

Model-Based Drug Development of a New Anti-HIV Drug

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I. INTRODUCTION

Maraviroc (UK427,857) is an antiretroviral drug in Phase 3 development that has a new mechanism of action: antagonism of the HIV co-receptor CCR5. It was decided to implement a model-based decision making approach through the development of this compound. Modeling and simulation activities started during the pre-clinical development with the design of the proof-of-concept (POC) trial (1). Being the first in class little information was available at that time when we had to make decisions. So an integrated PK-PD-disease model was developed to incorporate all relevant information generated during the development (2). A disease mechanistic model was developed to incorporate information from several sources (3,4). When clinical data from maraviroc became available, the model was updated and used to make predictions for other studies. Based on simulation results, we have decided not to do a stand alone Phase 2B but to merge Phase 2B and Phase 3. Doses for Phase 3 were selected based on trade-off analysis carried out on predicted efficacy and adverse events profile from Phase 1 studies (6).

II. OBJECTIVES

1. To develop a disease model and drug model that describes the relationship between dose, plasma concentrations and dynamics of viral load;
2. To identify and explore the impact of clinical factors/uncertainties with the help of the drug and disease model;
3. To optimize the proof-of-concept (POC) study in terms of number of patients per arm, dose range to be studied and trial strategies;
4. To perform simulations to aid in selection of doses to be studied in Phase 3 trials.

III. PK-PD-DISEASE MODEL

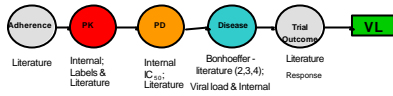


Figure 1: Schematic representation of the model

IV. ACTIVITIES CARRIED OUT PREPHASE 2A

Only PK, PD and Disease modules were used for simulations of the POC trial (2)

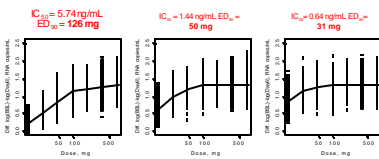
The model was built with data from different sources:

- PK – maraviroc concentration-time profile from first-in-man study;
- PD – Viral inhibition turnover from *in vitro* test;
- Disease – Viral load-time profile from another investigational compound and a disease model published in the literature (3,4).

1. To Identify and Assess the Impact of Uncertainties in Dose-Response Curve

- Three dose-response curves for low (0.64ng/mL), medium (1.44ng/mL) and high (5.74ng/mL) values of IC₅₀ were simulated.
- 1000 patients per arm were simulated; dose range: 12.5mg to 600mg BD.
- Log₁₀(BSL)-log₁₀(day 11) were analysed using an Emax model. ED₉₀ was estimated for each IC₅₀ scenario

Figure 2: Simulated dose-response curve of viral load decline for three scenarios of IC₅₀ values



- Based on the knowledge at that time and taking into account uncertainties the predicted ED₉₀ could be between 30 to 125 mg (Figure 2).
- The dose range of 25 to 500 mg BD would only cover the top of the dose-response curve of the change in viral load.

2. Trial Design Optimization

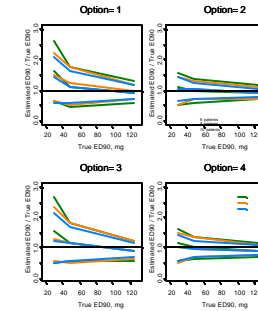
- The PK-PD-Disease model with IC₅₀ uncertainties were used to optimize trial design in terms of: # of patients (6, 8 or 10); dose range to be studied; and trial strategy to be followed (parallel or sequential).
- In options 2 and 4 (Figure 3) the lowest dose studied was 25 mg, whereas in options 1 and 3 the lowest dose studied was 50 mg.
- Each scenario was evaluated in terms of bias and performance. Bias was defined in terms of median (50th percentile) of the ratio estimated ED₉₀ and "true" ED₉₀. Precision was determined by the 10th and 90th percentile of the distribution of the ratio.

2. Trial Design Optimization (cont.)

The results of these simulations and presented in Figure 3 indicate that:

- More numbers of subjects per treatment arm only slightly improve the precision of the ED₉₀ estimates;
- The two options (2 and 4) with the lowest dose equal to 25 mg gave less bias and a better precision of the ED₉₀ estimates;

Figure 3: Trial performance for several dosage options. 10, 50 and 90 percentiles of the estimated ED₉₀ divided by the "true" ED₉₀ for the viral load difference log(BSL)-log(day 6)



3. Trial Strategy

- Considering the risks associated to the current quantified and not quantified limitations/assumptions/uncertainties, a sequential design would probably be an efficient approach to capture their impact on dose-response curve;
- Sequential trial design:
 - ❖ Uses the current knowledge and rationale based on the EC₅₀ and EC₉₀
 - ❖ Allow faster characterization of dose-response curve.
 - ❖ Expose less patients to sub-efficacious or unsafe doses.

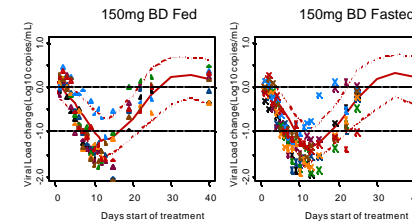
4. Validity of ED₉₀ Criterion for Selecting Doses

- 100 patients per arm for a period of 4 months were simulated. Each patient received a dose corresponding to the "true" ED₉₀.
- Results indicated that:
 - ❖ 10 to 20% of the patients treated with a dose corresponding to the ED₉₀ will not have a sustained decrease in viral load.
 - ❖ ED₉₀ is only an indication about the effective dose that could be given and not a target dose itself.
 - ❖ This information also indicates that the effective dose is in the top flat part of the Emax model and therefore it will be difficult to accurately estimate the right effective dose using mean viral load data only.

V. ACTIVITIES CARRIED OUT DURING PHASE 2A

- Only PK-PD-disease modules were used for simulations during the POC trial.
- The PK-PD-disease model described in section III was updated with data from POC trial:
 - ❖ PK – concentration-time profile from maraviroc POC trial;
 - ❖ PD – IC₅₀ from maraviroc POC trial;
 - ❖ Disease – viral load-time from maraviroc POC trial and literature information (3,4).
- The impact of food and dosing regimens on viral load decline was assessed through simulations using the updated model.
- The maraviroc dosing regimens simulated were: 150mg BD fed, 150mg BD fasted and 300mg OD fasted for 10 days of monotherapy.

Figure 4: Simulations of viral load decline -time profile of 150mg BD fed and fasted



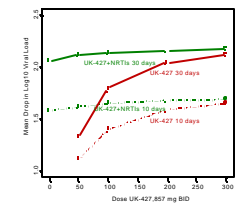
- The simulations predicted that OD regimens could be equivalent to BD regimens with half of the dose.
- These predictions were in agreement with the one measured in the trial as presented in Figure 4.

VI. ACTIVITIES CARRIED OUT PRE-PHASE 2B/3

1. Simulations of Phase 2B

- The PK-PD-disease model was updated when results from the second monotherapy study were available.
- Simulations were performed to assess the ability of a study with maraviroc given as combination therapy to provide information to select phase 3 doses.

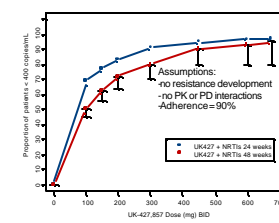
Figure 5: Simulation of UK-427,857 and NRTI given for 10 and 30 days



- Given the high response rates of triple regimens it will not be possible to differentiate between doses with a short- or medium-term trial with modest patient numbers
- Differences between doses will be seen when the combination therapy starts to fail and resistance develops.
- Standalone Phase 2B will not allow appropriate dose selection so it was decided to take 2 doses into large scale trials

2. Simulation for Dose Selection of Phase 3

Figure 6: Simulation of UK-427,857 in naïve patients. Bars show plausible dropouts (Intenit-treat)



- Compliance and trial outcome components were added to the PK-PD-disease model to simulate long-term outcome.
- The outcome of several doses were simulated to aid in the selection of doses for Phase 3.
- Several scenarios such as that of Figure 6 were considered to capture key uncertainties.

3. Risk/Benefit Assessment

- Doses were based in part on analysis trading off predicted efficacy and adverse events modeled with Phase 1 data across a broad dose range.
- This information with simulated efficacy are enough to find expected penalties by dose and a "best" dose by patient class.

VII. CONCLUSIONS

- The impact of uncertainties on dose-response curve was identified early in the development of maraviroc. A trial strategy was selected to cover for the uncertainties detected and characterize dose-response curve with reasonable precision.
- Modeling allowed prediction of the effect on viral load of different maraviroc doses as monotherapy in this patient population.
- The use of a model-based approach for selecting doses can accelerate drug development, by predicting long-term response from short-term data and by replacing some arms or trials with simulations.

VIII. REFERENCES

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