Leveraging Complicated PK/PD Models for the Development of a Bayesian Adaptive Dose-Ranging Design

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INTRODUCTION AND RATIONALE

- When designing a dose-ranging study, a common approach is to envisage the use of a Bayesian dose adaptive design, where the dose will be progressively adapted as patients are enrolled, to optimize a specific efficacy end-point and the confidence on the dose that gives the minimal required efficacy.
- Frequently, adaptive trial designs have been based upon simulations from assumption-rich, simplistic models relating dose to one or more efficacy end-points to optimally select the rules of adaptation, such as allocation and stopping rules.
- We will show how to leverage a sophisticated PK/PD model, relating dose to exposure (PK) and exposure to response (PD), including covariate effects.
- In so doing, we obviate the limitations inherent in empirical dose-response models and allow greater flexibility in exploring alternative trial design scenarios.

OBJECTIVE

- Our goal was to design a Phase II study that and to find the optimal dose, which was defined as the smallest dose that gives an expected proportion of 80% of patients with a score decreased by at least 50% at 2 weeks.

BACKGROUND

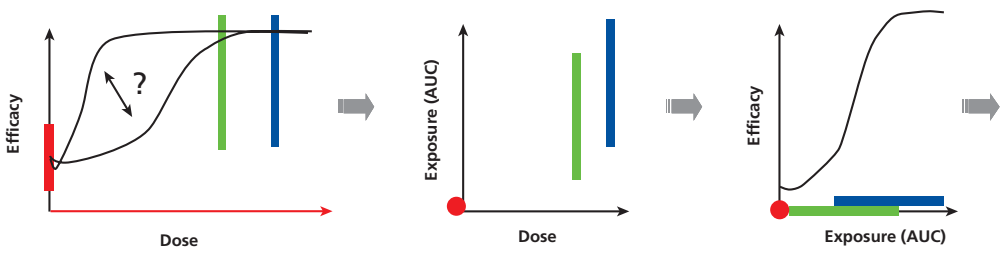
- A Phase II trial was already conducted at 2 doses (+placebo) that are potentially too high.
- Given the 2 high doses selected in the Phase II, it's impossible to establish a Dose-Response model.
- Thanks to the variability in exposure observed in that population of patients, it is possible to build an Exposure-Response model.
- The pharmacokinetics of the compound were well-described by a two-compartment model with first-order absorption.
- Exploratory analysis indicated that area under the plasma concentration curve during the preceding 14 days provided the best predictor of observed response at each study week.
- The pharmacodynamic time course was modeled using a simple inhibitory E_{max} model with an exponential time dependence on the parameter for maximum drug effect:

$$\text{Response} = \text{Baseline} - \frac{E_{\max}(t) \cdot AUC}{AUC + EAUC_{50}}$$

Where:

$$E_{\max}(t) = \theta_1 \cdot \left(1 - e^{-\theta_2 t}\right)$$

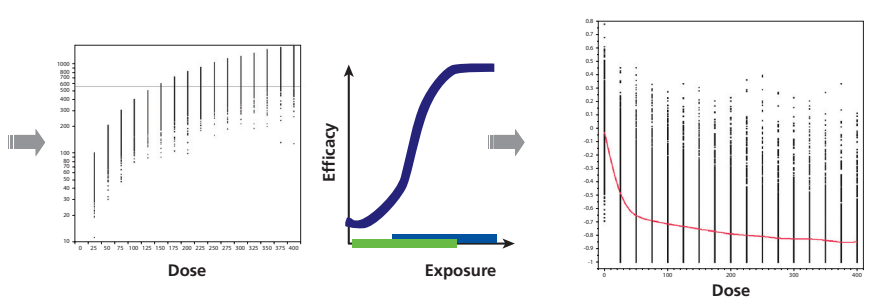
Figure 1: Sketch of current data available and PK/PD model established



METHODS

- Using Pharsight Trial Simulator (TS2), we simulate thousands of "virtual" patients, at a wide range of doses, relying on the PK/PD model. Those "virtual" patients are stored into a database.
- The range of doses is selected according to the precision required for the optimal dose. In this case, we want to estimate the optimal dose ±25 mg.

Figure 2: Sketch of simulated data and PK/PD model



- An Adaptive Dose ranging design is simulated by sampling from the data simulated by TS2.
- To relate the efficacy end-points to the Dose, a Bayesian Normal Dynamic Linear Model (NDLM) model, implemented in Winbugs, is considered.

The model is as follows: $Y_{ij}|x_j \sim N\left(\theta_j, \tau\right)$,

Where τ is the residual precision (i.e., the inverse variance), and for j>1:

$$\theta_j = \theta_{j-1} + \left(x_j - x_j\right)\delta_{j-1} + \omega_j, \qquad \omega_j \sim N\left(0, \tau / W_\theta\right)$$

and

$$\delta_j = \delta_{j-1} + \gamma_j, \qquad \gamma_j \sim N\left(0, \tau / W_\delta\right)$$

RESULTS

Simulations

Simulations are performed with the following considerations:

- 20 patients randomized in cohorts, fixed 20% to Placebo
- Maximum of 10 cohorts → 200 patients
- Response measured at 2 weeks
- First cohort with placebo + 4 doses
- For remaining cohorts, doses are chosen adaptively, according to a weighted variance function
- Wide range of doses envisaged in simulations
- Practical i.v. doses to be selected based on simulations

Results for the Adaptive design

Figure 3: Average number of patients allocated by dose, at each cohort

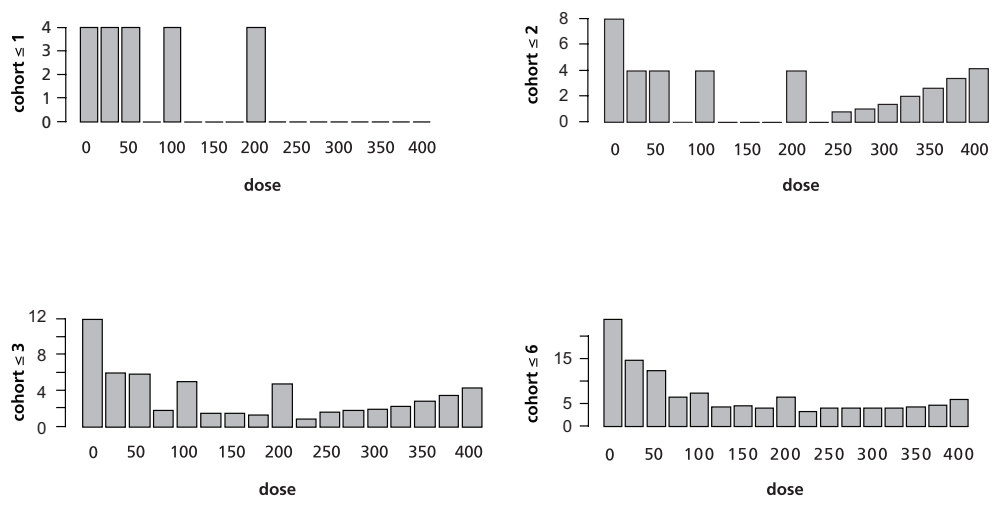
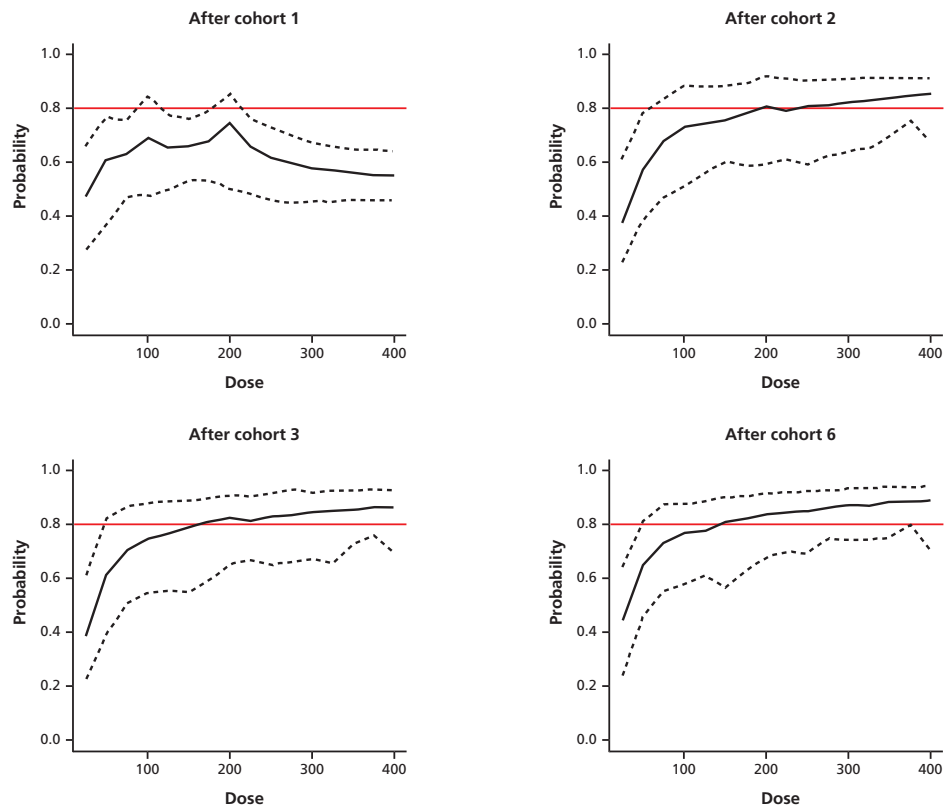


Figure 4: Expected proportion of patients with a score decreased by at least 50% at 2 weeks with the 2.5% and 97.5% quantiles



- Regarding **the allocation of patients**, emphasis is rapidly put on the lowest doses (≤100mg)
- Regarding **the estimated efficacy dose**: 125 mg ±25 mg becomes area of interest

CONCLUSIONS

- The proposed approach is an alternative to the traditional approach based on empirical models that relate dose to efficacy response, because it integrates all the richness and uncertainty up to the present stage of development.
- This alleviates the need to make strong assumptions for the model that relates dose and response.
- In addition, as far as PK/PD models enable the use of appropriate covariates, it's even possible to investigate and optimize the population of interest to be included into an adaptive study.