Bayesian modelling for combination dose-escalation trial that incorporates pharmacokinetic data

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Topics covered

- Rationale for novel modelling approach
- Bayesian dose exposure model
  - Definition
  - Integration into dose-escalation decision process
- Robust prior derivation
- Implementation in PhI studies at Novartis
- Conclusion

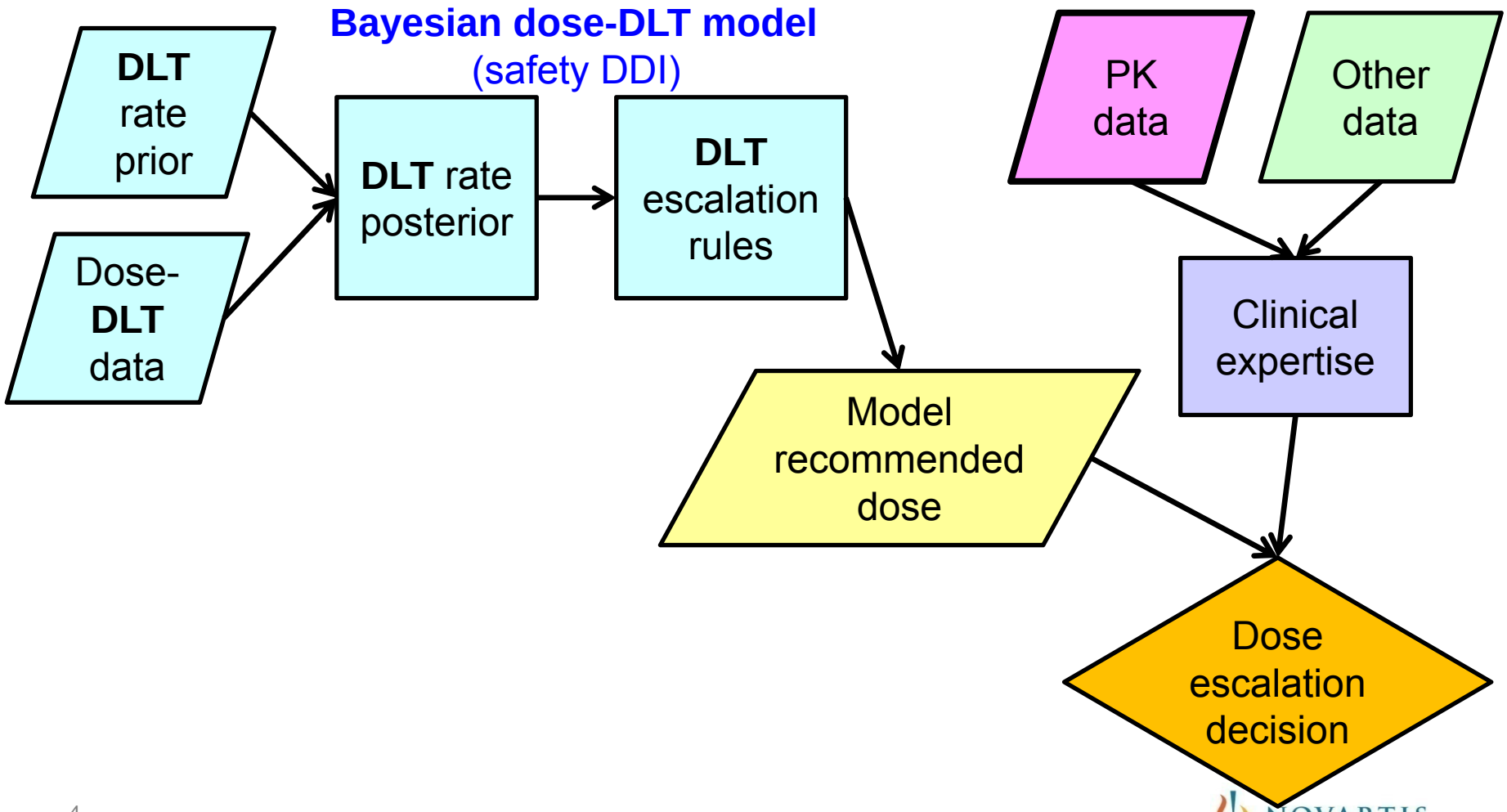
Background

- PhIb combination dose-escalation trials: both drugs may be novel, both drugs may be escalated
- Two types of drug-drug interactions (DDI)
  - **Safety DDI**:
    - Increased/decreased DLT rate from that expected as monotherapy
    - BLRM models dose-DLT relationship and estimates safety DDI
  - **PK DDI:** exposure of one or both drug(s) are increased/decreased from that expected as monotherapy
  - Link between PK DDI and safety DDI can be complex
    - PK DDI may explain only parts of overall safety DDI
    - Safety DDI can be seen without PK DDI
- How to incorporate PK information in a robust way into dose escalation decision?

Bayesian dose-DLT model

Current use of PK data for dose selection

PK data are already used in the decision



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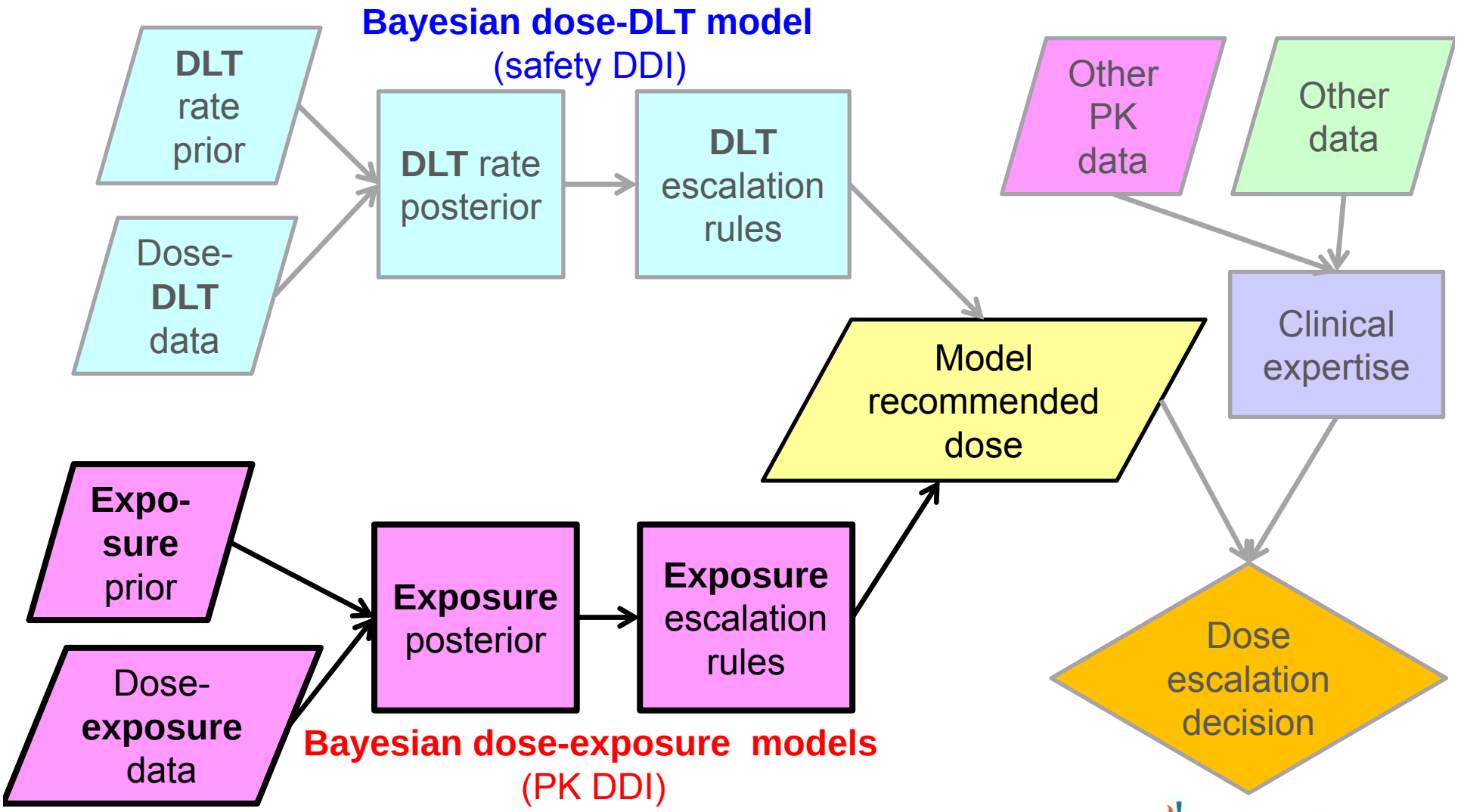
Adding Bayesian dose-exposure models

New use of PK data for dose selection



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Evolution in dose-escalation paradigm

- New primary objective: identify ‘safe’ dose with desired exposure
- Combine outputs from independant modeling of dose-DLT and dose-exposure relationships to establish MTD/RDE with optimal exposure of both agents
- Safety comes first! Highest doses allowed by Bayesian Logistic Regression Model (BLRM) following Escalation With Over-dose Control (EWOC) principle to control risk of over-toxicity
- Desired exposure driven by safety, pharmacodynamic and clinical activity (especially true for new targeted therapies with safer profile)
- Feasible since PK measured in all trials. Can be tailored to more complex settings
- Doesn’t prevent escalation to proceed on the basis of safety data only (when PK data not available and not critical for next decision)

Added value of integrating dose-exposure modelling

Simulation study [details in Cotteril (2015)]

- Decrease subjectivity of its use
- Increase efficiency of decision process
  - Escalation paths more varied and escalation of both drugs more likely
- Increase precision of the resulting dose recommendation
  - Less dose pairs declared as the final recommended dose
- Minimise number of patients treated at sub-optimal dose levels
  - Escalation faster when negative DDI
- Minimise number of patients overdosed
  - Escalation more cautious when positive DDI

One BLRM + two dose-exposure models

- 5-parameter BLRM for combination is used [Neuenschwander (2014)]
- Empirical bayesian dose-exposure model for each compound A and B:

$$\log(pkA_{dA,dB}) = \varphi_{1A} I_{(dB=0)} + \varphi_{2A} \log(dA/dA^*)) + \varphi_{3A} I_{(dB>0)} + \varphi_{4A} \log(1+dB/dB^*) + \varepsilon_A$$

«single-agent» models

Dose-independent Interactions

Dose-dependent Interactions

$$\log(pkB_{dA,dB}) = \varphi_{1B} I_{(dA=0)} + \varphi_{2B} \log(dB/dB^*)) + \varphi_{3B} I_{(dA>0)} + \varphi_{4B} \log(1+dA/dA^*) + \varepsilon_B$$

$\varepsilon_A \sim N(0, 1/\tau_A^2)$

$\varepsilon_B \sim N(0, 1/\tau_B^2)$

Defining target exposures

- Define target exposures T_A and T_B: typically exposures at s.a. RP2Ds but could be lower (e.g. if indicated by preclinical studies)
- Define relevant posterior summaries for each combination of interest:
  - Median exposures (with probability intervals)
  - Distance between posterior distribution of exposures and target exposures

$$g_h = \sqrt{\left(\frac{T_A - \text{pkA}_h(d_A, d_B)}{1/\tau_{A_h}}\right)^2 + \left(\frac{T_B - \text{pkB}_h(d_A, d_B)}{1/\tau_{B_h}}\right)^2}$$

$$g = \frac{\sum_{h=1}^{H} g_h}{H}$$ For H iterations of MCMC;

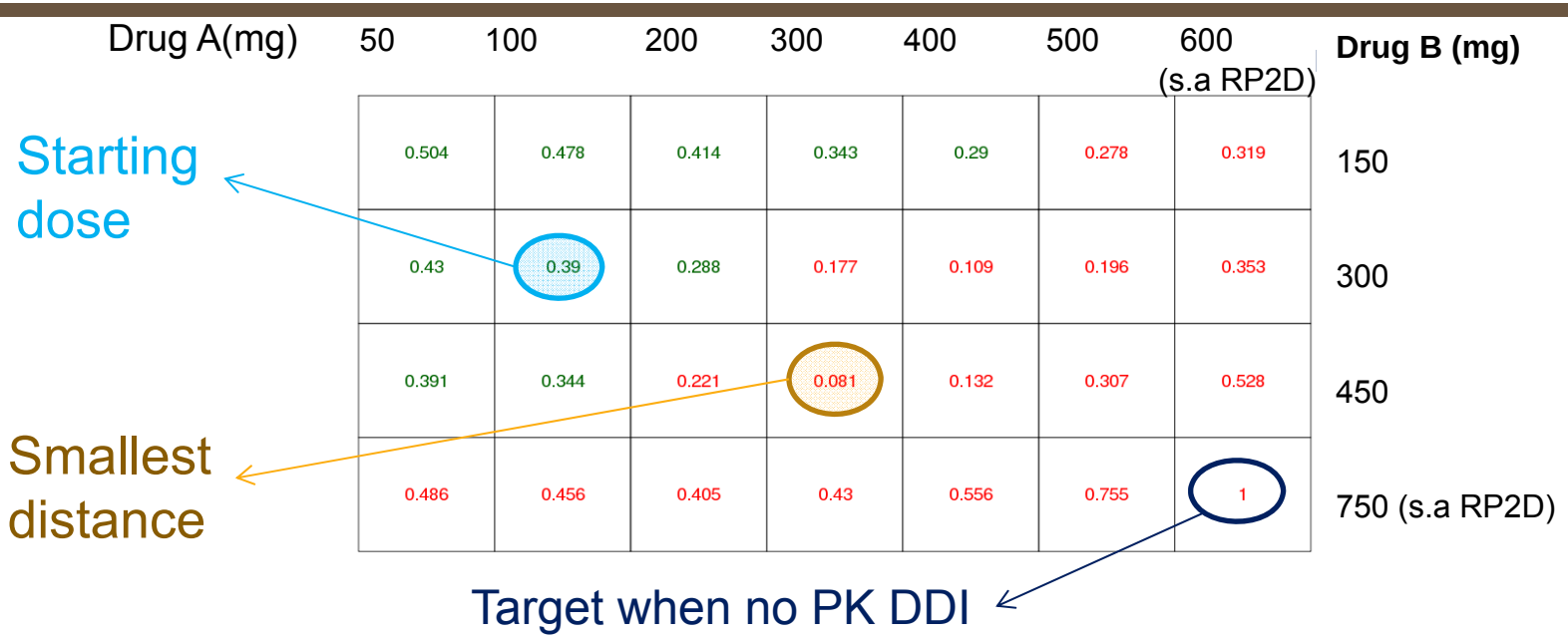
  - Probabilities of under/over exposure, e.g.

$$p = \text{P}(\text{pkA}(d_A, d_B) \in [T_{A_{low}}, T_{A_{high}}] \text{ and } \text{pkB}(d_A, d_B) \in [T_{B_{low}}, T_{B_{high}}])$$

Defining target exposures (cont.)

- Identify ‘safe’ combinations (as per EWOC) that allow to reach predefined target exposures for both drugs (as per metrics chosen)
- If there is too much uncertainty about target exposure, better not to use target exposure. Instead rely on estimates to learn about interaction.

Illustration after 1 cohort of 3 patients with large DDI



Recommended next dose based on BLRM (mg) A/B	Posterior probability of the BLRM recommended next dose			Estimated exposure (ng*h/ml) 90% probability interval	
	Underdose [0%,16%)	Target toxicity [16%,35%)	Excessive toxicity [35%,100%]	A *(target=22640)*	B *(target=20335)*
200/300	0.3998	0.4387	0.1615	8848 *[2569 ; 30070]*	12880 *[3693 ; 44480]*
100/450	0.3672	0.4817	0.1505	4057 *[1098 ; 14930]*	18760 *[7294 ; 48681]*

Prior buidling and robustification

- A 4-step approach to combine all sources of prior information
- Step 1: leverage single agent data (+ relevant combination data)
  - Fit bayesian models (using non-informative priors) to obtain informative priors for s.a. parameters φ_1, φ_2 and for inter patient variability ε
  - Non-informative priors obtained for parameters related to DDI
  - Down-weight posterior variances so that effective sample size corresponds to moderate/substantial heterogeneity between historical data and on-study data (meta-analytic-predictive prior can also be used)
  - PK information may only be available in external publication as summary statistics

Prior buidling and robustification (cont.)

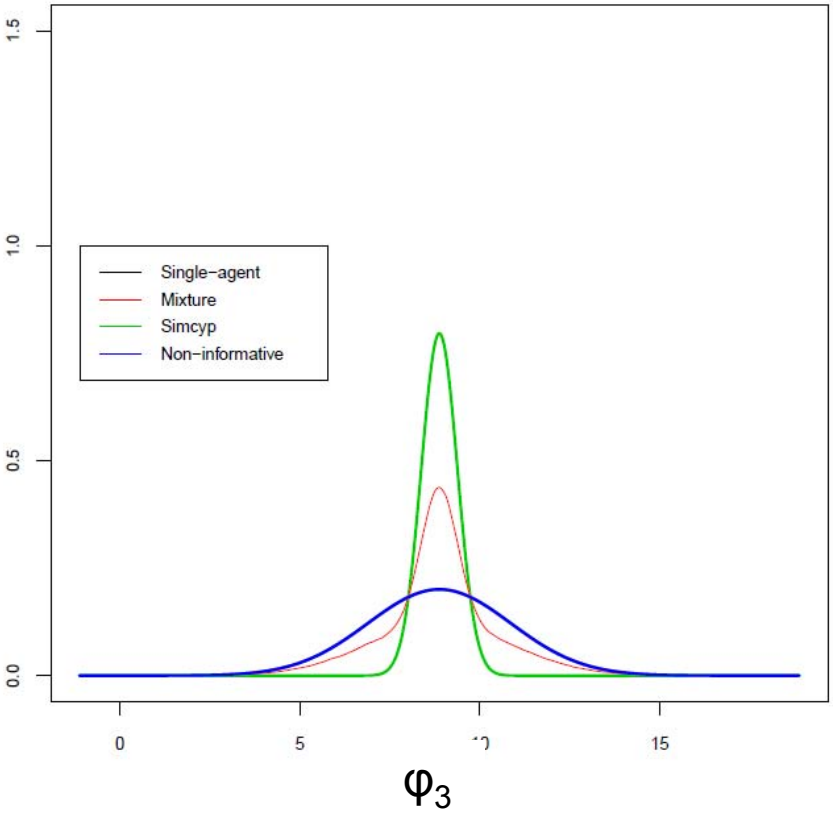
- Step 2: integrate DDI predictions from PB/PK modelling:
  - Simcyp is a population-based simulator:
    - Incorporates numerous databases containing human physiological, genetic and epidemiological information.
    - Allows to integrate this information with in vitro and clinical data to predict PK behavior in 'real-world' populations.
  - Used to adapt parametrization of empirical Bayesian model to likely mechanism of DDI
  - Build informative priors for all parameters, including those related to DDI: φ_3, φ_4 and also ε
    - Use PB/PK model to simulate pkA and pkB for virtual patients
    - Fit bayesian models on pkA and pkB (using non-informative priors)
    - Down-weight posterior variances so that effective sample size corresponds to substantial/large heterogeneity between PB/PK DDI predictions and DDI in trial population

Prior buidling and robustification (cont.)

- Step 3: build a non-informative (NI) prior for all parameters:
  - Same as Simcyp prior but with further down-weighting so that effective sample size corresponds to one observation
- Step 4: combine 3 priors in a mixture that provides good behavior to the model even when conflict between prior and data
  - Define prior weights, e.g. 0.4, 0.4 and 0.2 for SA, Simcyp and NI priors, respectively
  - Prior weights are updated into posterior weights when model is updated with data

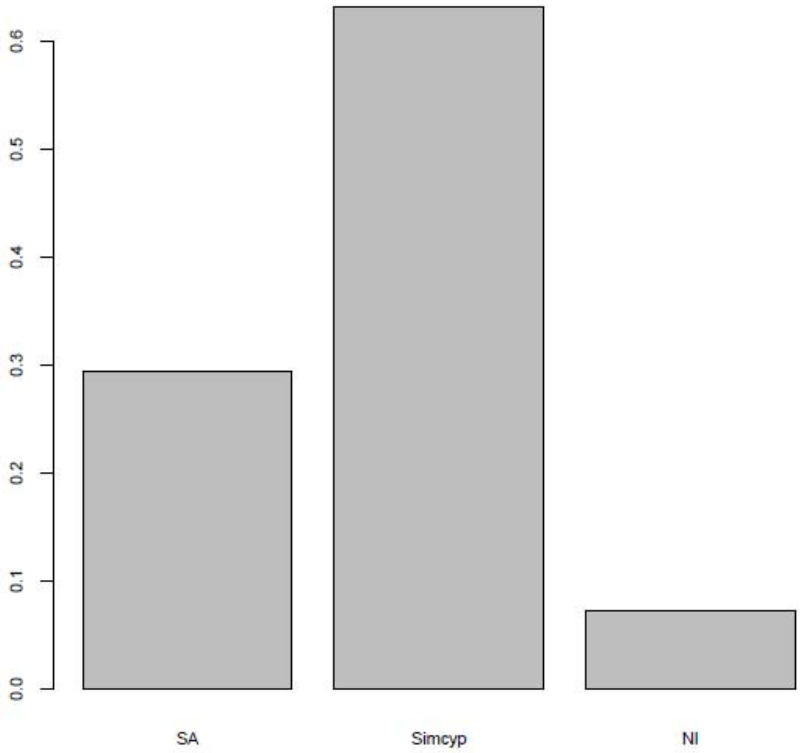
Illustration of mixture prior

Mixture for dose-independent DDI parameter



Posterior weights when data aligned with Simcyp prior

prior weights: 0.4(SA), 0.4(Simcyp), 0.2(NI)



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Implementation in protocol

- Selected PK parameters are co-primary or key secondary endpoints
- Flexible wording regarding the recommendations provided by the Bayesian dose-exposure model
- Estimated exposures provide additional information to further guide the dose selection
- No additional constraint on the dose escalation:
  - For later cohorts, the dose escalation may occur without having the full PK data available, on condition that the EWOC criterion is met
  - Higher escalation step allowed when negative PK DDI

Implemented in 6 Novartis Oncology PhI trials so far

- 5 combinations trials:
  - Combination treatment where significant PK DDI is expected
  - PK data of single agent studies available
  - Bayesian model parametrization can be tailored to design features (e.g. when s.a. PK run-in is added)
- 1 single agent trial:
  - Limited toxicity anticipated + RP2D should have similar exposure than competitors
- No challenge from HA and IRBs so far

Concluding remarks

- **Evolution** from current dose-escalation paradigm since the identification of the RDE/RP2D gives more weight to non-DLT data
- Current approach benefited from **cross functional collaboration** (biostatistics, clinical pharmacology, drug metabolism & pharmacokinetics, clinical)
- Requires an **early and close collaboration** at project team level
  - DDI risk should be discussed and addressed early in protocol concept
- Requires more time to set up but lead to design with **increased efficiency**
- Method is still novel and adaptations are expected from learnings during execution phase of trials

References

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