Bayesian modeling of a PK-PD relationship to support an adaptive dose-finding trial

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1 – Introduction

An adaptive sequential, within patient, dose-escalation design is proposed for a phase I study (N=12) to establish the relationship between the concentrations of a drug and the effects on a biomarker. Selection of the doses are planned to be guided by a Bayesian modeling of the PK-PD relationship.

The Bayesian modeling approach is expected to provide (i) higher chance to correctly estimate the PKPD parameters, even on a few number of patients compared to frequentist methods implemented in Nonmem VI and (ii) a more effective and timely determination of the adequate doses.

2 – Objective

To evaluate the operation characteristics of the adaptive design and to assess the efficiency of Bayesian modeling approach for data analysis

3 – Models and Assumptions

▪ A two-compartment pop PK model (Cl, Q, V1, V2) with between-subject variabilities (BSV) below 40% and a residual error of 12% has been established on previous Phase I data.

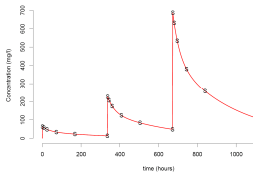
▪ An indirect response model with inhibition of the production rate of effect (kin) is assumed to describe the PK-PD relationship (the maximum effect is fixed to 100%). For simulation purpose, the change from baseline rather than raw data has been considered: the ratio kin over kout is equal to 1. The PD parameters to be estimated are kout and IC50. A BSV of 30% on those parameters and a residual error of 10% are considered.

$$\frac{\partial R(t)}{\partial t} = kin \times \left(1 - \frac{Conc(t)}{IC_{50} + Conc(t)}\right) - kout \times R(t)$$

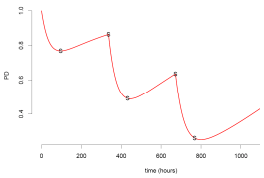
4 – Study Design

▪ 12 patients divided into 4 cohorts of 3 patients each will be enrolled. Within a cohort, 3 sequentially escalating IV doses will be administered to each patient every 2 weeks. The maximum dose to be explored is 30 mg/kg and the first dose sequence (1st cohort) is fixed: 3, 10 and 30 mg/kg doses every 2 weeks.

▪ For each dose, 6 PK samples will be collected at pre-dose and at 1, 8, 24, 72, 168 hr post-dose . The PD endpoints will be measured at baseline and after each administration : either at the max of effect (1 PD-measurement per dose) or at pre-dose and the max of effect (2-PD measurements per dose).

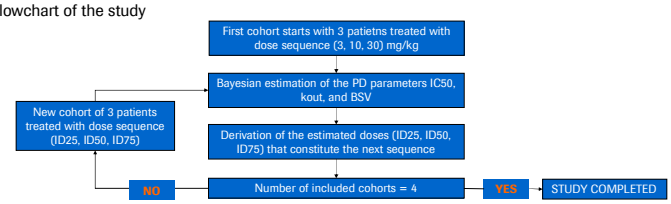


Mean PK profile after sequence (3, 10, 30) mg/kg
(mean weight of 70 kg)



Mean PD profile
(kout = 0.02, IC50 = 100 mg/l, Tmax = 4 days)

▪ Flowchart of the study



5 – Bayesian estimation of the PD parameters

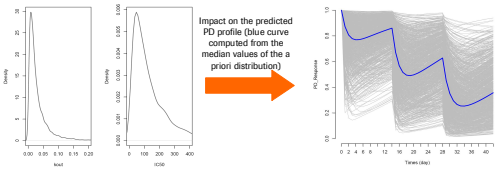
▪ The Bayesian hierarchical model is implemented in Winbugs 1.4 [1] using the WBDIFF package [2] for ODE system. The code is written in R, using the R2WinBUGS library [3], which offers an easy interface to Winbugs.

$$\log(R_{ij}) \sim N(\log(\hat{R}_{ij}), tau_{PD})\ I(,0)$$
$$\log(\hat{R}_{ij}) = solODE[i, j, 3])$$
$$\log\begin{bmatrix} kout_i \\ IC50_i \end{bmatrix} \sim N\left(\log\begin{bmatrix} \mu_{kout} \\ \mu_{IC50} \end{bmatrix}, T\right) \text{ with } T = \Omega^{-1} \text{ and } \Omega = \begin{bmatrix} \omega^2_{kout} & \omega_{kout,\,IC50} \\ \omega_{kout,\,IC50} & \omega^2_{IC50} \end{bmatrix}$$

```
solODE[i,j,1:dim] <- ode.block(...)
{
D(C[i,1],t) <- -(CL[i]+Q[i])/V1[i]*C[i,1]+Q[i]/V2[i]*C[i,2]+RATE[i]
D(C[i,2],t) <- Q[i]*(1/V2[i]*C[i,2]-1/V1[i]*C[i,1])
D(C[i,3],t) <- kout[i]*(1-C[i,3]-C[i,1]/V1[i]/(IC50[i]+(C[i,1]/V1[i])))
}
```

▪ A set of a priori distribution for the population parameters is specified. This set remains unchanged after the analysis of new cohort data.

$$\log\begin{bmatrix} \mu_{kout} \\ \mu_{IC50} \end{bmatrix} \sim N\left(\log\begin{bmatrix} 0.02 \\ 100 \end{bmatrix}, \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}\right)$$
$$T \sim W\left(\begin{bmatrix} 0.2 & 0 \\ 0 & 0.2 \end{bmatrix}, 2\right)$$
$$tau_{PD} \sim \Gamma(0.001, 0.001)$$



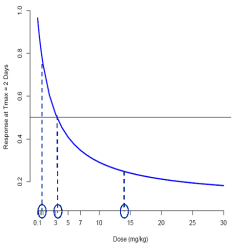
▪ The estimation is performed using 15000 iterations, including 10000 iterations for the burn-in phase. 3 chains are launched with kout and IC50 set to (0.05, 250), (0.03, 150) and (0.01, 50) respectively.

6 – Derivation of the estimated doses (ID25, ID50, ID75) after each cohort

▪ After each cohort of 3 patients, a Bayesian estimation of the PD parameter distributions is performed, based on the whole observations of the previous cohorts.

▪ From the median values of the a posteriori distributions, a dose/response curve is built and the doses ID25, ID50, ID75 giving respectively 25, 50, 75% of response are derived.

▪ The selected three doses are then rounded to the closest values in the given set of possible doses: 0.10, 0.25, 0.50, 0.75, 1, 3, 5, 7, 10, 15, 20, 25, 30 mg/kg.



7 – Evaluation of the operation characteristics of the adaptive design strategy

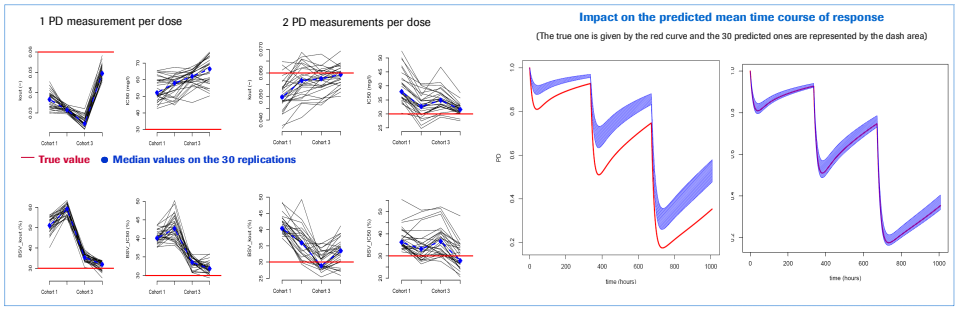
▪ Different possible scenarios, i.e. different values for kout and IC50, were simulated. Those scenarios included different time for max of response (Tmax) (from 2 to 10 days), different expected levels of response (IC50 from 0 to 60% after the 1st dose, from 20% to 80% after the 2nd dose, from 60% to 100% after the 3rd dose).

▪ For each scenario, simulations of 30 replications of the adaptive trial were performed.

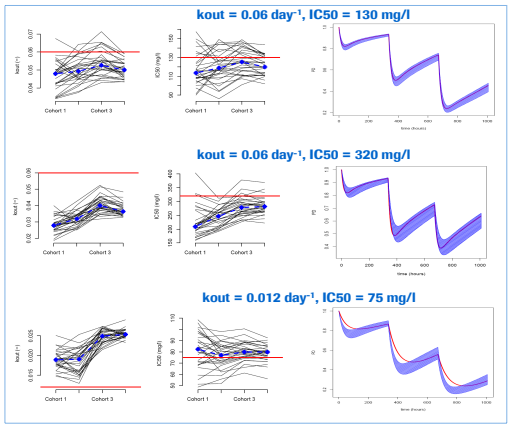
▪ The level of information at the end of Cohort 4 was evaluated, focusing on the ability to estimate the true IC50 with the adaptive design strategy. That ability was also compared between the 2 design strategies: one-PD measurement per dose vs. two-PD measurements per dose.

8 – Simulation results

Scenario: kout = 0.06 day^{-1}(Tmax_effect = 2 days), IC50= 30 mg/l



Other simulated scenarios - 2 PD measurements per dose



▪ At the end of Cohort 4, a correct estimation of the mean parameter IC50 can be achieved, whatever its value, with 2 PD measurements per dose; the corresponding between-subjects variability is also adequately estimated. The mean value of IC50 can not be adequately estimated with only one measurement per dose, and, as a consequence, the time course of the response is not correctly predicted.

▪ The estimation of the kout parameter is more difficult, even with 2 measurements per dose. However the impact on the prediction of the time course of response is less influential.

9 – Conclusion

The evaluation of the Bayesian adaptive design using simulations demonstrates the feasibility of this design when using 2 PD-measurements per dose.
Bayesian methodology combined with an adaptive design strategy offers an opportunity to efficiently gain more information about the dose-response curve early in the development.
The use of simulations to evaluate the feasibility of an adaptive design is recommended and this is mainly facilitated by the availability of software packages such as the R2WinBUGS library of R.

References 1- http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml 2- http://www.winbugs-development.org.uk/ 3- http://cran.r-project.org/web/packages/R2WinBUGS/index.html