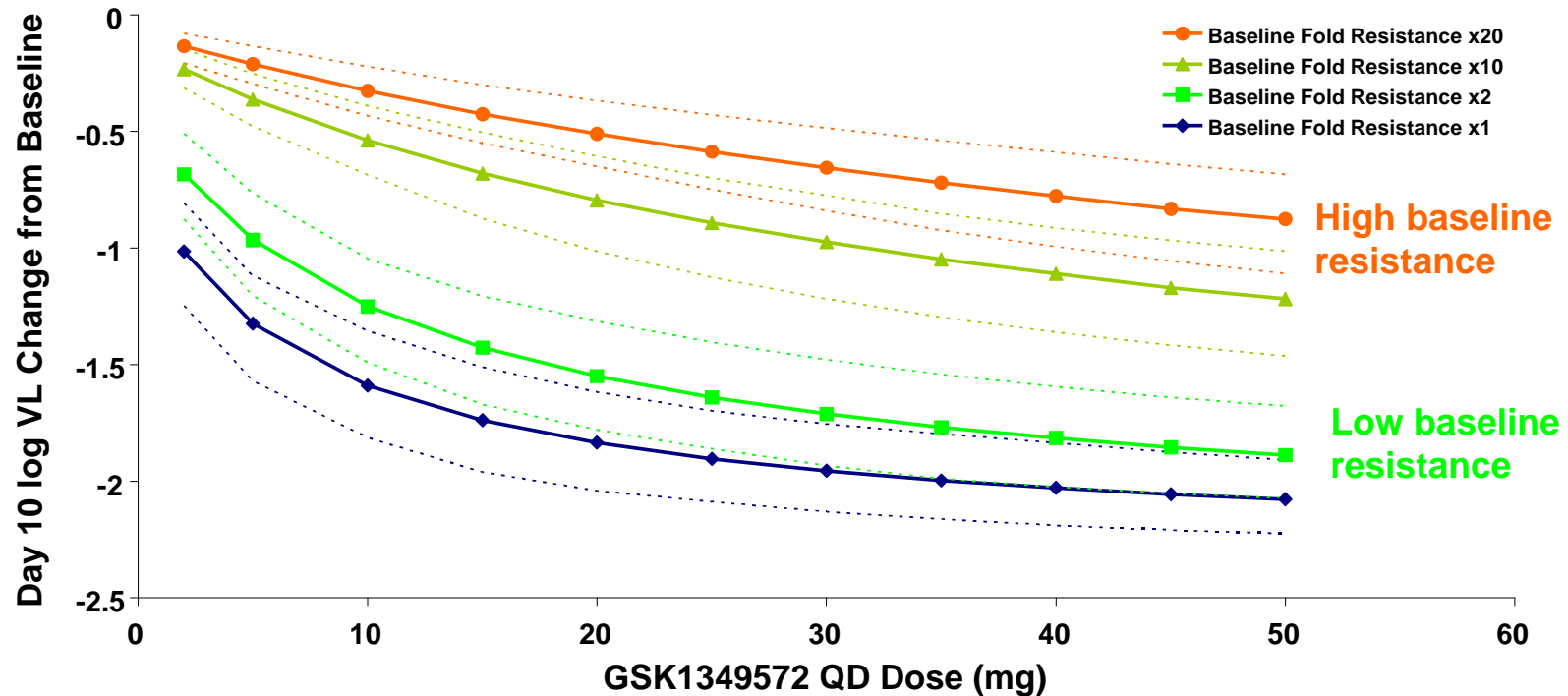
Predicted %<50c/mL at week 48 in treatment-exp population
BLVL: 4.5 (0.75), n=400/scenario,
RAL-like non-virological discontinuation



- Impact on study design/inclusion criteria: # of active drugs in optimal background antiviral therapy (OBT) affects the overall activity of combination therapy with 572

Simulation Results: Treatment-Experienced /INI Resistant Population in 10-day Monotherapy

Simulated Day 10 Log VL Change from Baseline in Heavily Treatment Patients on Failed INI-containing Therapy
BLVL: 4.5 (0.8)



- Recommendation for pilot study (VIKING) based on simulation:
 - 50mg QD was selected
 - Short-term antiviral response depends on baseline fold resistance
 - Two group with different baseline resistance were to be studied

Summary

- **Integrated PK-viral dynamic modeling and trial simulation is a useful and powerful tool for clinical trial design and decision-making**
- **572 will likely exhibit desirable long-term clinical efficacy in a broad range of HIV-infected patient populations**
- **This work supports the selection of 572 doses ranging from 10mg to 50mg once daily in Phase IIb studies**