

## Strategic Consulting Services

### **Dose Selection for HIV Therapy: Case Study of a Pfizer-Pharsight Collaboration**



# How can Phase 2a studies most efficiently determine doses for maraviroc for HIV?

## ● Critical Issue

- Phase 2a studies needed to determine doses for a combined Phase 2b/3 program.
  - Also to determine dose frequency (once or twice a day) and food restrictions if needed
  - Go/no-go decisions implicit in predictions relative to competition

## ● Approach & Technologies Utilized

- Integrated PK-PD-response model predicts response.
  - PK model, based on Phase 1, finds “Equivalent Constant Concentration” vs. dose
  - PD model is Emax model for viral inhibition by drug, together with viral and T-cell dynamics
  - Response is viral load drop after short-term treatment (with inter-subject variability)
- Model was updated each time more data became available.
  - Before Phase 2, key efficacy parameter IC50 had to be based on in-vitro data only
  - Update after first stage of first Phase 2a study (2 dose arms of 7-8 patients each)
  - Update after rest of this study (2 more active dose arms)
  - Update after second Phase 2a study (4 more arms, varying food and dose frequency)

## ● Results

- Each model update was smaller with reduced prediction uncertainty.

## ● Impact

- Phase 2a studies determined Phase 2b/3 doses. New confidence in model might allow reducing future Phase 2a program to one study, saving ~½ year development time.

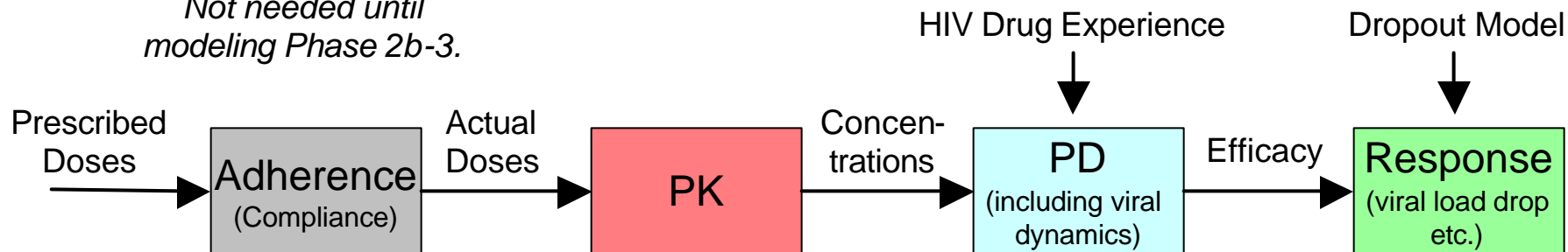
Background: Maraviroc is in a new class; if approved, it will compete against 20+ drugs.

- No cure for HIV yet, because virus gets “archived” in long-lived cells and rebounds after treatment stops.
- Maraviroc blocks the CCR5 co-receptor that HIV uses to enter T-cells. It might work better than current drugs.
  - The 20 currently approved drugs fall into four other mechanistic classes, blocking different steps in the HIV life cycle.
- Patients usually start on three drugs and replace one or all every few years/months as resistance develops.
  - Some patients still exhaust all current treatment options.
- Phase 2a HIV study designs: short-term monotherapy (7-14 days), usually in treatment-naive patients.
- Phase 2b/3 study designs: long-term combination therapy, in treatment-experienced patients and in treatment-naive patients (48-96 weeks).

Case study reference: Muirhead G et al. 2005, “Pharmacokinetic/Pharmacodynamic-Disease modelling and simulation in the development of Maraviroc (UK-427,857),” 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec, April 2005, Abstract 2.

# An integrated PK-PD-response model is needed for good predictions.

*Not needed until modeling Phase 2b-3.*



## Data Sources

Literature survey, bottle monitor data

Internal company data (subject-level); labels and literature (other drugs)

Internal in-vitro and clinical IC50 data; literature IC50s (other drugs)

Internal viral load data (patient-level); literature responses (other drugs)

## Model

Random long-run average adherence, dose-taking, and dose timing

Population PK compartmental model, or Equivalent Constant Concentration

Continuous-time Emax model by patient in viral dynamics differential equations; resistance steps by drug class

Trial protocol with inclusion/exclusion criteria; random dose-dependent or time-dependent dropouts

The PK of this drug was complex but could be summarized simply for the integrated model. 

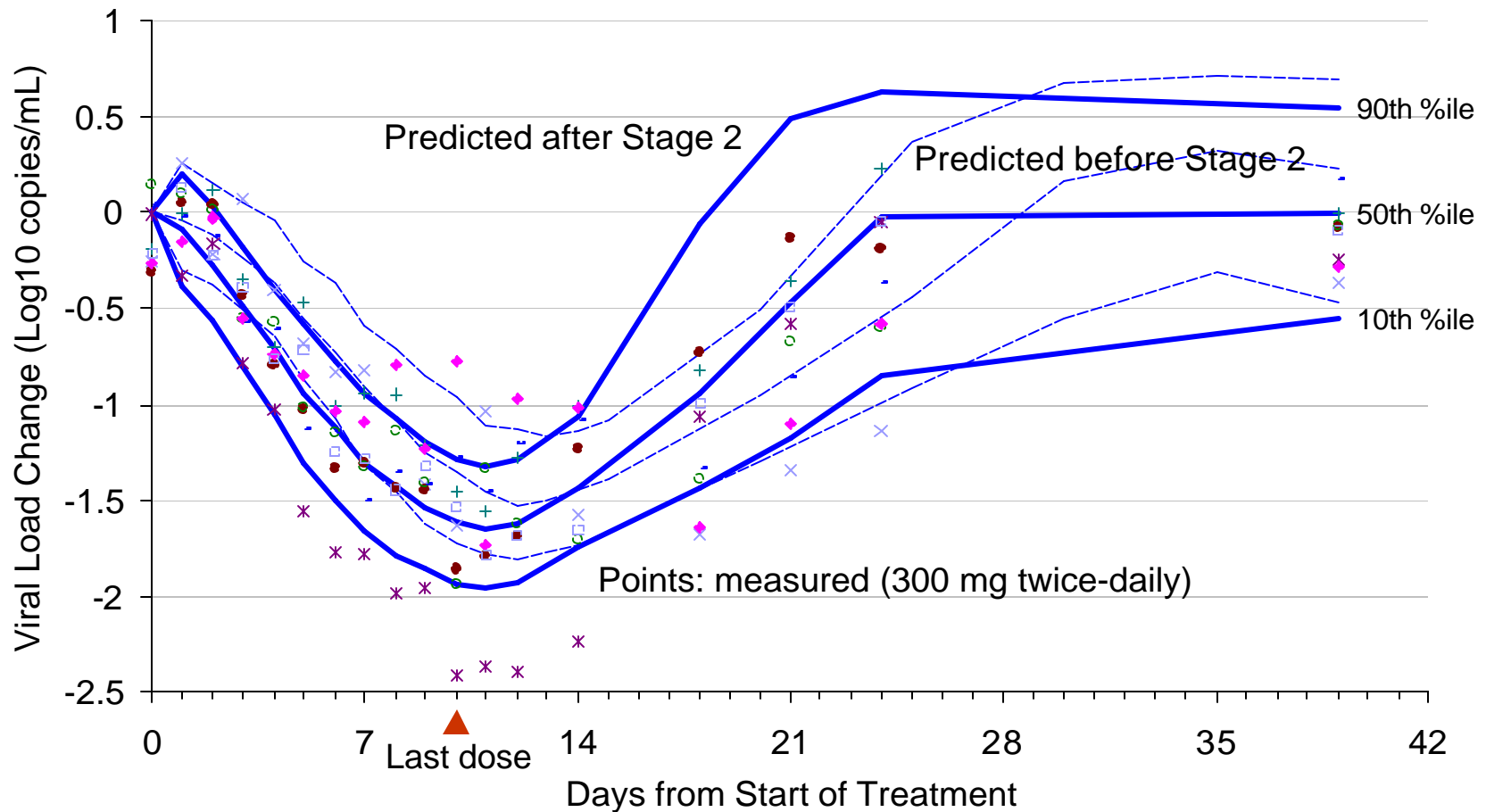
- Equivalent Constant Concentration (ECC) is the constant concentration that produces the same average viral inhibition over time as the full concentration time-profile.
  - Calculate by averaging inhibition =  $\text{conc.}/(\text{conc.} + \text{IC}_{50})$  and then solving backwards for concentration.
- Model:  $\text{ECC} = (\text{base value}) (\text{daily dose})^d (\text{fed multiplier})^{\text{Fed?}} (\text{Daily-dose multiplier})^{\text{Daily?}} e^e$ , where
  - Fed? and Daily? are 0 or 1
  - d and the two multipliers are estimated
  - e expresses estimated inter-subject variability.
- The ECC model quickly showed that once-a-day dosing did not substantially reduce relevant concentrations, relative to twice-a-day at the same daily total dose.



Key parameters such as IC50 were estimated with monotherapy study data, with others fixed to literature estimates.

- NONMEM was used to estimate IC50 and four key rates of viral dynamics with variability, using all available monotherapy study data.
  - **Before** Phase 2: no monotherapy data, so in-vitro IC90 and receptor binding information were used to select initial doses.
  - **After first 2** dose arms (25 mg daily & 100 mg twice-daily): IC50 and literature-based viral dynamics parameters were updated, and Stage 2 (50 & 300 mg twice-daily) was planned.
  - **After Stage 2** dose arms, estimates changed much less, and the new high dose (300mg twice-daily) reduced viral load as predicted.
  - **After last 4** dose levels (2<sup>nd</sup> study), estimates changed even less, indicating parameters were reliable for this population and study type.
- Phase 2b/3 predictions and design were then based on a solid short-term model...
  - due to clear identification of dose response (24-fold range of doses studied).
  - Resistance development remained a key, unavoidable uncertainty.

The measured mean viral load drop at the high dose was 1.6 log, vs. 1.5 predicted after Stage 1—the model needed only minor adjustments.



# Modeling and simulation proved useful before, during, and after Phase 2a.

- Improved design of monotherapy studies:
  - Few patients per arm
  - Informative doses
  - Second monotherapy study was predicted so well that “next time” it might be skipped.
- Added confidence to dose selection for Phase 2b/3.
- Tracked progress from highly uncertain predictions for Phase 2a to moderately uncertain ones for Phase 2b/3.
- Model was a knowledge repository for:
  - efficacy of maraviroc;
  - efficacy of competitors;
  - understanding of viral dynamics of treatment-naive patients – useful for compounds in other classes.