Introduction
In recent years, Bayesian techniques applied to Phase I dose escalation studies have received increasing attention\(^1\),\(^2\). The advantage in adopting Bayesian methods is twofold: not only parameter uncertainties are fully accounted, but also posterior densities are easily obtained. Both benefits allow a safer escalation to newly enrolled subjects and a more precise individual risk assessment.

Objectives
Evaluate different modeling approaches and decision making criteria by comparing a traditional NONMEM estimation procedure with a novel Bayesian Escalation Tool (BEsT), featuring both Empirical Bayes and Markov Chain Monte Carlo (MCMC) estimation\(^3\). Though comparable to NONMEM in most cases, BEsT shows superior performances in some critical but realistic scenarios.

Methods
Data
Ten Phase I studies and 20 simulated datasets were analyzed both in NONMEM VI (FOCE interaction, additive intersubject variability and residual error) and BEsT, using a fully Bayesian approach based on MCMC.

Model assumptions
The dose-response relationship adopted was a linear mixed-effects model using log-transformed doses and exposures (either Cmax or AUC).

\[ y_i = (\beta_0 + \varepsilon_i) + (\beta_1 + \epsilon_i) d_{isy} + \epsilon_i \]

where hyperparameters:

\[ \sigma_0^2 = \text{Var}[\beta_0], \quad \sigma_1^2 = \text{Var}[\beta_1], \quad \sigma^2 = \text{Var}[\epsilon_i] \]

BEsT implementation
BEsT is a user-friendly tool based on R and WinBUGS (for the MCMC core). As a result of the estimation process, BEsT produces an extensive report and plots for immediate analysis, both for enrolled subjects and for a generic, untested one:

- **Prediction plot** (Fig. 1, top): individual regression curve with its associated credible limits, together with the predictive distribution at a future dose.

- **Risk plot** (Fig. 1, bottom): probability of exceeding the safety limit as a function of dose. It also displays the critical dose and the future dose risk.

Conclusions
- NONMEM, though providing satisfactory point estimates, tends to systematically underestimate prediction intervals if the sample size is small, possibly due to the Maximum Likelihood bias in estimating variance components\(^1\) and the neglecting of fixed effects uncertainty. Also, rigorous individual confidence limits are not easily obtained.

- Conversely, realistic estimates and reliable prediction intervals, suitable for individual risk assessment, were obtained with the new Bayesian tool. Both the higher accuracy and the individual prediction capabilities provided by our Bayesian approach proved to impact positively on the quality of risk assessment during dose escalation.

References
