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Use of modeling & simulation to support the design and analysis of a new dose and regimen finding study

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M&S Modeling & Simulation

Background (1)

- Small molecule delivered by lung inhalation to create bronchodilation with an established drug class

- Drug effect measured using spirometry
- Focus on forced expiratory volume in 1 second (FEV1) measured at morning trough (prior to next dose inhalation)

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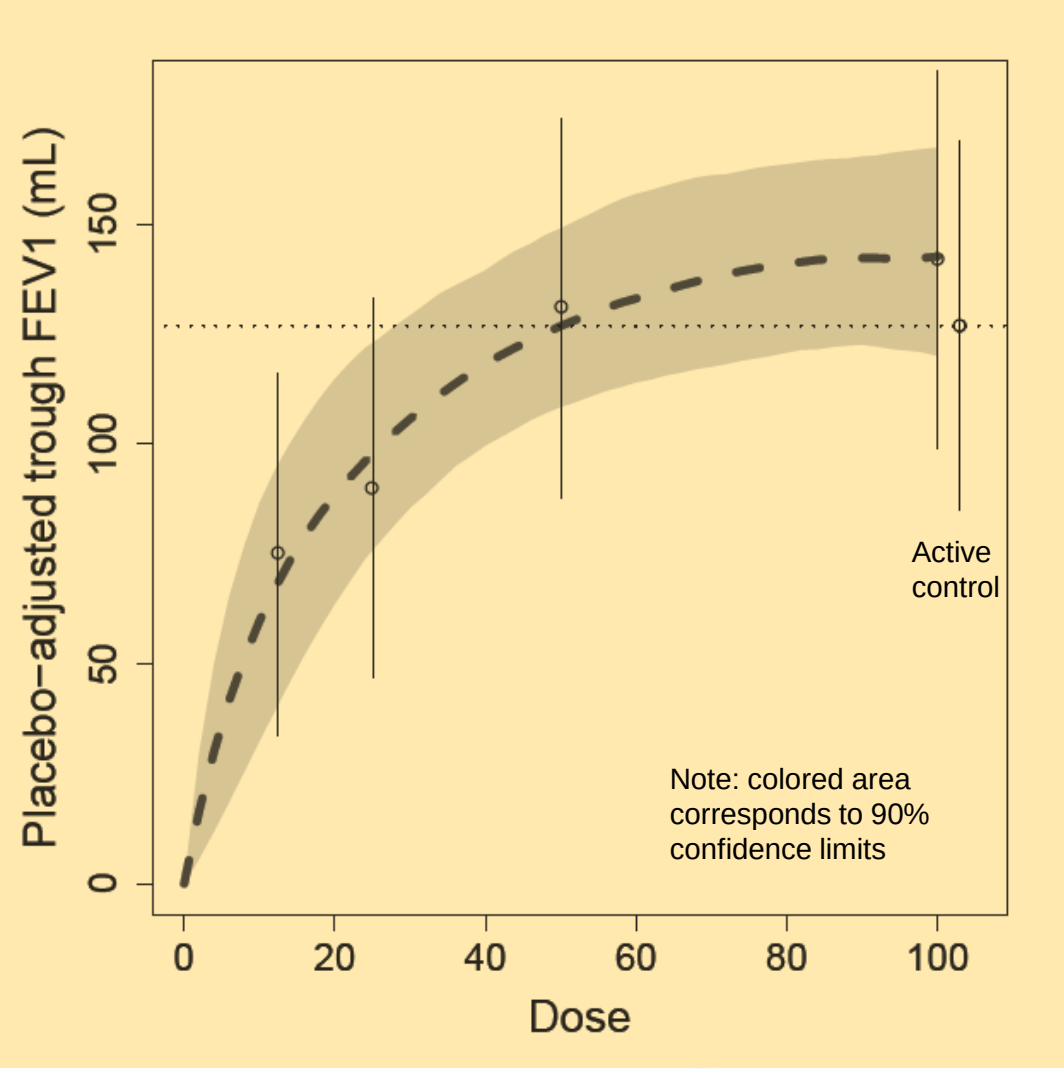
Background (2)

- Dose ranging study had been performed with once daily administration
- FDA required us to investigate additional dosing intervals hence need to design a new study to support choice of dose and dosing interval for Phase 3
- Respiratory field has been quite conservative in statistical methods for dose finding, often relying on ANCOVA approach for dose selection purposes



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New dose and regimen finding study

General approach

- Rely on modeling & simulation as a general tool to make informed recommendations on the following aspects of the new study protocol:
  - Trial design (Stage I)
  - Sample size (Stage II)
  - Analysis methodology (Stage III)
- Note: A key trial design decision was about the use of a model-based approach instead of ANCOVA for the data analysis.

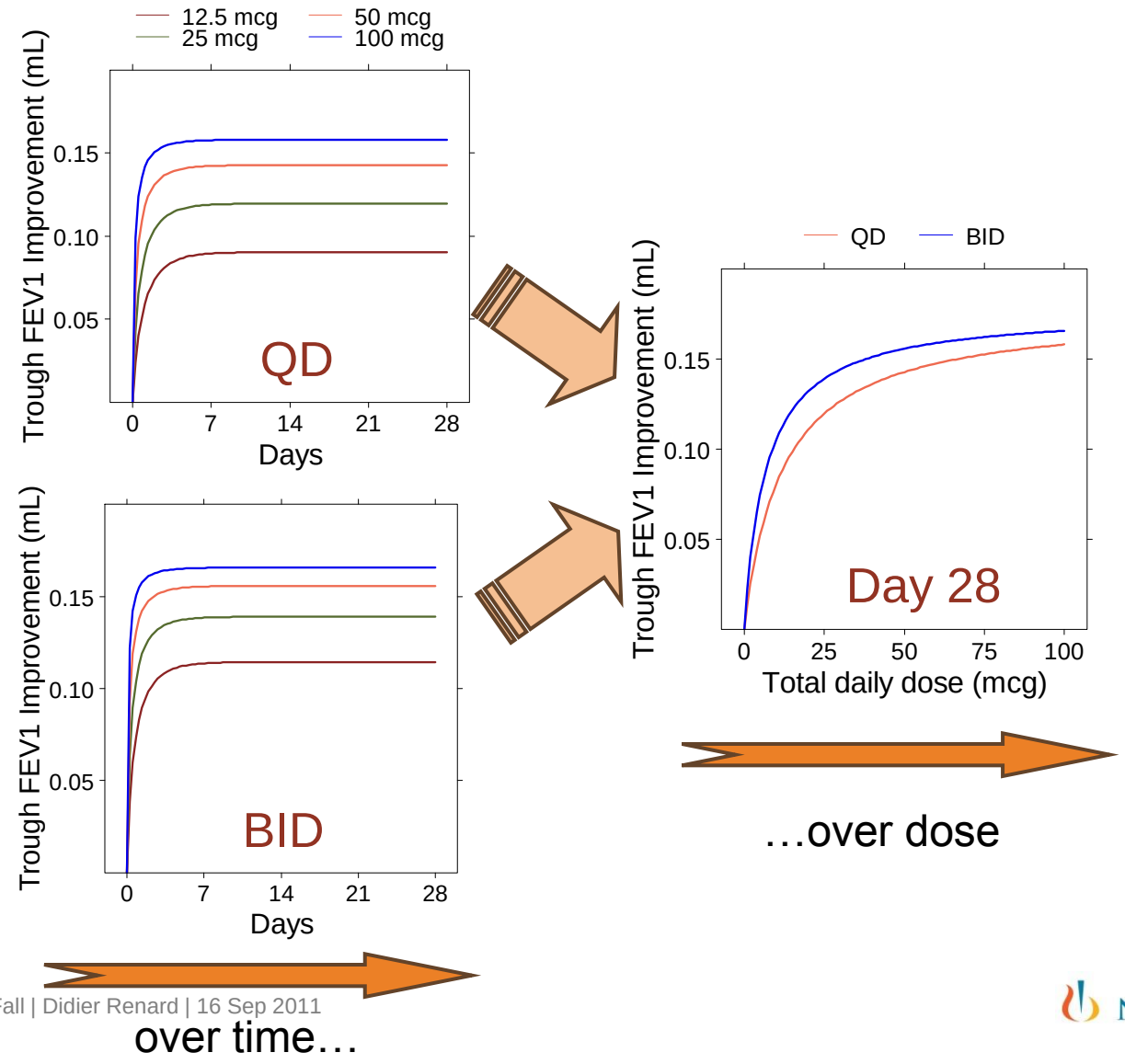
Proposed analysis approach

Key principles underlying model-based analysis

- The proposed methodology was articulated along the following key principles:
  - The dose-response relationship is of Emax type. This has been observed to be a reasonable assumption based on data from previous trials.
  - To gain efficiency the totality of trough FEV1 data is included in the analysis (i.e. longitudinal approach).
  - Several candidate models, deemed a priori reasonable to describe the data, are considered.
  - Model averaging is employed to conduct more robust inference.

Proposed analysis approach

Model-based analysis should integrate data…



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Candidate models

Key assumptions underlying model-based analysis

- Dose response component is of Emax or sigmoidal Emax type
- Regimen acts as a potency modifier (θ)
- Common maximal effect (Emax) is assumed
- Key differentiating feature is how each model describes the evolution of the response over time:
  - Steady state: $$E\{FEV_1\} = E_0 + \frac{E_{max} \times dose}{ED_{50} \times \lambda^{I(day=1)} / \theta^{I(BID)} + dose}$$
  - Longitudinal Emax: $$E\{FEV_1\} = E_0 + \frac{day}{ET_{50} + day} \times \frac{E_{max} \times dose}{ED_{50} / \theta^{I(BID)} + dose}$$
  - Time-varying potency: $$E\{FEV_1\} = E_0 + \frac{E_{max} \times dose}{ED_{50} / (\frac{day}{ETP_{50} + day}) / \theta^{I(BID)} + dose}$$
  - KPD: $$E\{FEV_1\} = E_0 + \frac{E_{max} \times dose}{ED_{50} / (\Theta^{I(BID)} \times \exp(-k / 2^{I(BID)}) \times (1 - \exp(-k \times day)) / (1 - \exp(-k / 2^{I(BID)}) / 2^{I(BID)}) + dose}$$
- Models should further be adjusted for relevant covariates and include sources of variability (IIV – IOV – residual)

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Model averaging

As a mean to obtain more conservative model inference

- BIC weights are calculated for each model

$$\frac{\exp(-0.5 \times BIC_{m},)}{\sum_{m} \exp(-0.5 \times BIC_{m})}$$

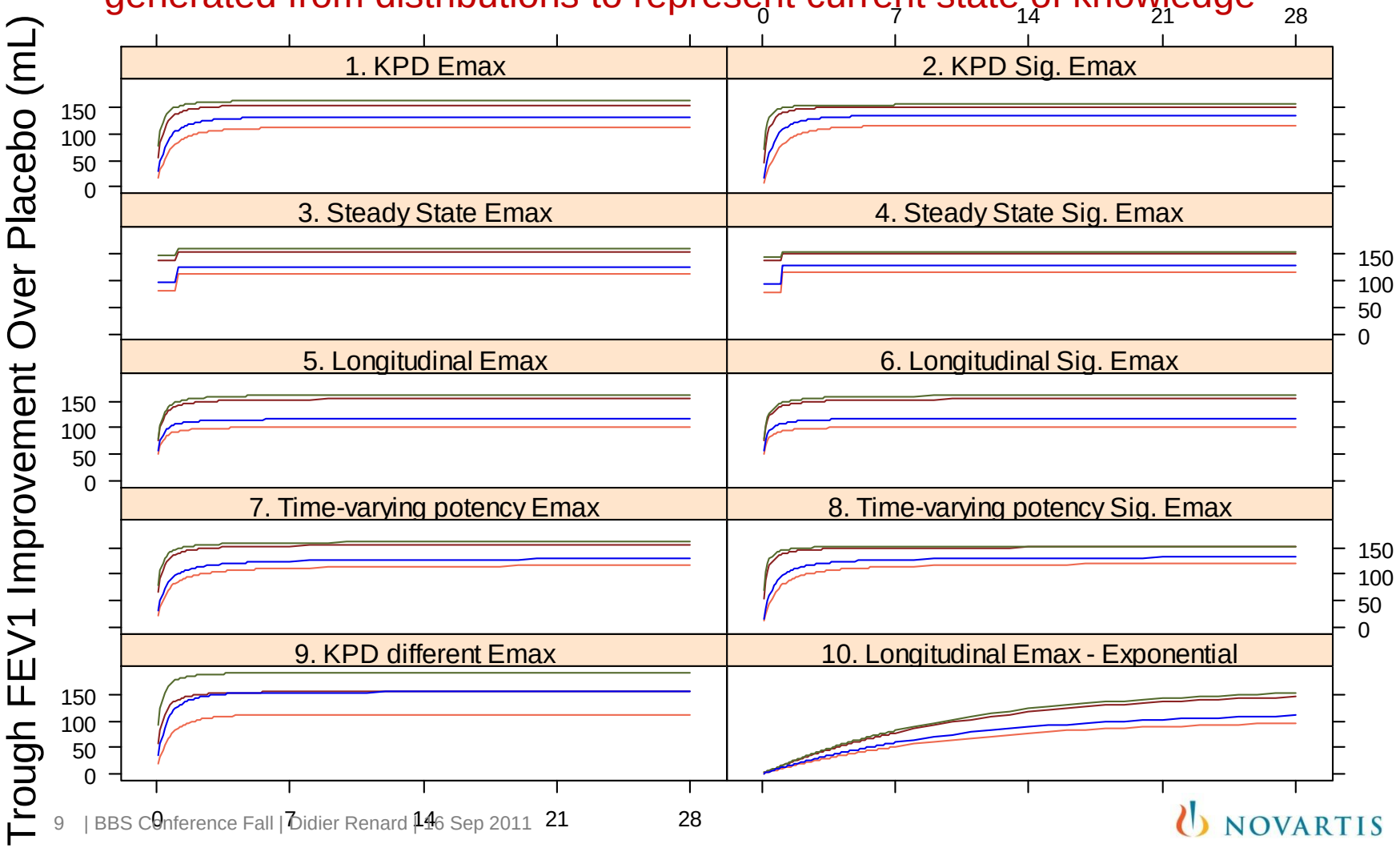
- Dose response is obtained as a weighted average of individual model predictions using BIC weights
  - Models that better represent the data carry a greater weight in the prediction
- Repeat the following procedure a large number of times to obtain empirical distributions for estimates of interest:

  1. Sample a model proportionally to BIC weights (multinomial dist.)
  2. Conditionally on chosen model, sample a set of parameter values (fixing parameter estimates and associated covariance matrix) and obtain the desired value

Evaluation of analysis methodology

Representation of time- and dose-response scenarios

For each scenario, 5000 datasets were simulated with parameter values generated from distributions to represent current state of knowledge



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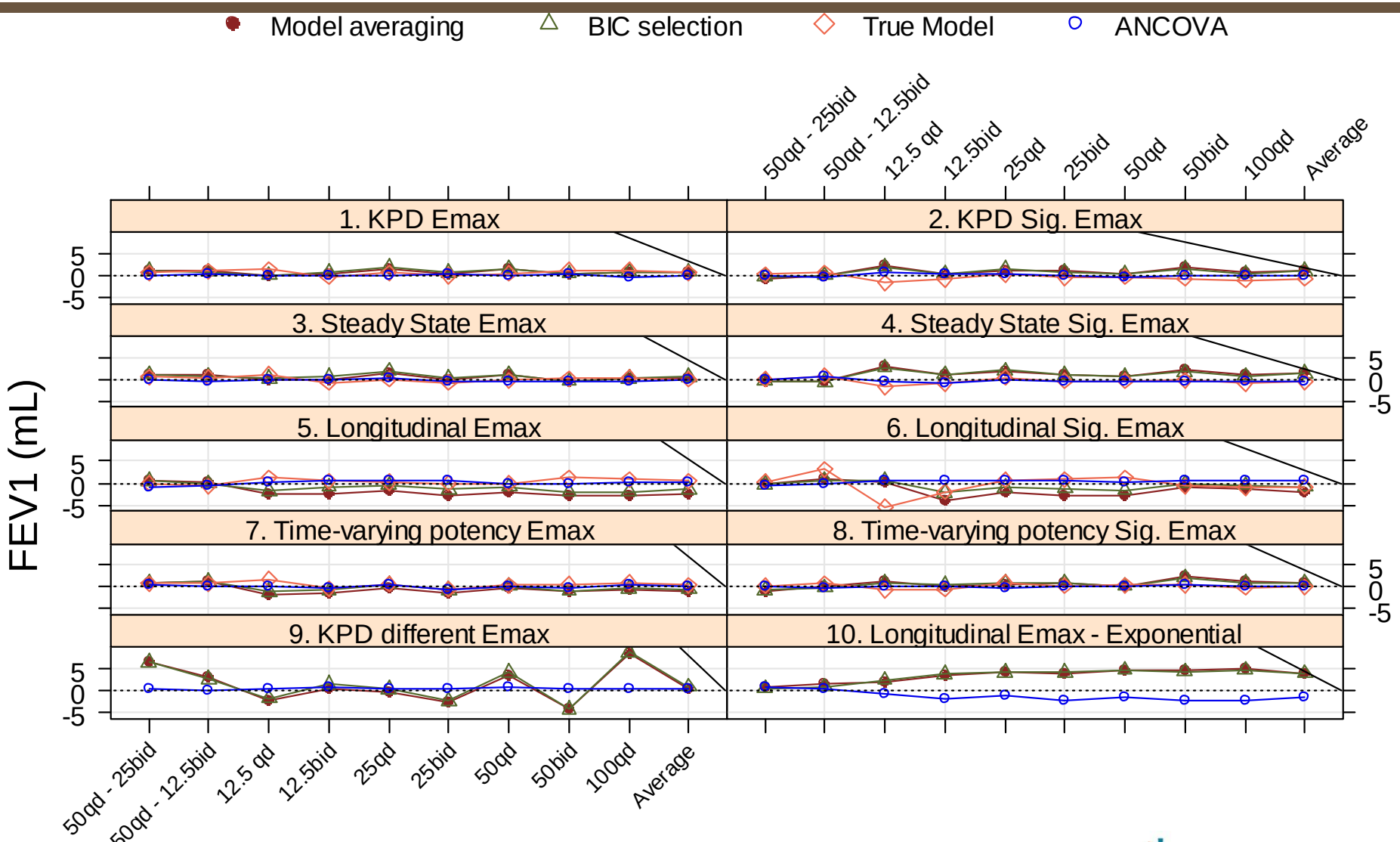
Evaluation of analysis methodology

Mean bias across scenarios



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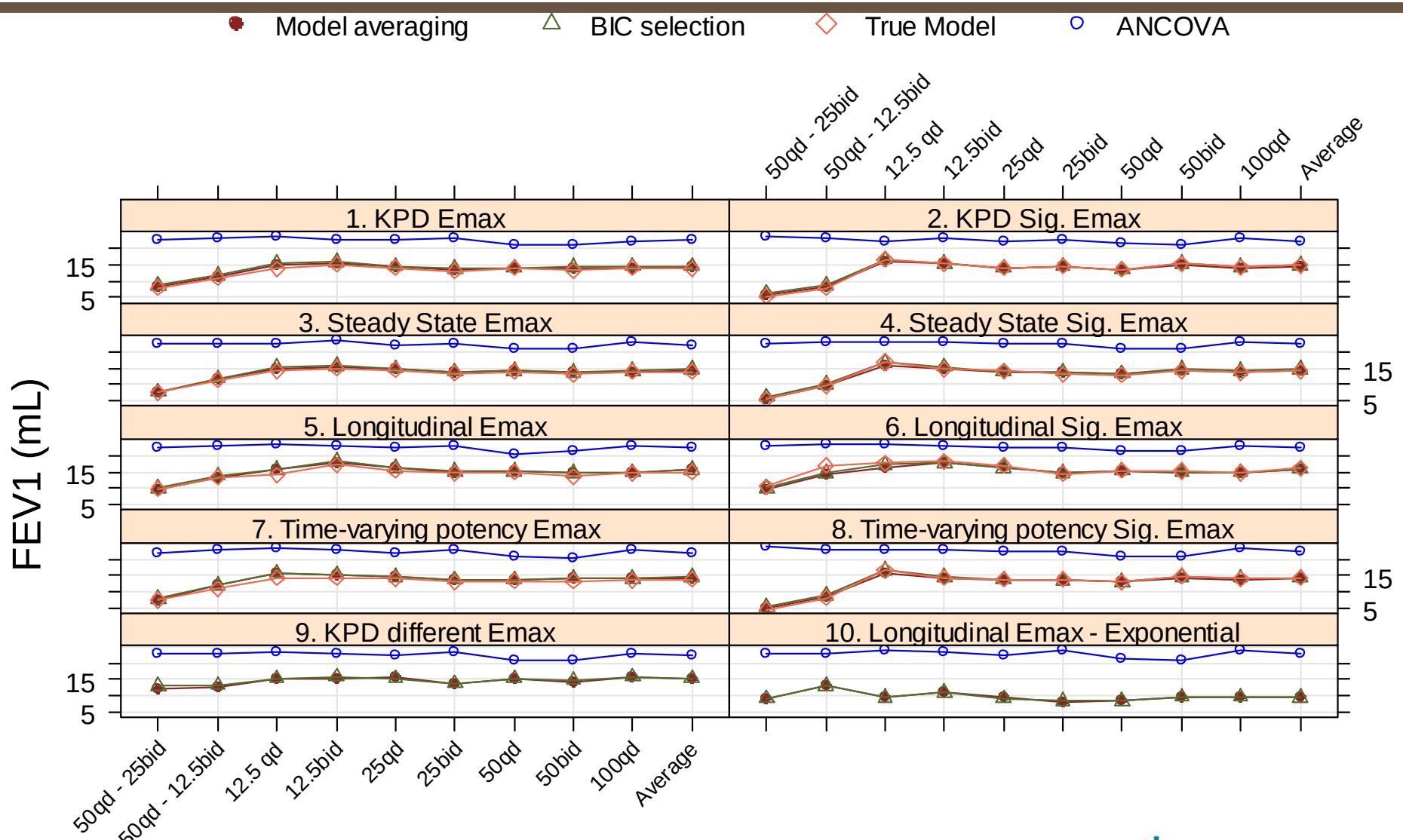
Evaluation of analysis methodology

Median absolute deviation (MAD) across scenarios



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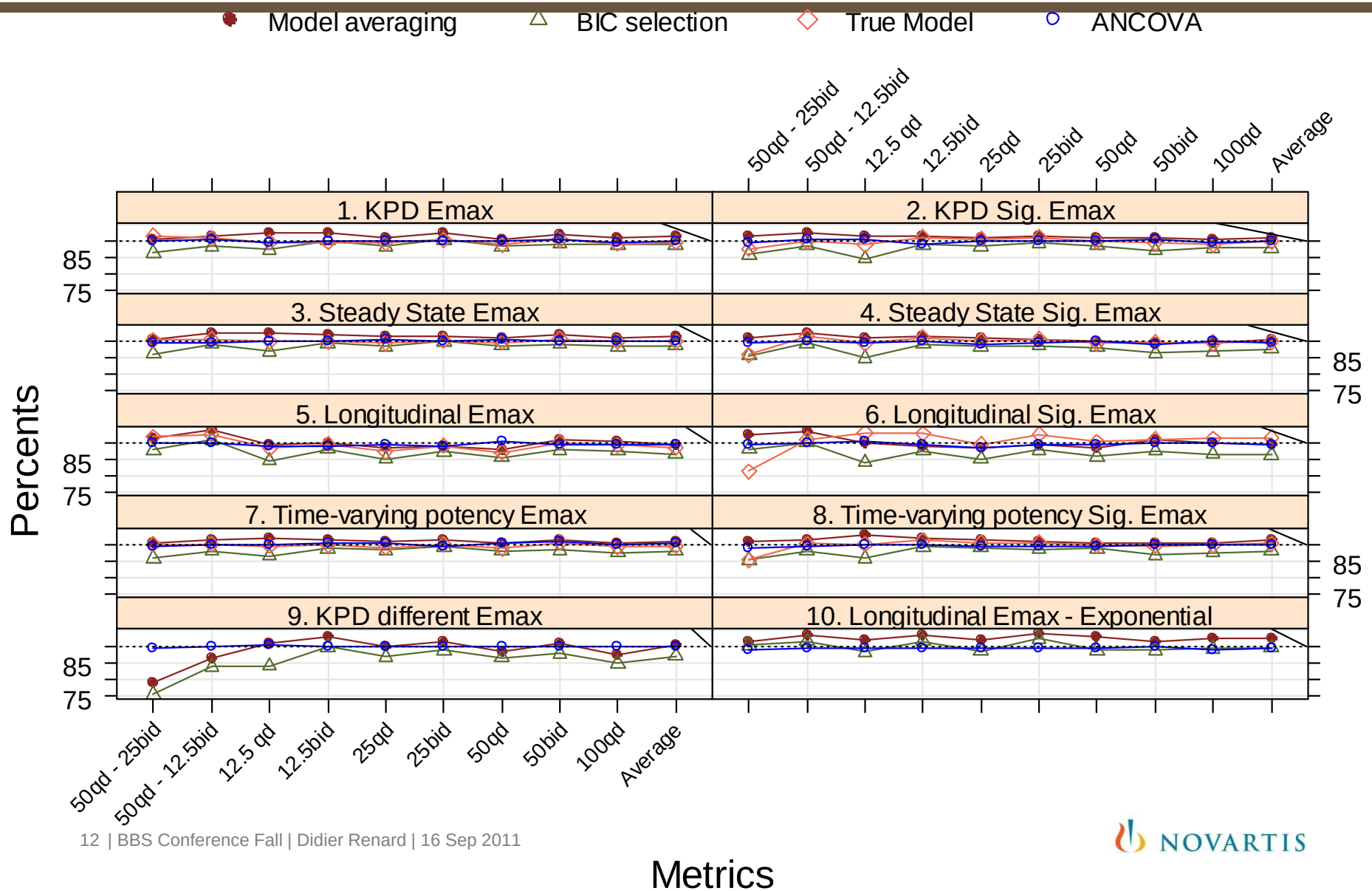
Evaluation of analysis methodology

Coverage probability of 90% CI across scenarios



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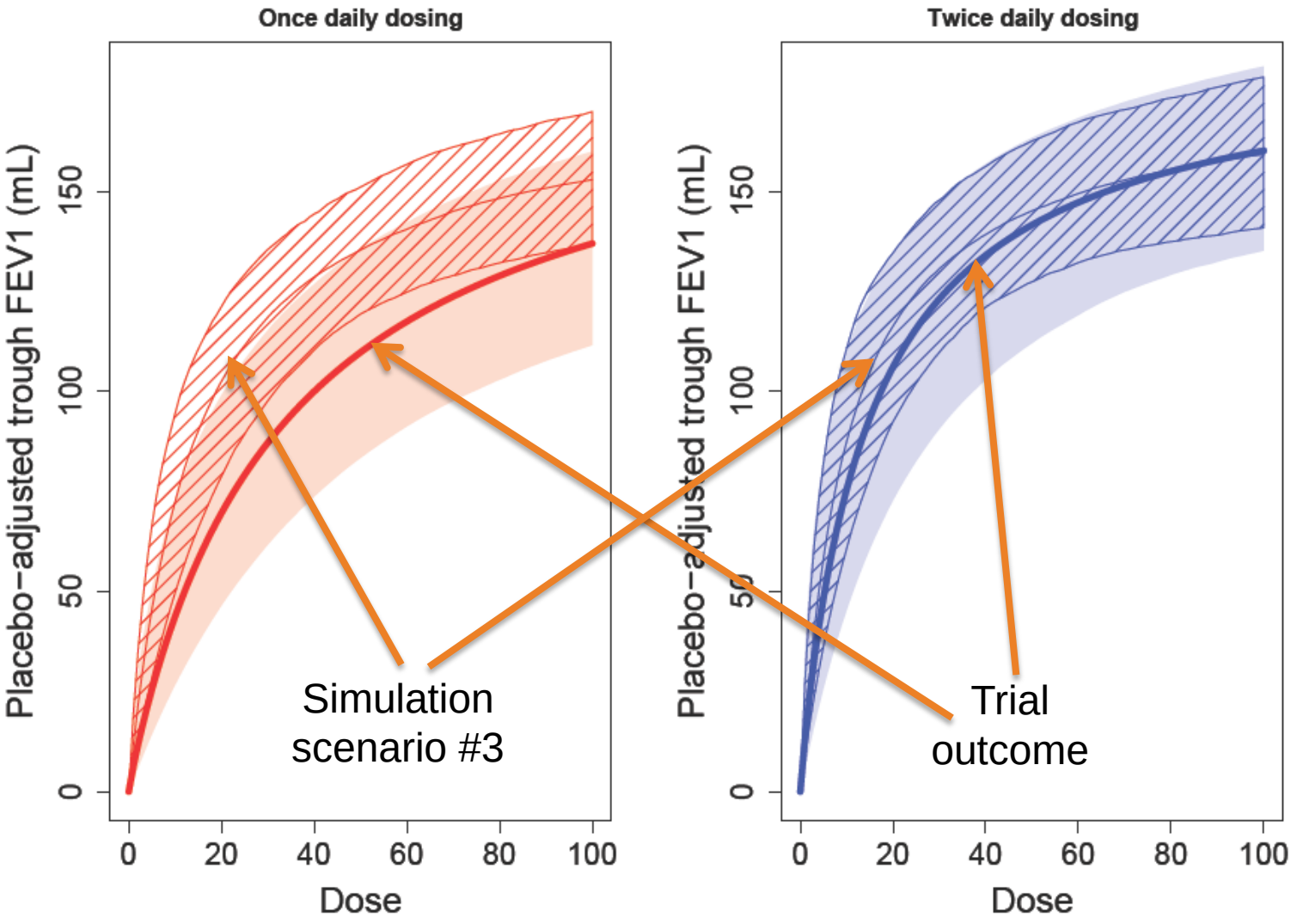
How well could we anticipate the trial outcome ?



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Summary and discussion (1)

- An extensive simulation study was conducted to make informed recommendations on trial design, sample size, and analysis methodology
- The choice of a model-based method in place of the conventional approach was the most discriminative feature among those investigated
  - Other design attributes such as parallel groups vs. crossover resulted in net benefits one order of magnitude lower
- Own learning:
  - Endpoint analysis: marginal improvement of model-based approach
  - Longitudinal analysis: marginal improvement of MMRM approach
  - Combining the two aspects (longitudinal model-based) provides the best bang for the buck!!

Summary and discussion (2)

- Model-based analyses are typically exploratory (i.e. post-hoc) in nature
- Model averaging was employed to enable pre-specification of a robust model-based analysis (i.e. satisfy high-level regulatory requirements)
- Revealed good properties, with a favorable trade-off between bias and precision.
  - Slightly conservative when examining coverage probabilities
- Showed significant gains in efficiency over ANCOVA
- Greater benefits were seen when comparing active doses, this is where the model-based approach truly shines
- Make the approach more robust by including a wider range of models (very simple to very complex, eg MMRM)

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