

# Dose escalation studies for mAb: prior distributions selection and software comparison



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## Introduction / Objectives

During first in human– dose escalation studies, pharmacokinetic (PK) data may be required to compare the exposure to the toxicological limits or to relate the pharmacodynamic findings and adjust the doses to be evaluated accordingly. However, for mAb –due to the long half-life ( $t_{1/2}$ )- at the time of dose escalation decision, only a truncated PK profile is available – usually less than one  $t_{1/2}$ – making it difficult to predict exposure variables such as  $AUC_{0-\infty}$  accurately. The human PK of monoclonal antibodies (mAb) is in general well predicted from animal data. Therefore, a Bayesian framework with the use of prior information could be useful to support dose escalation studies.

- The aim of this work was:
- To define the prior distributions for mAb PK
  - To evaluate the performance of the NONMEM prior functionality compared to a full Bayesian method when applied to PK analysis of mAb.

## Methodology

### • FIM study design:

- ✓ Single dose (IV administration), dose escalating study
- ✓ Dose adaptation: PK, Safety and tolerability
- ✓ 1 placebo and 3 active subjects at each dose level
- ✓ Data review meeting before each dose escalation:  
→ 14 day safety data & 7 days PK data
- ✓ Drug → mAb

### • The problem/the solution:

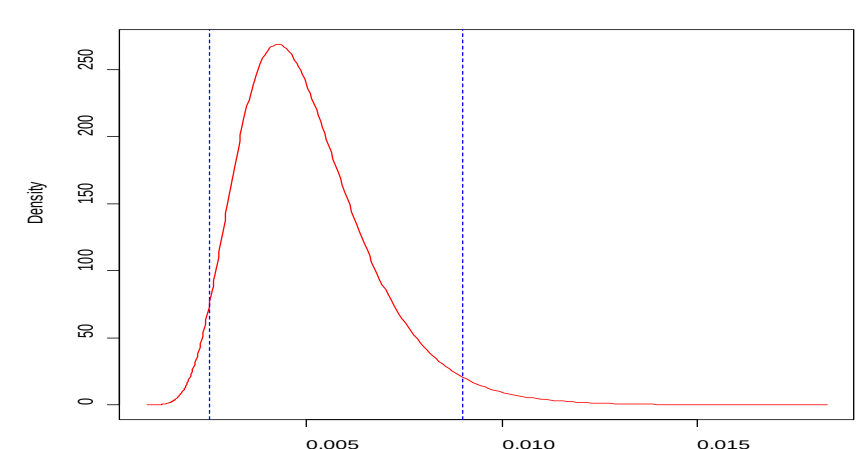
Find the predicted probability that the  $AUC_{0-\infty}$  at the next planned dose level exceeds a pre-specified threshold (e.g. NOAE AUC) based on limited data (truncated PK profile of 7 days).

Bayesian approach: to integrate observed data in the trial with prior knowledge!

### • Prior knowledge and prior distributions:

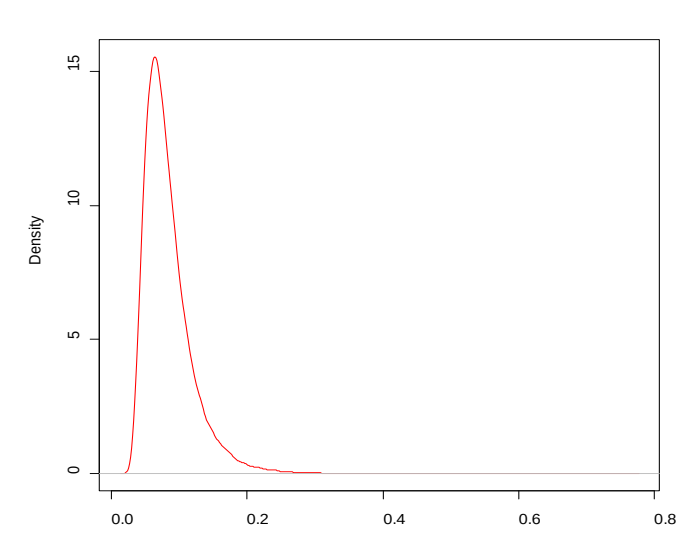
- ✓ A two compartment PK model with linear and nonlinear elimination as structural PK model
- ✓ Prior distributions for fixed and random effects in the model, based on in-house (i.e. primate PK parameters allometrically scaled, other mAb parameter values from clinical data) and literature data.

- Prior knowledge for population mean:**
- Drug X pre-clinical CL allometrically scaled to human: 0.00364 L/kg/day
  - Drug Y pre-clinical CL allometrically scaled to human: 0.0058 L/kg/day
  - Drug Z CL in healthy volunteers: 0.0059 L/kg/day
  - literature data range of CL from other antibodies: 0.0024 to 0.0086 L/kg/day
  - Data were combined to get 95% of CL values to be between 0.0024 and 0.0090 L/kg/day:
    - $\text{popCL} \sim \text{logNorm}(\mu = \log(0.00475), \text{sd} = 0.33)$



- Prior knowledge for interindividual variability:**
- Drug X in healthy volunteers CV%=38.2
  - Drug Y in healthy volunteers CV%=27%
  - Range of plausible values 20% (var=0.04) to 40% (var=0.16)

- $\text{varCL} \sim \text{InvGamma}(\text{shape} = 7, \text{rate} = 0.5)$



The model used to support the escalation steps was initially implemented in WinBUGS (version 1.4). Utlieriorly, the performance of the prior functionality (NWPRI) in NONMEM VII was compared in terms of parameter estimates, predictions of the next dose level exposure and computational time.

## Results & Discussion

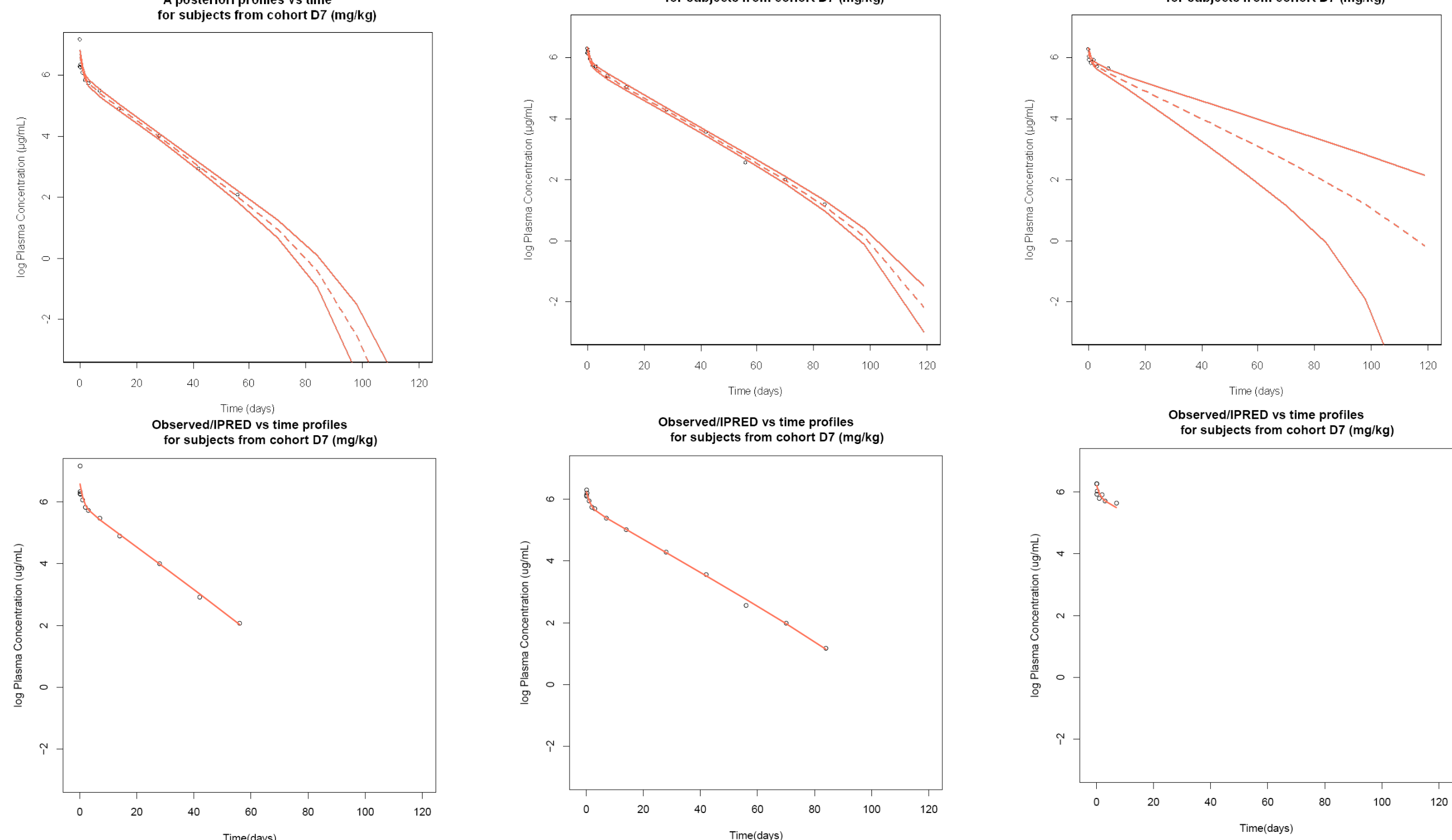
PK model parameters were estimated at each escalation step and resulted in close agreement with prior values. Both methodologies provided similar results as can be seen in Table 1, which shows the prior vs the posterior parameter values obtained by NONMEM and WinBUGS for the last escalation step.

Table 1. Prior values and 95% percentiles together with posterior parameter estimates by WinBUGS and NONMEM based on data from the last dose escalation step

| Parameter        | Prior values                                                 |          |          | WinBUGS Posterior estimates |          |          | NONMEM Posterior estimates |          |          |
|------------------|--------------------------------------------------------------|----------|----------|-----------------------------|----------|----------|----------------------------|----------|----------|
|                  | Median, 2.5 <sup>th</sup> and 97.5 <sup>th</sup> percentiles |          |          | Median                      | lower_CI | upper_CI | Typical value              | lower_CI | upper_CI |
| CL (L/Kg/day)    | 0.0047                                                       | 0.0025   | 0.0091   | 0.0045                      | 0.0040   | 0.0050   | 0.0044                     | 0.0041   | 0.0048   |
| V1 (L/Kg)        | 0.052                                                        | 0.039    | 0.070    | 0.0536                      | 0.05034  | 0.0571   | 0.0545                     | 0.0513   | 0.0578   |
| Q (L/Kg/day)     | 0.080                                                        | 0.017    | 0.3838   | 0.0162                      | 0.0135   | 0.0196   | 0.0158                     | 0.0133   | 0.0187   |
| V2 (L/Kg)        | 0.0395                                                       | 0.0199   | 0.0784   | 0.0297                      | 0.0259   | 0.0341   | 0.0302                     | 0.0266   | 0.0342   |
| Vmax (mg/Kg/day) | 0.0498                                                       | 1.53E-10 | 16191549 | 0.0031                      | 0.0025   | 0.0039   | 0.0028                     | 0.0022   | 0.0035   |
| Km (ug/mL)       | 0.0907                                                       | 0.0128   | 0.6440   | 0.0809                      | 0.0397   | 0.1601   | 0.0789                     | 0.0371   | 0.1674   |
| IIV CL (CV%)     | 29.67                                                        | 18.97    | 40.37    | 22.00                       | 17.15    | 29.05    | 19.7                       | 12.1     | 27.3     |
| IIV V1 (CV%)     | 16.407                                                       | 13.674   | 19.140   | 15.16                       | 13.19    | 17.70    | 15.3                       | 12.75    | 17.8     |
| IIV V2 (CV%)     | 25.614                                                       | 17.219   | 34.008   | 25.60                       | 19.57    | 34.47    | 26.2                       | 19.3     | 33.1     |
| RE prop. (CV%)   | -                                                            | -        | -        | 10.34                       | 9.34     | 11.50    | 9.434                      | 8.236    | 10.496   |
| RE add (sd)      | -                                                            | -        | -        | 0.01                        | 0.009    | 0.0101   | 0.01                       | 0.003    | 0.014    |

(\*) Prior distribution assumptions: Population means (log-Normal – WinBUGS and NONMEM); inter-individual variability terms (Inv-Gamma – WinBUGS and Normal – NONMEM)  
Km and Vmax uninformative priors were used.

Fig 3. Plasma concentration-time profiles for the 3 individuals randomized to the last dose level. Top panels show observed data, median and 95% credible intervals from WinBUGS and bottom panels observed and individual predicted profiles from NONMEM.



The model provided a good overall description of the PK data with both methodologies (Fig. 3).

Table 1 and Fig. 4 show the amount of information in the data at each escalation step for the model parameters. Fig. 4 demonstrates how the information increases as we move in the escalation process, decreasing the posterior uncertainty around the parameter estimates. It also points out the relevance that having good prior distributions will have in the first escalation step where the posterior is driven by the prior.

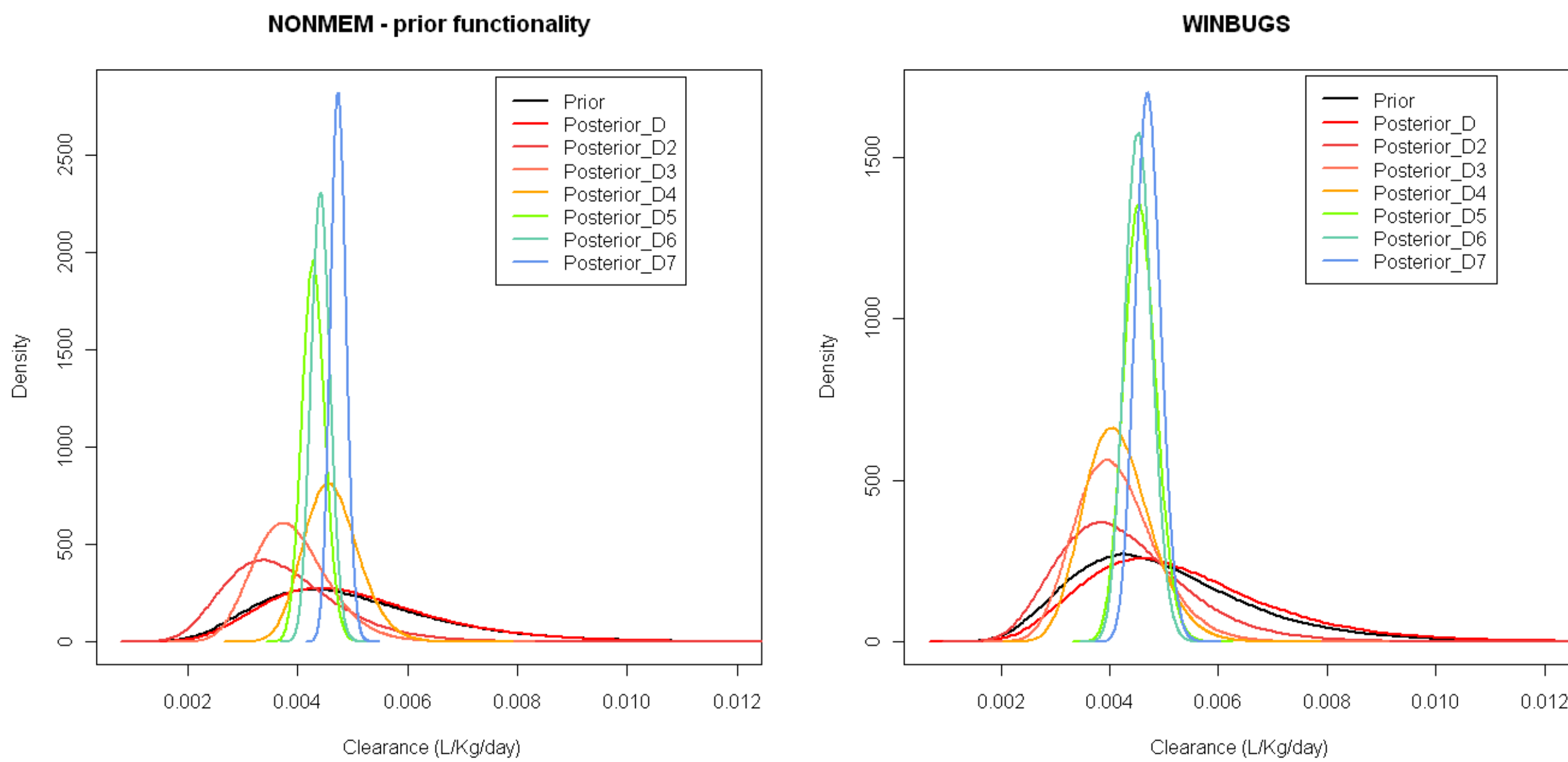


Fig 4. Prior versus Posterior distributions for Clearance in the different escalation steps is shown

The ultimate goal was to make use of the PK model to inform the dose escalation process by predicting the next dose level  $AUC_{0-\infty}$  to assure it does not exceed the pre-specified threshold. Fig. 5 shows the expected  $AUC_{0-\infty}$  distributions for each dose level based on 3000 simulated individuals performed at each escalation step. Good agreement between predictions and the subsequent observed  $AUC_{0-\infty}$  are found. No major differences between predictions performed based on the full Bayesian analysis or NONMEM analysis with prior functionality can be observed.

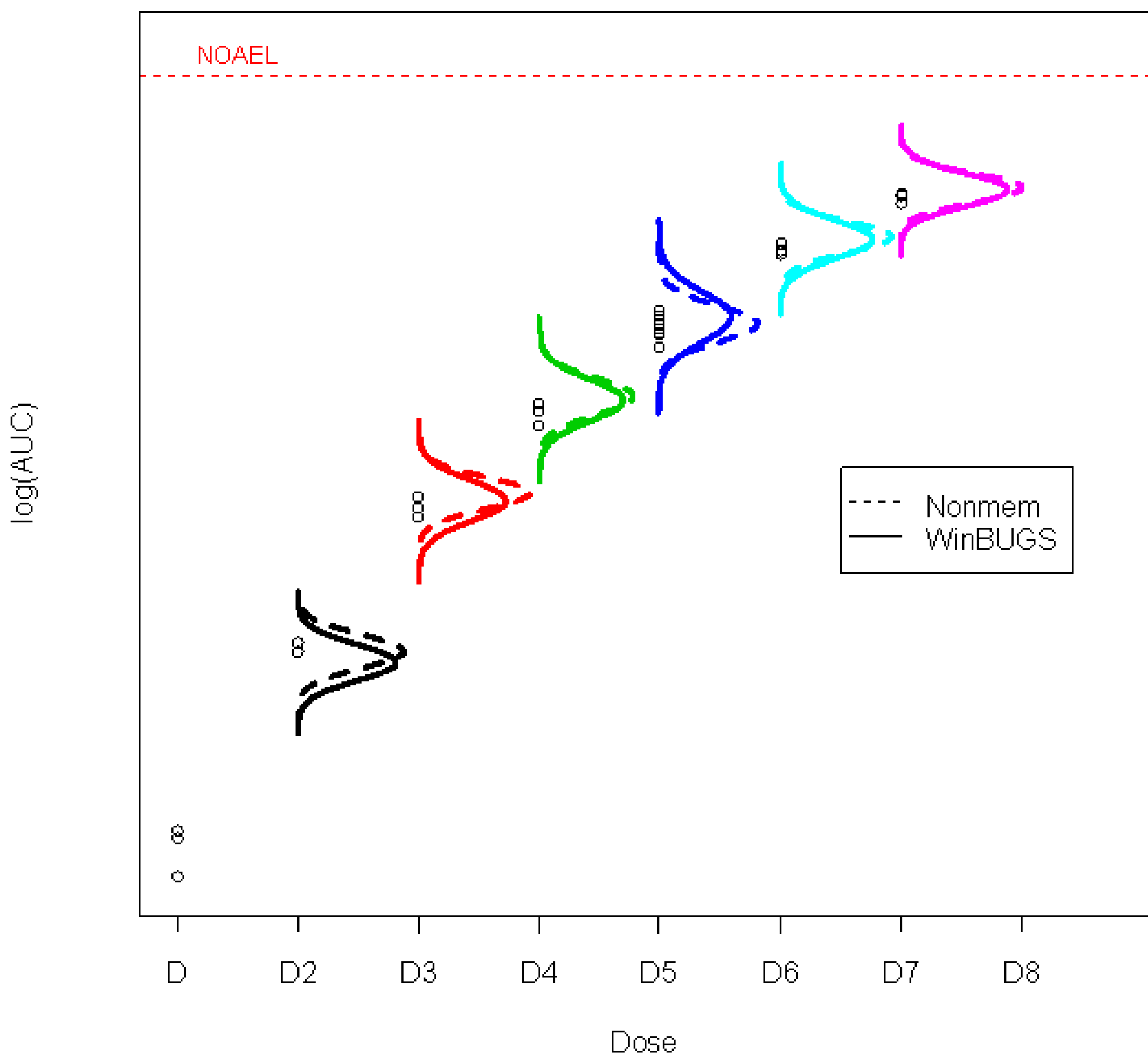


Fig 5. Predicted exposure distributions ( $AUC_{0-\infty}$ ) at the next dose level based on the limited data available from previous cohorts at each escalation step based on model parameters obtained by WinBUGS versus those obtained by NONMEM. Dots represent the observed  $AUC_{0-\infty}$  calculated based in all data available (a posteriori).

## Conclusions

• A Bayesian framework for dose escalation in FIM studies for mAb has been established, allowing a good estimation of the model parameters and a reliable prediction of the exposure at the next dose level based on the integration of limited PK data (7 days from latest dose level and PK from previous doses) with prior information.

• The use of the prior functionality in NONMEM yielded similar results and it showed to reduce run times as compare to the full Bayesian approach in WinBUGS (few hours vs. few minutes runs).



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