Adaptive model-based dose selection methods

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NCS 2008, Leuven, 24 Sept. 2008

Outline

Adaptive modelling strategy

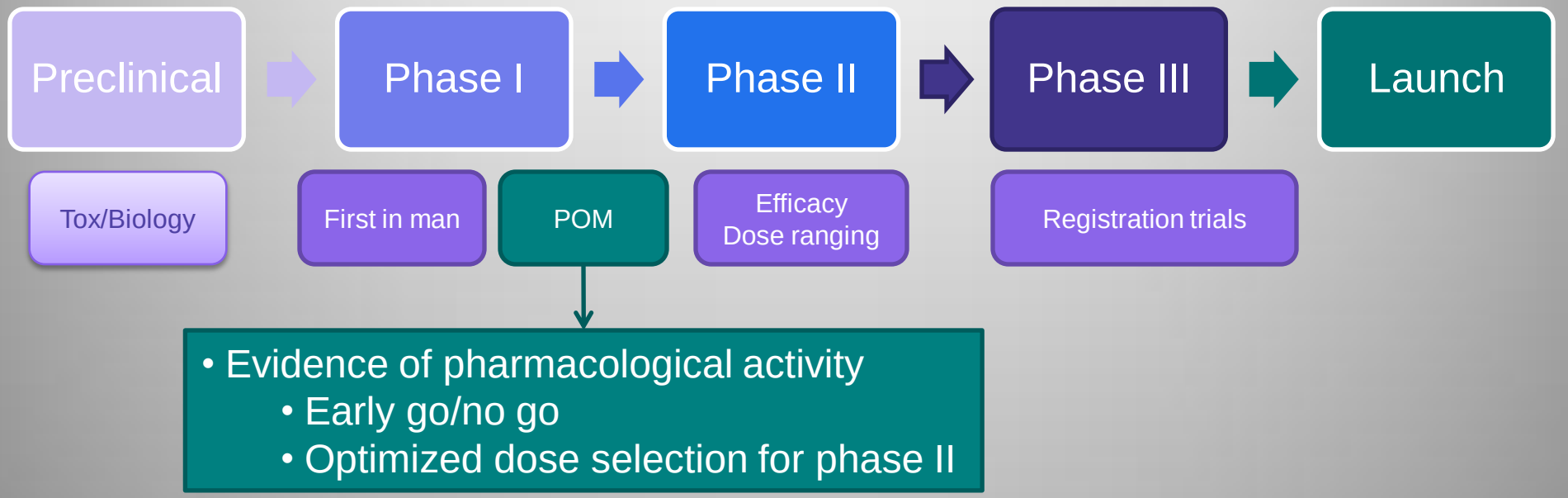
Background and example

Principles and components

Analysis of a case study

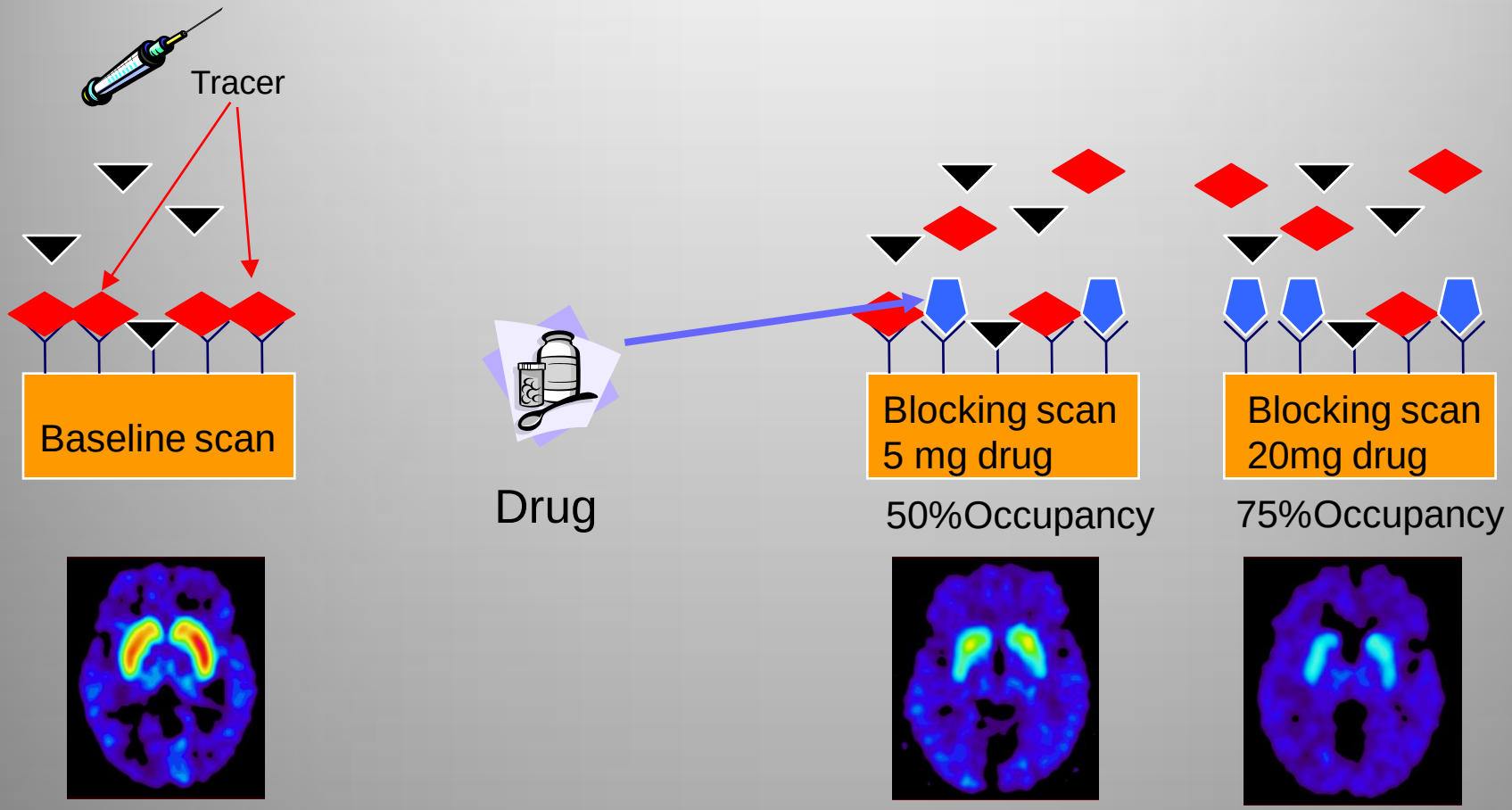
Conclusions

Proof of mechanism

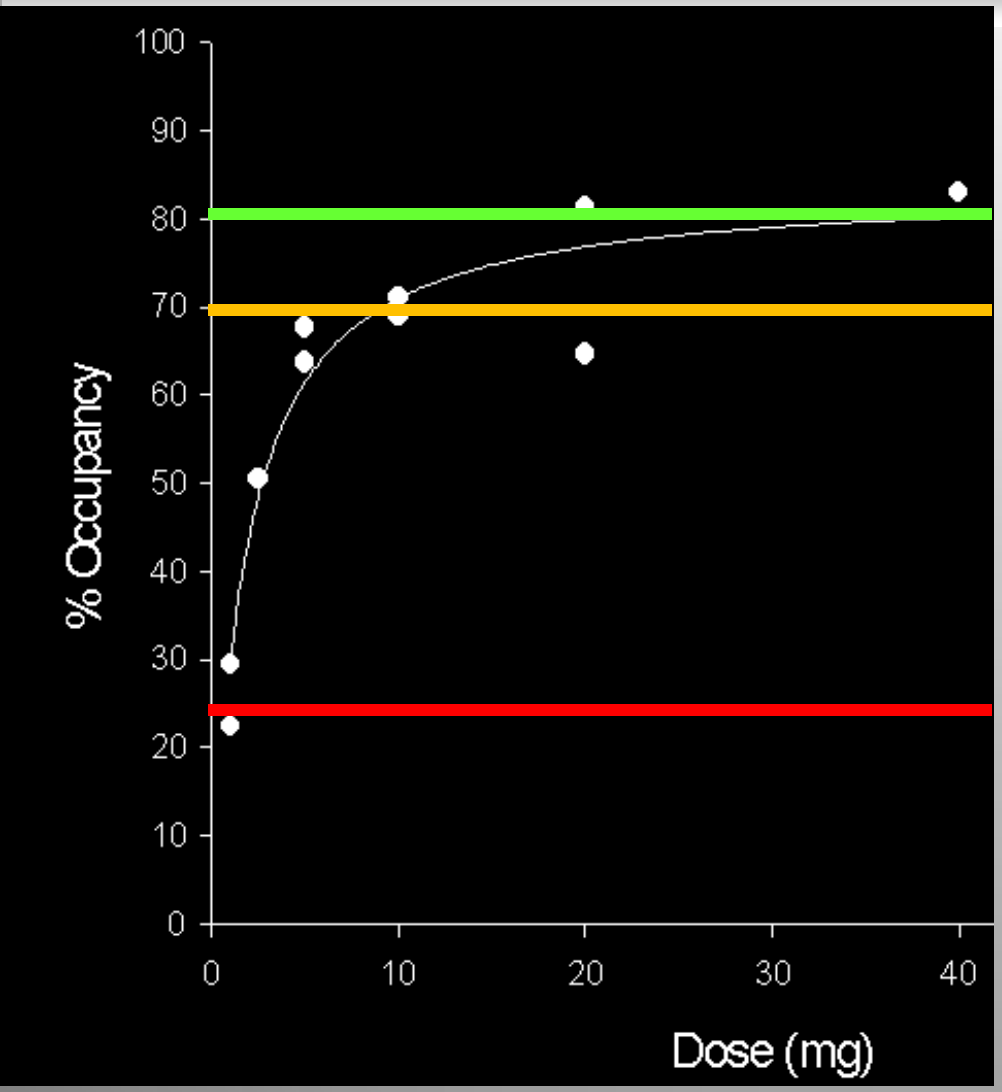


- Challenges:
  - *Availability of a validated biomarker*
  - Cost effectiveness
  - Predictivity

Example: Receptor Occupancy PET

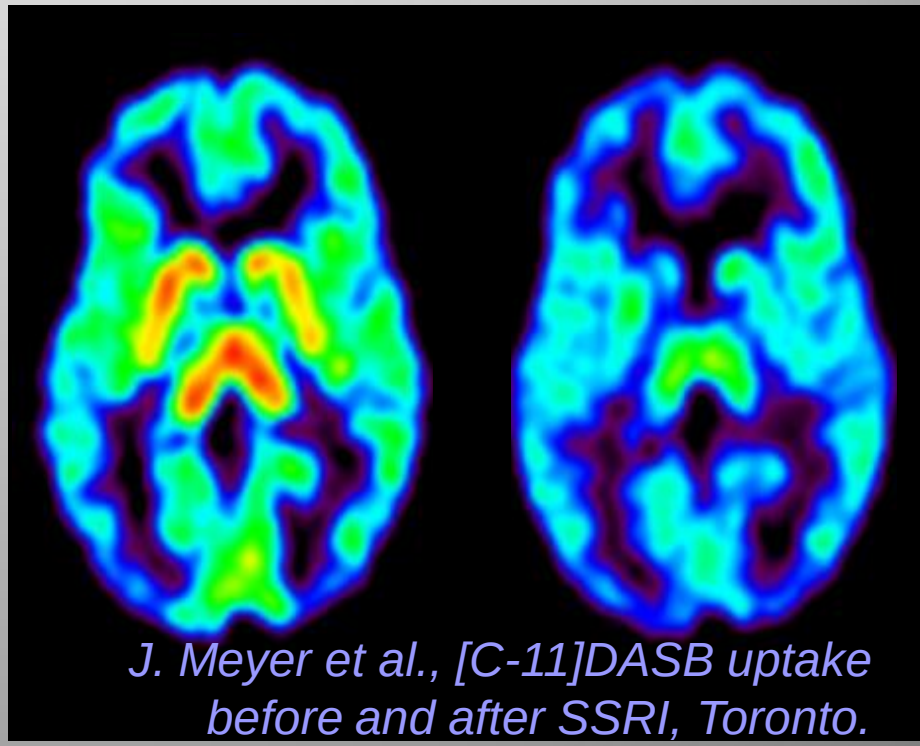


Dose-Occupancy Relationship



No occupancy :
- ❖Quick kill

Dose selection:
- ❖Quantiles of dose-response



J. Meyer et al., [C-11]DASB uptake before and after SSRI, Toronto.

Adaptive Modelling Strategy

- Parametric dose-response model

$$RO = f(dose, \theta)$$

  - E.g., Emax model or 4PL
- Bayesian inference

$$p(\theta \mid RO) \propto p(\theta) L(RO \mid \theta)$$

  - Uses available prior information p(θ) from preclinical assays or competitors.
  - Posterior update possible after every subject

Adaptive Modelling Strategy (II)

- Adaptive dose selection during study:
  - Select next dose dz that optimizes a property of $p(\theta \mid RO_{hist}, RO_{dz})$
  - E.g., D-optimal design: min |Var(θ)|
- Decision to stop POM trial
  - Stop enrolment when
    - Precision around f(dose, θ) is sufficient, or
    - For futility, when, eg: Pr[f(dose, θ)>50%]<5%.

Adaptive Modelling Strategy (III)

- Predicting relevant doses for phase II:
  - Based on posterior predictive distribution:

$$p(RO_{\text{patient}} \mid RO_{POM}) = \int p(RO_{\text{patient}} \mid \theta, RO_{POM})\, p(\theta \mid RO_{POM})\, d\theta$$

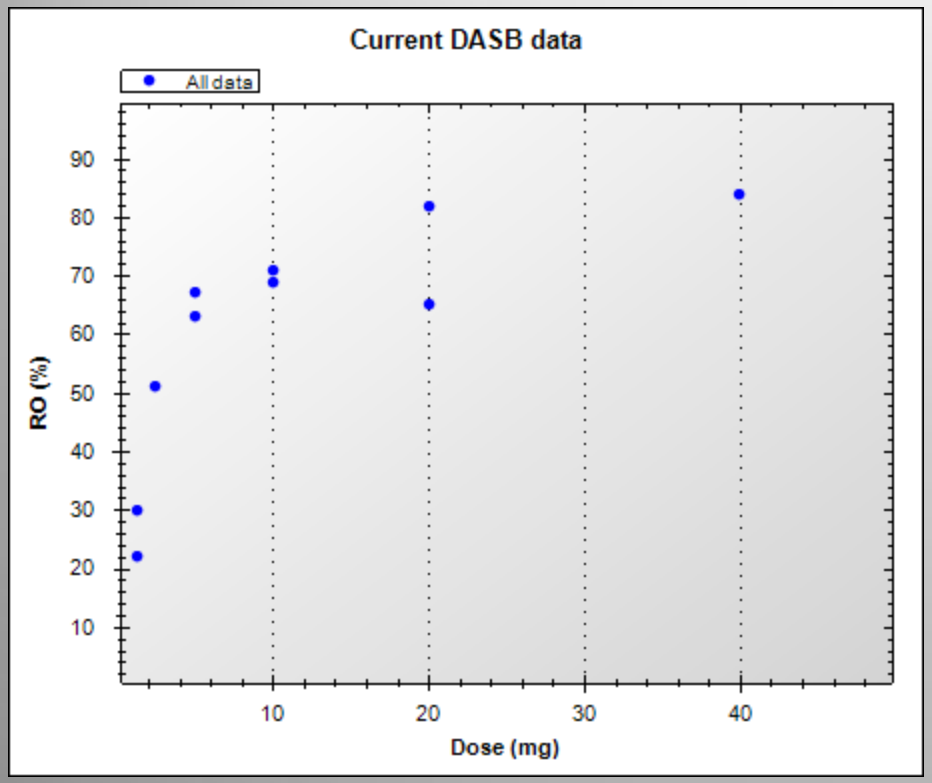
  - E.g.:

$$p(RO_{\text{patient}} > 70\% \mid RO_{POM}) > 90\%$$

$$p(RO_{\text{patient}} > 70\% \mid RO_{POM}) \approx 50\%$$

$$p(RO_{\text{patient}} > 70\% \mid RO_{POM}) < 10\%$$

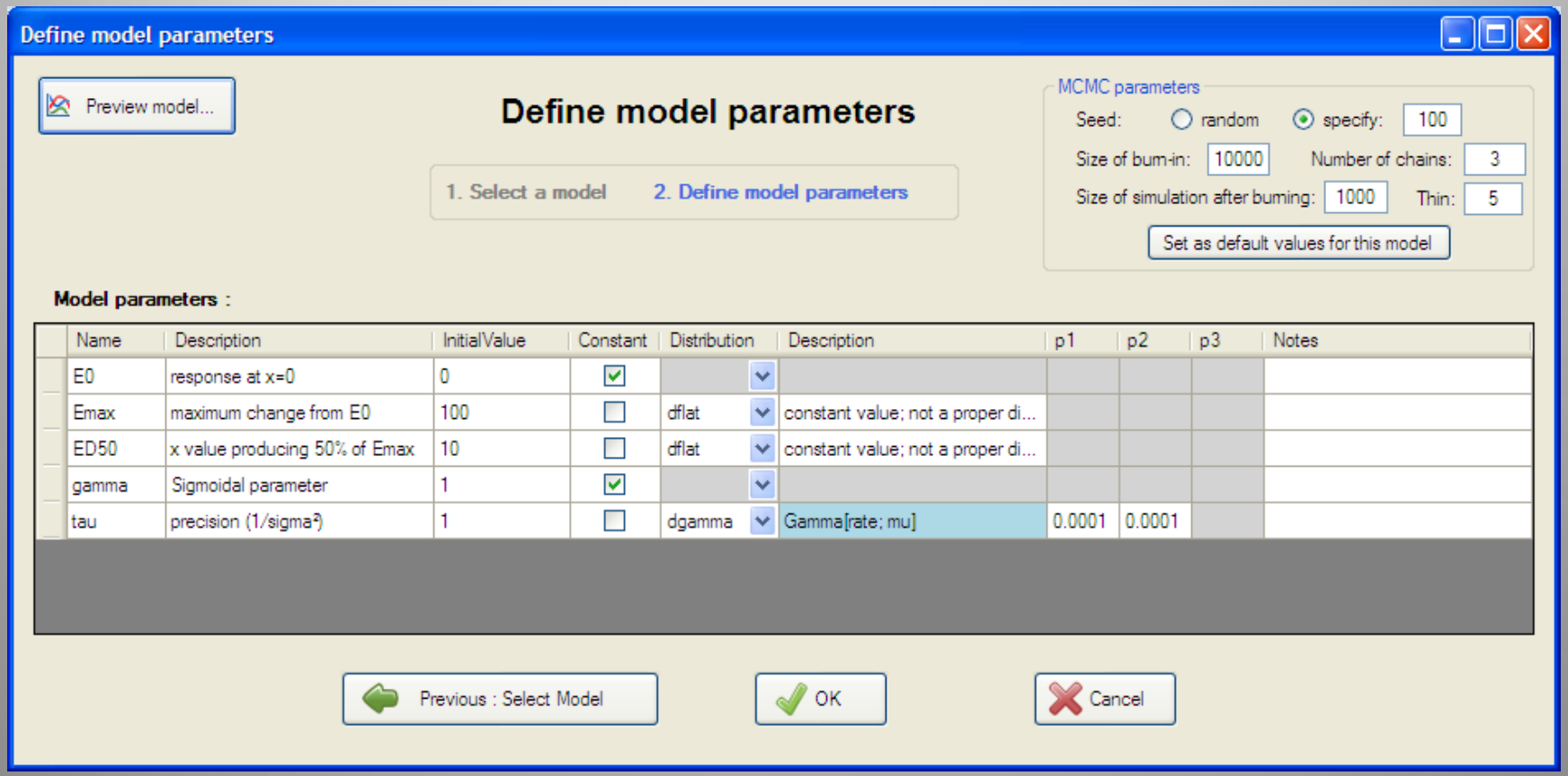
DASB Case Study



Design and analysis settings:

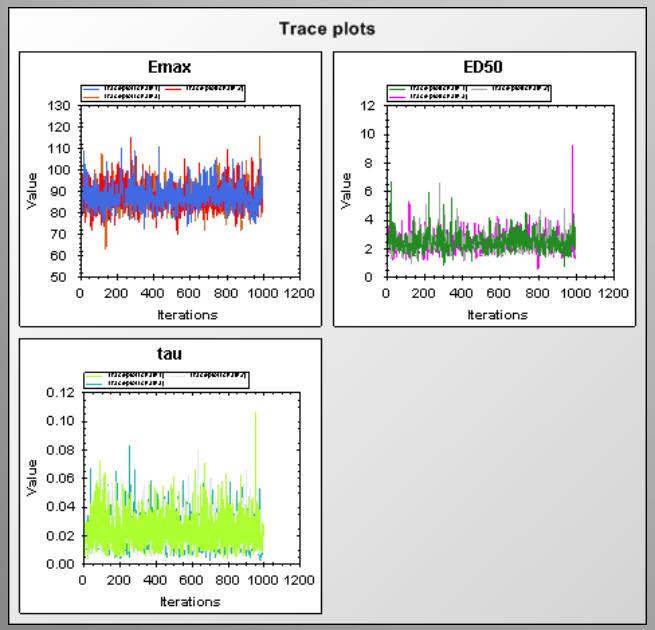
- Emax model (flat priors)
- Next dose: D-optimal
- Stop study if
  - CV(ED50)<30% or
  - Pr[Emax<50%]>95%.
- Phase II doses based on PP(RO>70%)

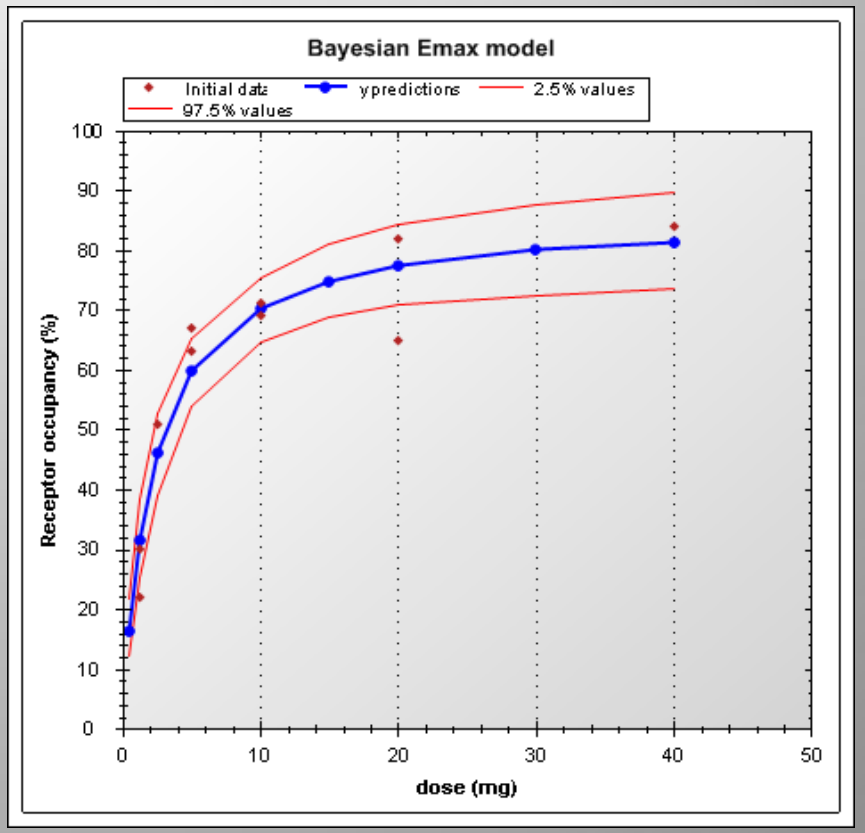
Emax model and Priors



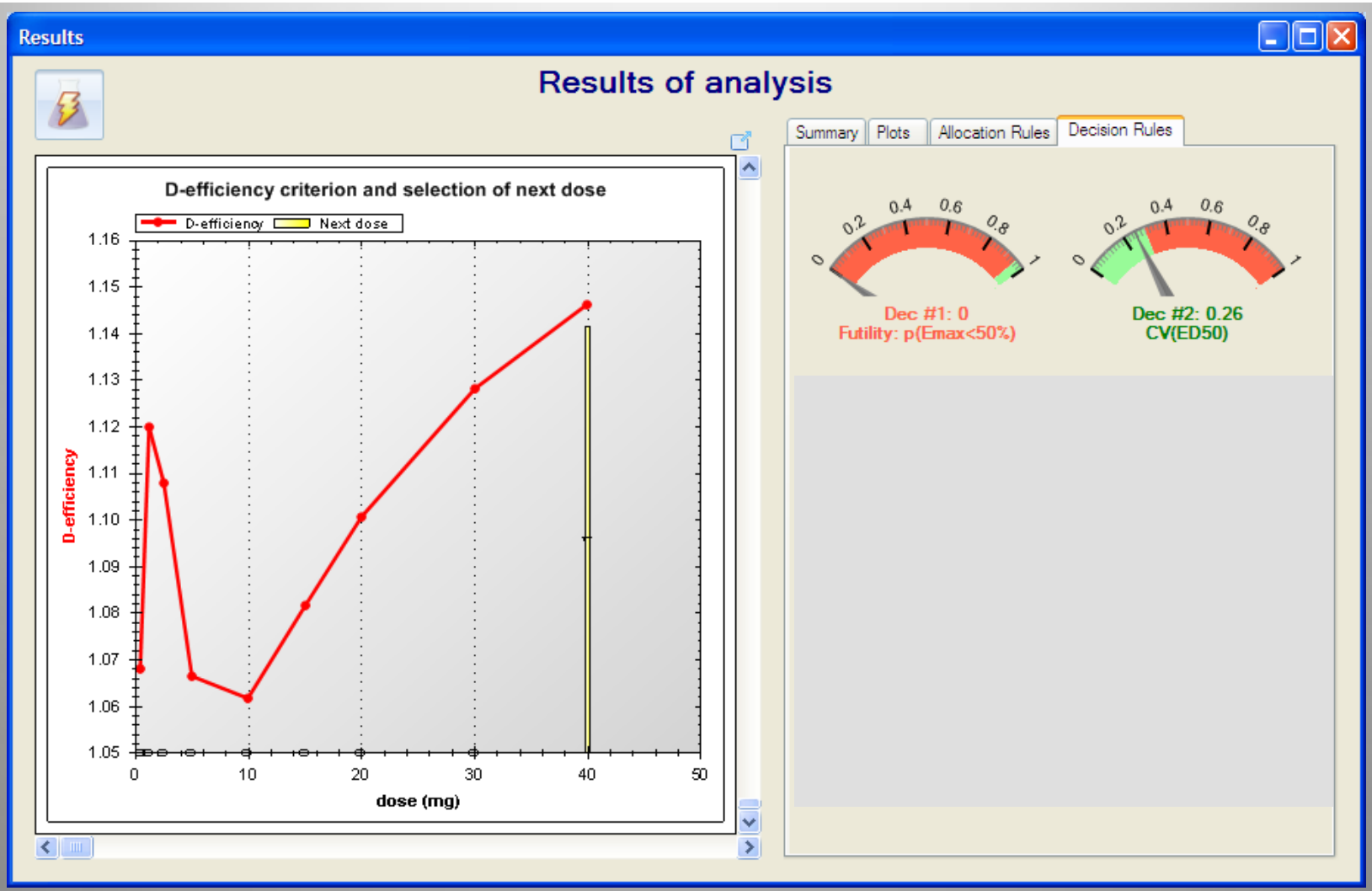
Bayesian Emax model fit

Param	mean	sd	2.5%	median	97.5%
Emax	85.82	5.191	76.54	85.47	97.06
ED50	2.199	0.539	1.39	2.154	3.398
tau	0.022	0.011	0.006	0.021	0.046

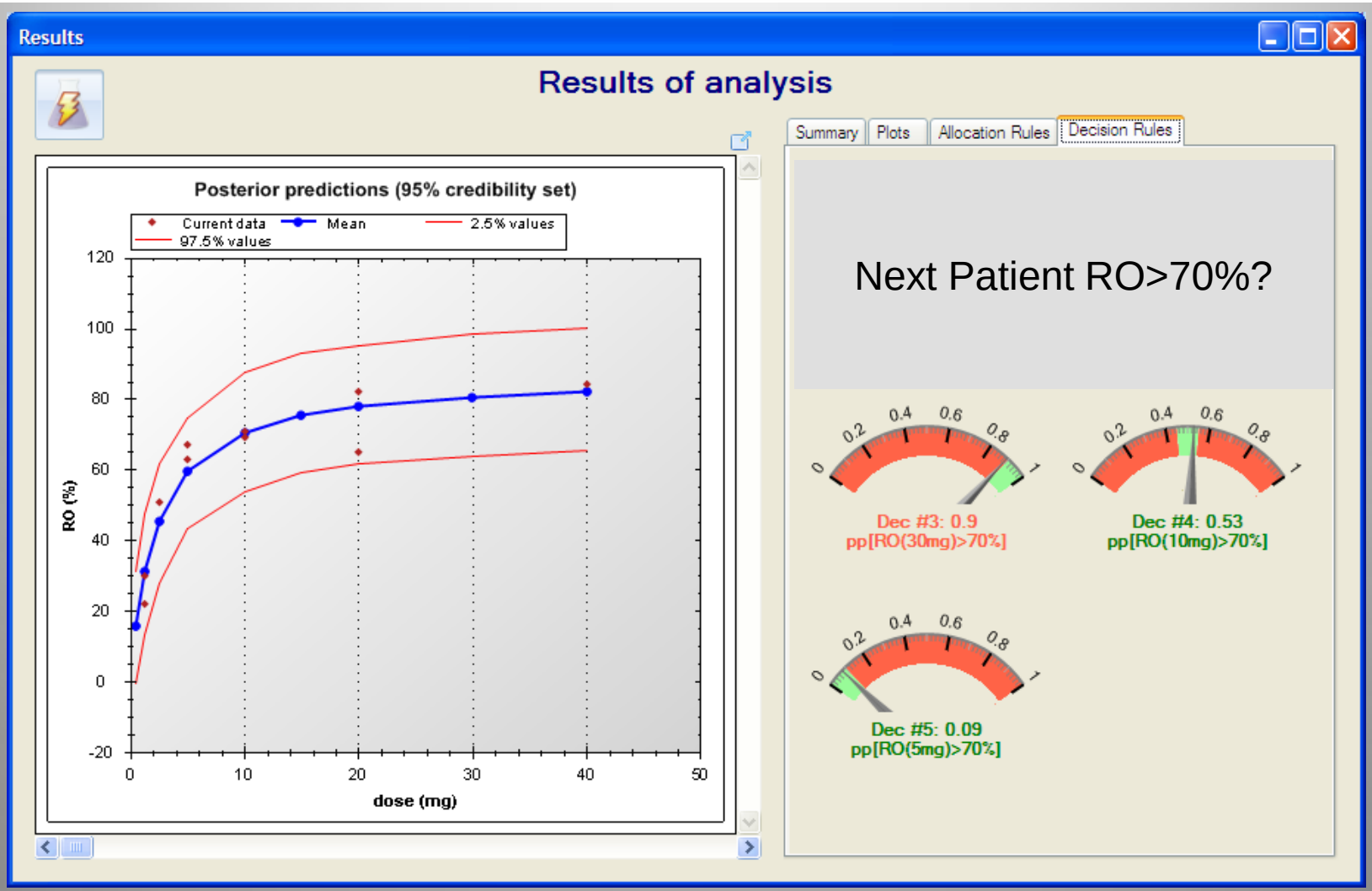




Next dose and stopping rules



Dose selection for Phase II



Conclusions

- Adaptive modelling strategy permits quantitative, data-driven decisions:
  - Within study:
    - Dose selection
    - Trial termination
  - Across drug development:
    - Probability of failure (success) drives go/no go decisions
    - Summary of all historical data
    - Prediction of future patient responses
- Technical challenges when using quantitative methods:
  - More work upfront on definition of decision tree.
  - Trial simulations to validate strategy.
  - Software availability as a key enabler.

Thank you!

Any Question?