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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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Background (1)



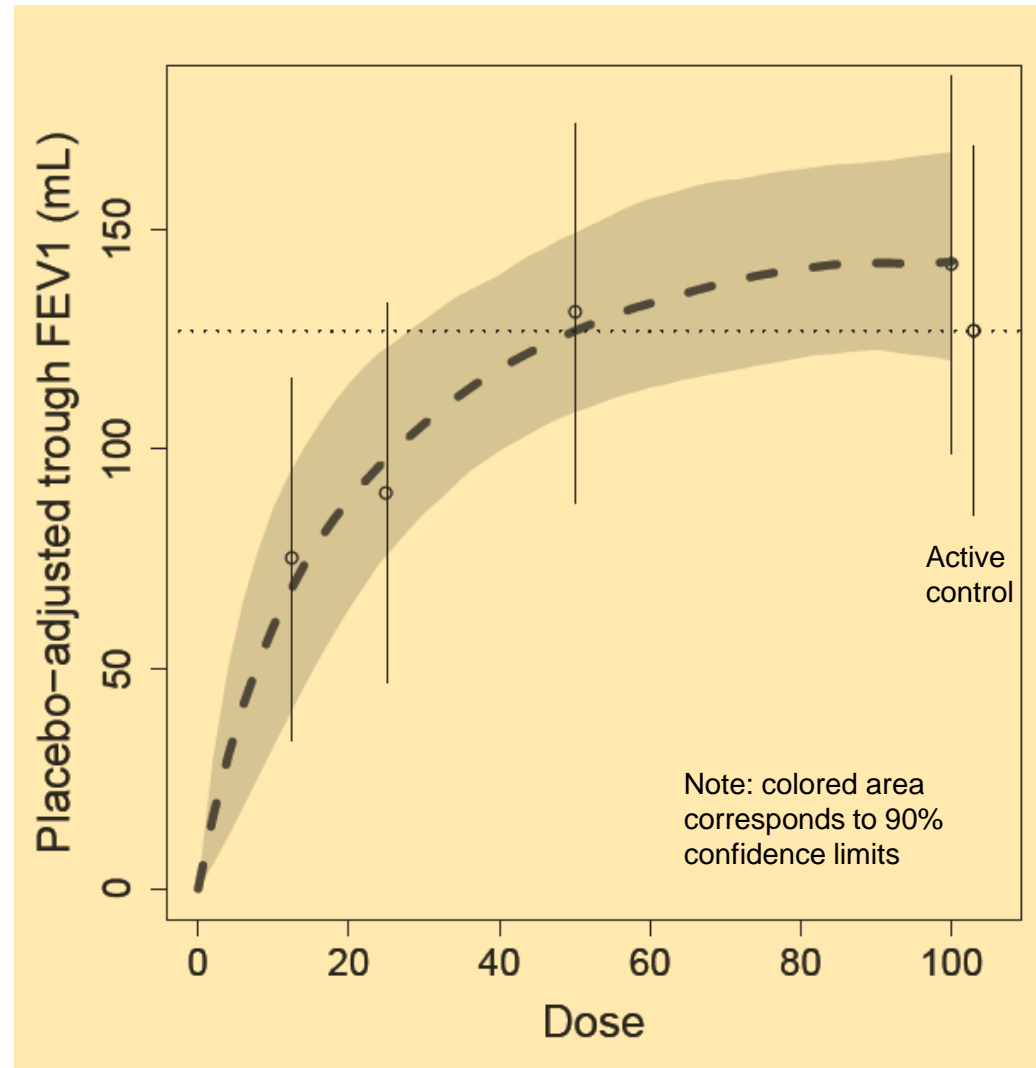
- Drug effect measured using spirometry
- Focus on forced expiratory volume in 1 second (FEV1) measured at morning trough (prior to next dose inhalation)

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



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



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.

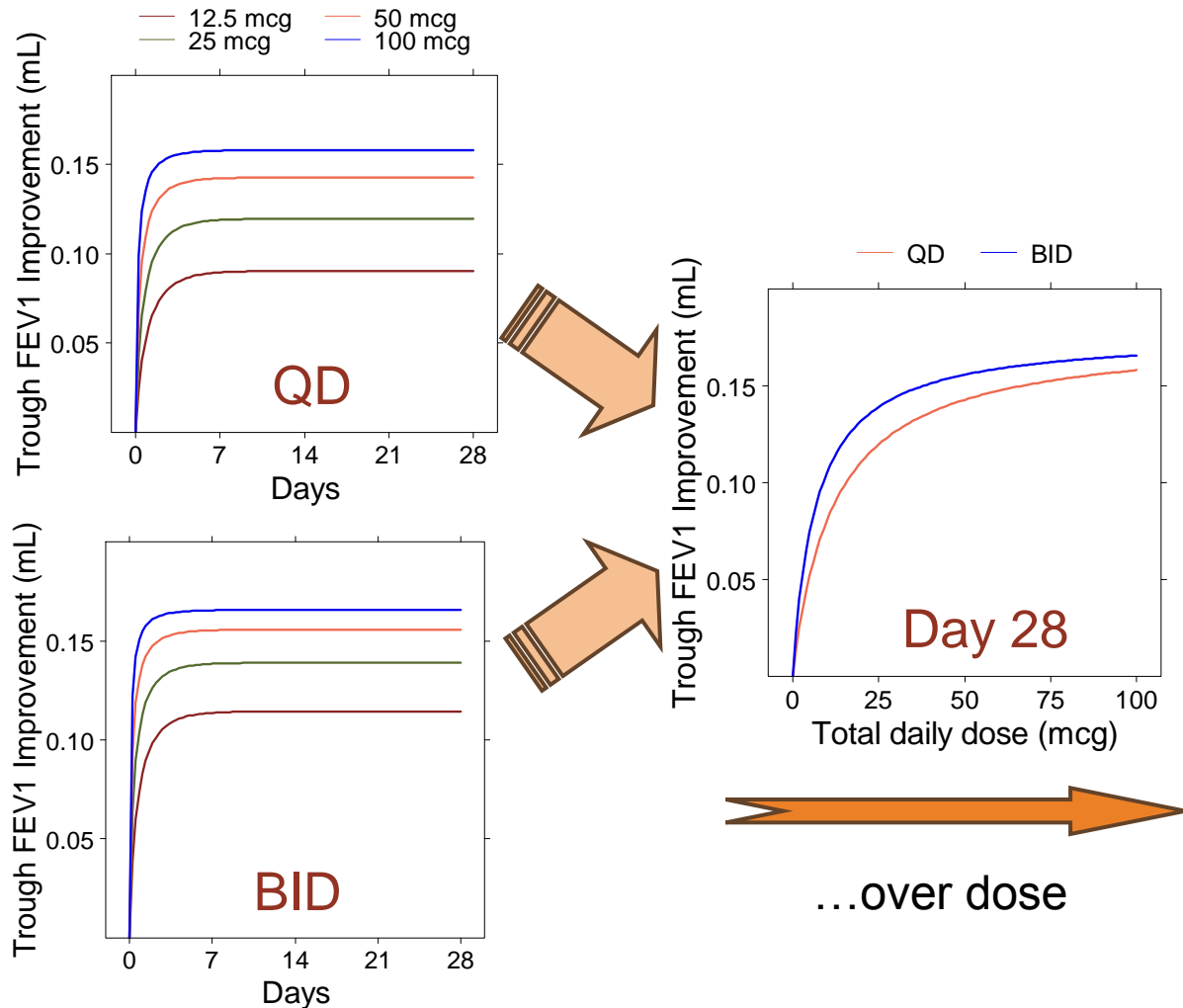
Proposed analysis approach

Key principles underlying model-based analysis

- The proposed methodology was articulated along the following **key principles**:
 - The dose-response relationship is of **E_{max} 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...



...over dose



over time...

Candidate models

Key assumptions underlying model-based analysis

- Dose response component is of **E_{max} or sigmoidal E_{max} type**
- Regimen acts as a **potency modifier (θ)**
- **Common maximal effect (E_{max})** is assumed
- Key differentiating feature is how each model describes the **evolution of the response over time**:

- Steady state:
$$E\{FEV_1\} = E_0 + \frac{E_{\max} \times \text{dose}}{ED_{50} \times \lambda^{I(\text{day}=1)} / \theta^{I(\text{BID})} + \text{dose}}$$

- Longitudinal E_{max}:
$$E\{FEV_1\} = E_0 + \frac{\text{day}}{ET_{50} + \text{day}} \times \frac{E_{\max} \times \text{dose}}{ED_{50} / \theta^{I(\text{BID})} + \text{dose}}$$

- Time-varying potency:
$$E\{FEV_1\} = E_0 + \frac{E_{\max} \times \text{dose}}{ED_{50} / \left(\frac{\text{day}}{ETP_{50} + \text{day}}\right) / \theta^{I(\text{BID})} + \text{dose}}$$

- KPD:
$$E\{FEV_1\} = E_0 + \frac{E_{\max} \times \text{dose}}{ED_{50} / (\Theta^{I(\text{BID})} \times \exp(-k / 2^{I(\text{BID})}) \times (1 - \exp(-k \times \text{day})) / (1 - \exp(-k / 2^{I(\text{BID})}) / 2^{I(\text{BID})}) + \text{dose}}$$

- Models should further be **adjusted** for relevant covariates and include sources of variability (IIV – IOV – residual)

Model averaging

As a mean to obtain more conservative model inference

- BIC weights are calculated for each model

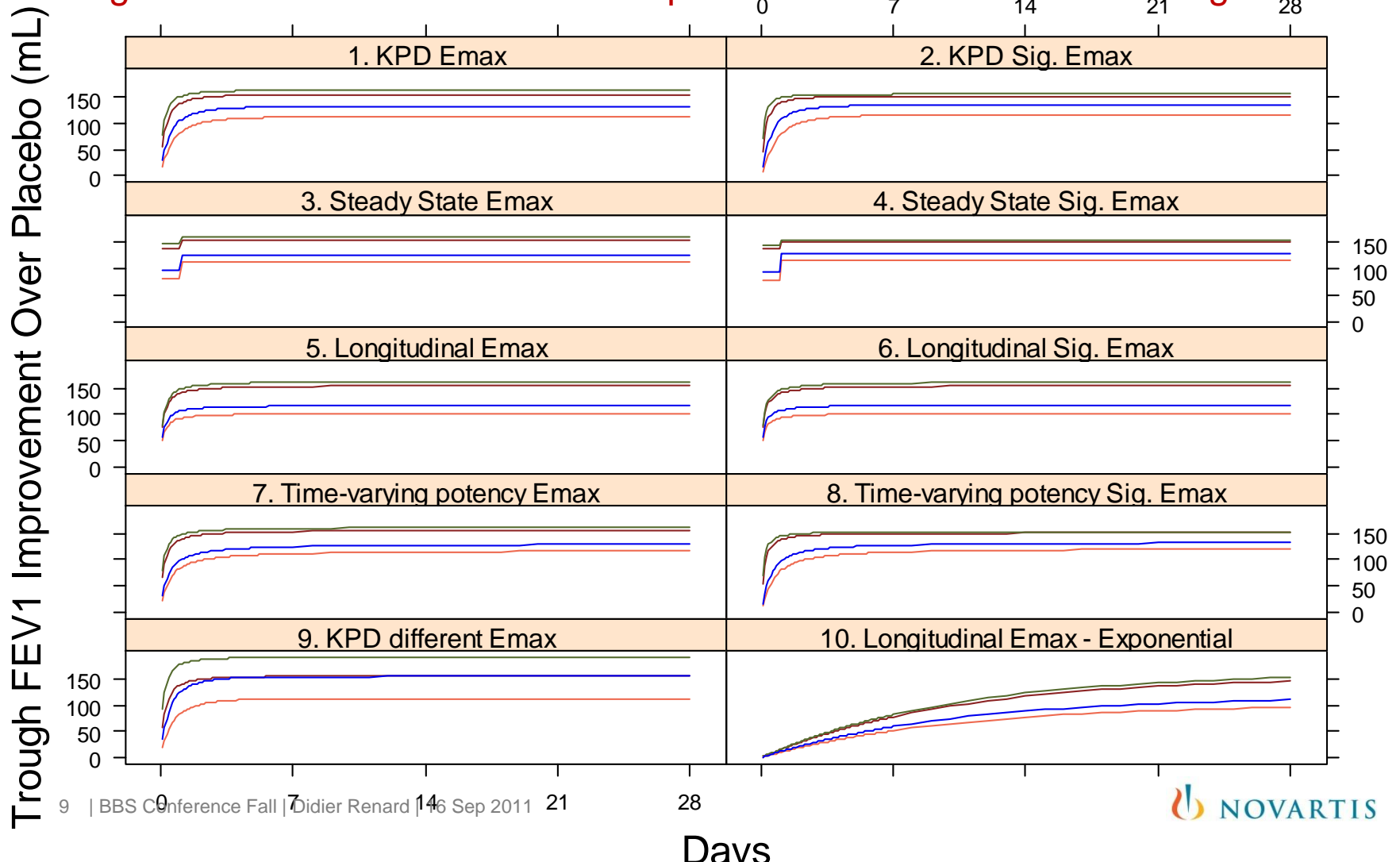
$$\frac{\exp(-0.5 \times BIC_m)}{\sum_m \exp(-0.5 \times BIC_m)}$$

- 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

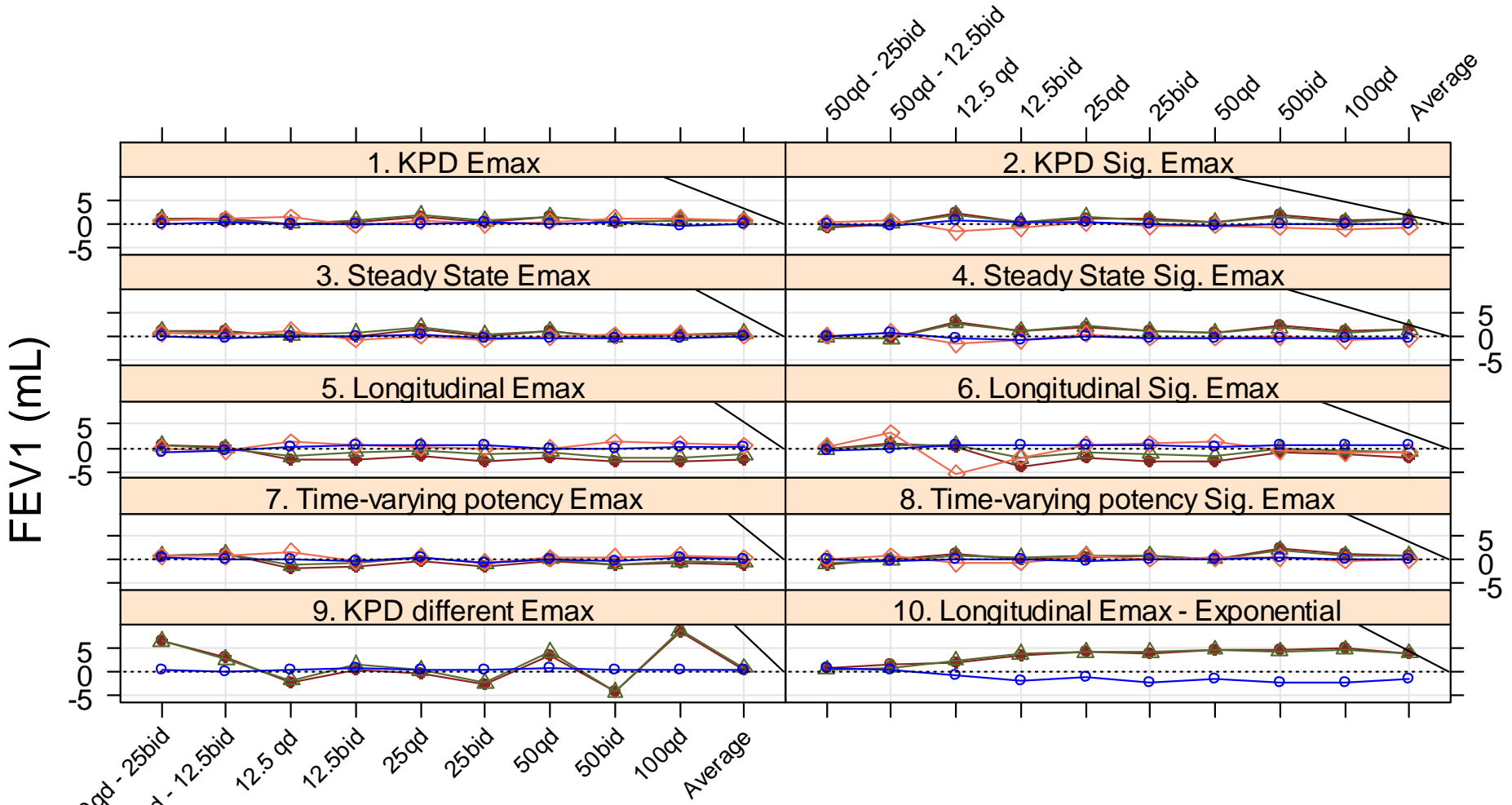
For each scenario, 5000 datasets were simulated with parameter values generated from distributions to represent current state of knowledge



Evaluation of analysis methodology

Mean bias across scenarios

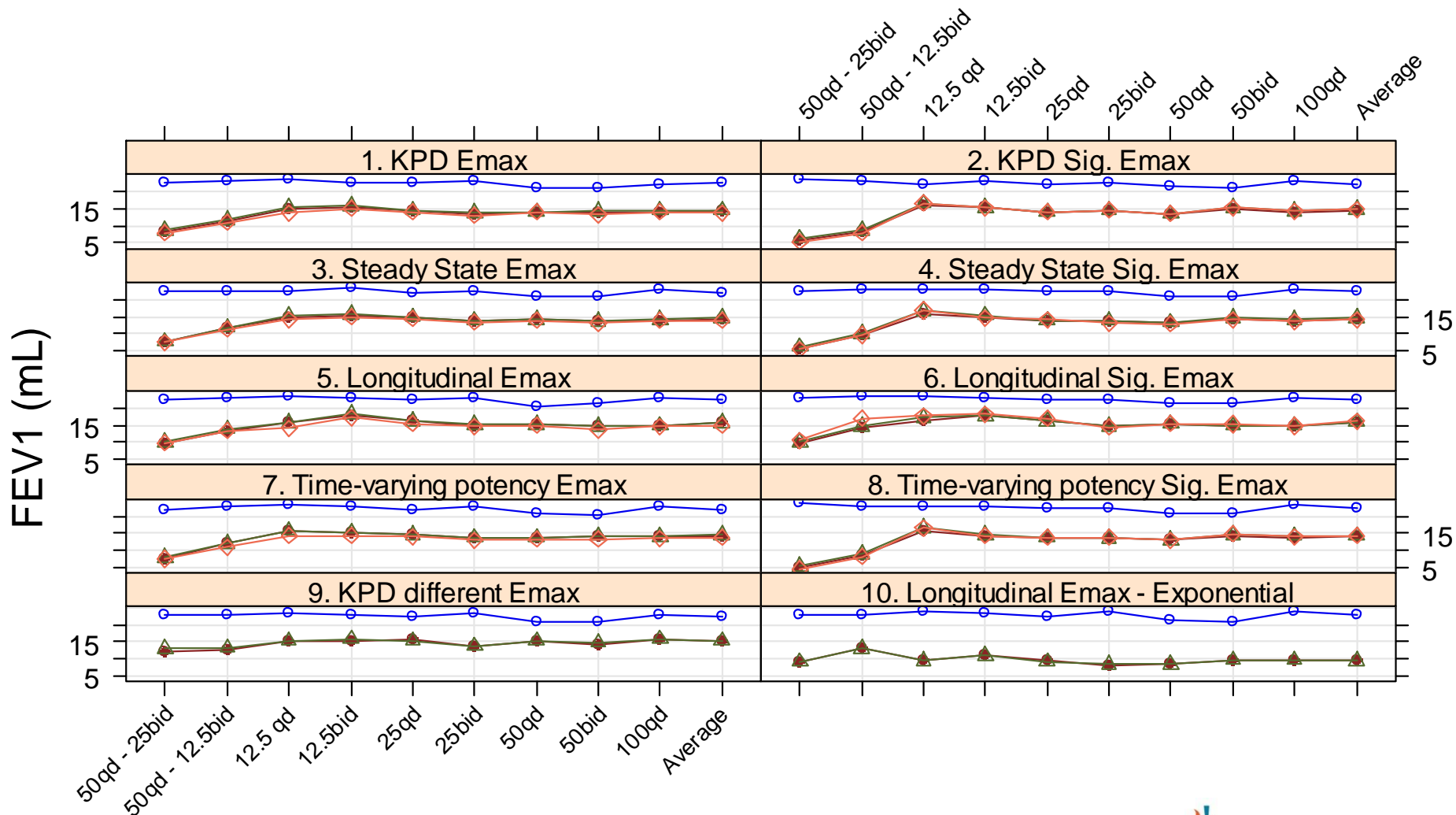
● Model averaging
 △ BIC selection
 ◇ True Model
 ○ ANCOVA



Evaluation of analysis methodology

Median absolute deviation (MAD) across scenarios

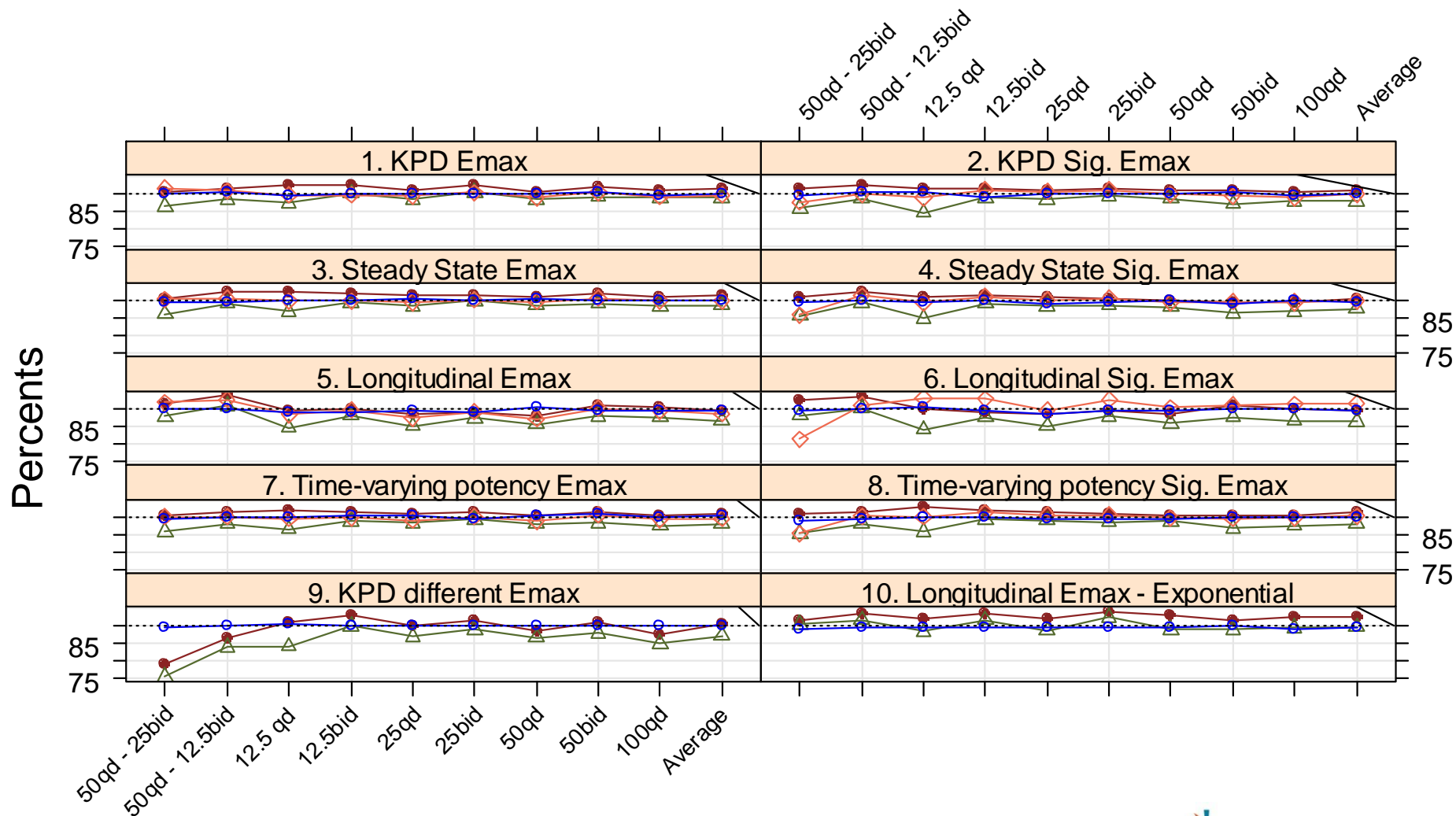
◆ Model averaging
 △ BIC selection
 ◇ True Model
 ○ ANCOVA



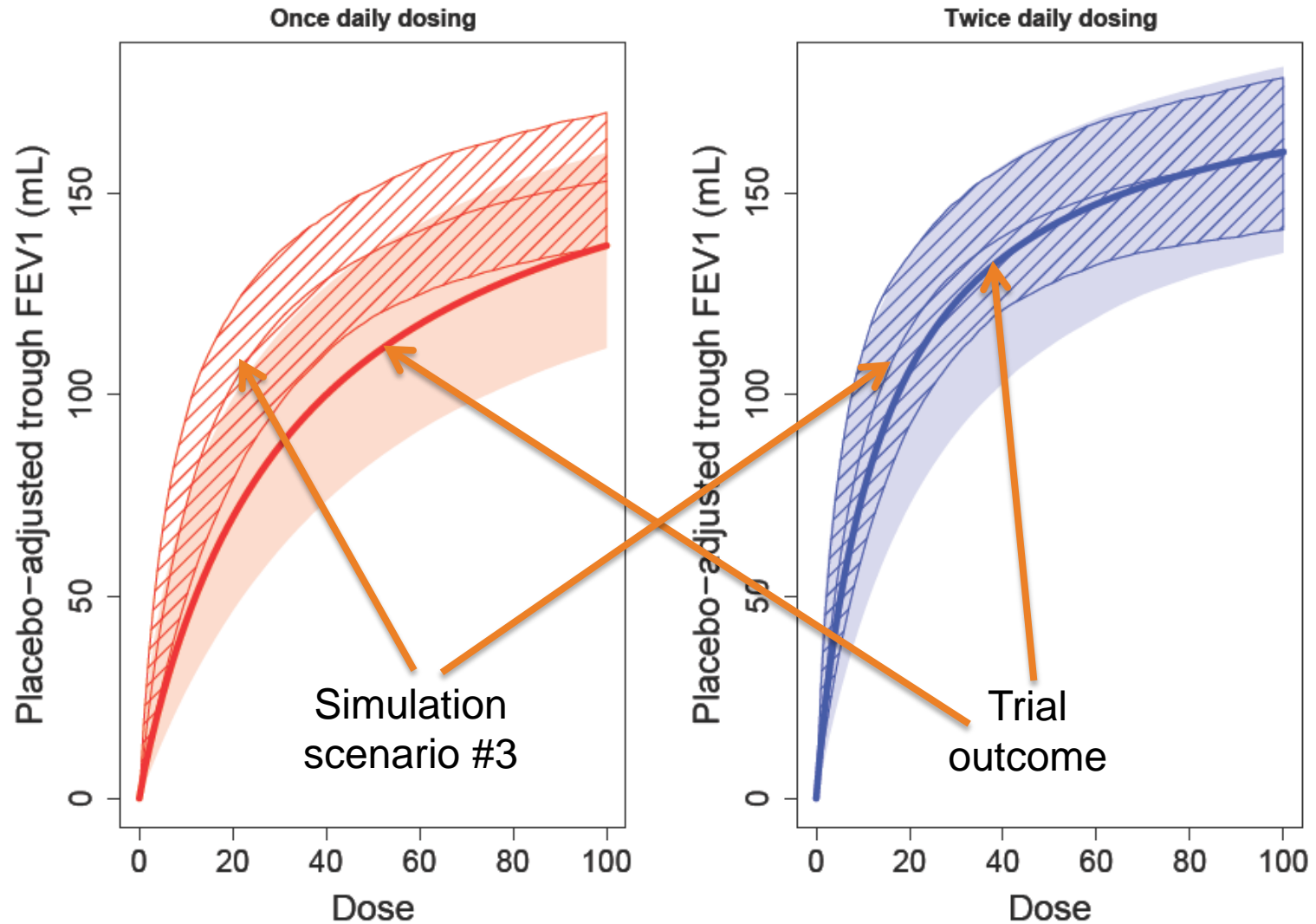
Evaluation of analysis methodology

Coverage probability of 90% CI across scenarios

● Model averaging
 △ BIC selection
 ◇ True Model
 ○ ANCOVA



How well could we anticipate the trial outcome ?



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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