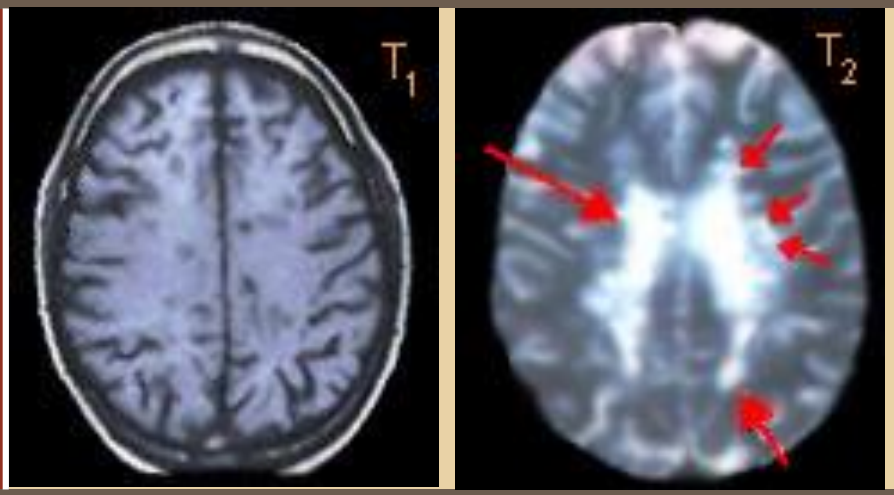


Adaptive Dose-Ranging Study in Multiple Sclerosis

F. Mercier, Novartis (M&S)

J. Pinheiro, Johnson & Johnson (Adaptive design)

07-Oct-2010

Outline

- Clinical setting
- Methodological challenges
- Simulations
- Conclusions

Clinical setting

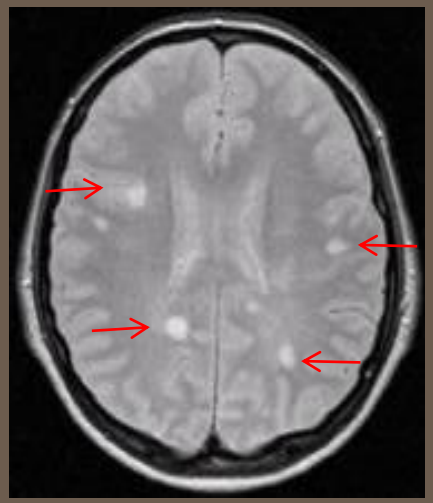
- MS is a chronic dysimmune inflammatory disease of the CNS, affecting up to 2.5 million people worldwide (~400,000 US), mainly young adults; women are affected twice as often as men
- Disease has profound effects on an individual's daily activities
  - Cognitive and physical disability associated to relapses and progression lead to severe limitations related to work and social functioning
  - Within 15 years of onset, if untreated, 50% will require aids for ambulation or worse
- Marketed compounds: IFN, GA, Mitox., Nataliz.; Increasing number of effective therapy choices (Fingolimod, Cladribine, x-umab)
- Need to sharpen the dose-exposure-response characterization to optimize the strategy of ph3 trials,
- Need to minimize exposure to placebo

Clinical setting

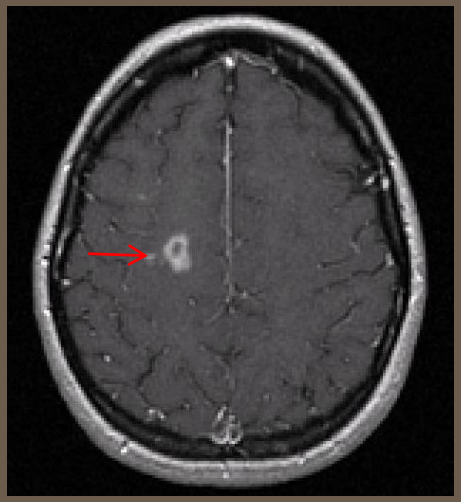
Challenges in assessing efficacy in ph2 MS trials

- In typical ph2 study in RRMS, the primary clinical endpoint is the change in lesion pattern of the CNS detected by magnetic resonance imaging (MRI)

Hyperintense T_2-weighted lesions



Gd-enhanced T_1-weighted lesions



- Such changes serve as basis for study design (dose, N, duration, population)

Clinical setting
Key efficacy questions

1. Test for the presence of a dose response signal
2. Determine if clinical relevant effect can be achieved within available dose range (i.e., is there a dose with an appropriate clinical response?)
3. Select dose(s) for ph3 program (with measure of precision/confidence)
4. Develop model to represent dose-response (DR) signal and estimate DR profile

Purpose and rationale:

The purpose of this study is to determine the dose-response curve for the MRI-based efficacy of [redacted] compared with placebo in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), and to characterize its safety and tolerability (including effects on blood pressure) for the selection of an optimal dose in a later phase III study.

Objectives:

Primary objective

The primary objective of this study is to evaluate the dose response relationship among five doses of [redacted] and placebo during 3 months of treatment in patients with RRMS, as measured by the number of combined unique active [MRI] lesions (CUAL).

Methodological challenges

A. Primary endpoint, number of new Gd-enhanced and new/newly enlarged T2 lesions is a count variable: traditional statistical analysis methods (e.g., ANCOVA model) can not be used

B. Longitudinal measurements on each patient – need to model dose and time response

C. Unknown DR shape for primary endpoint – model uncertainty

D. Unclear what dose range is more informative for learning about DR

E. Need to make decision on continuing/stopping trial based on interim data (stop for futility)

Methodological challenges

A+B

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Methodological challenges

Modeling count endpoint

- Negative binomial (NB) regression model used to describe monthly counts (new GdE + new/newly enlarged T2 lesions)
- NB model parameterized by mean lesion count (i.e., expected number of new lesions) and dispersion parameter
- Dose and time response represented in NB model:

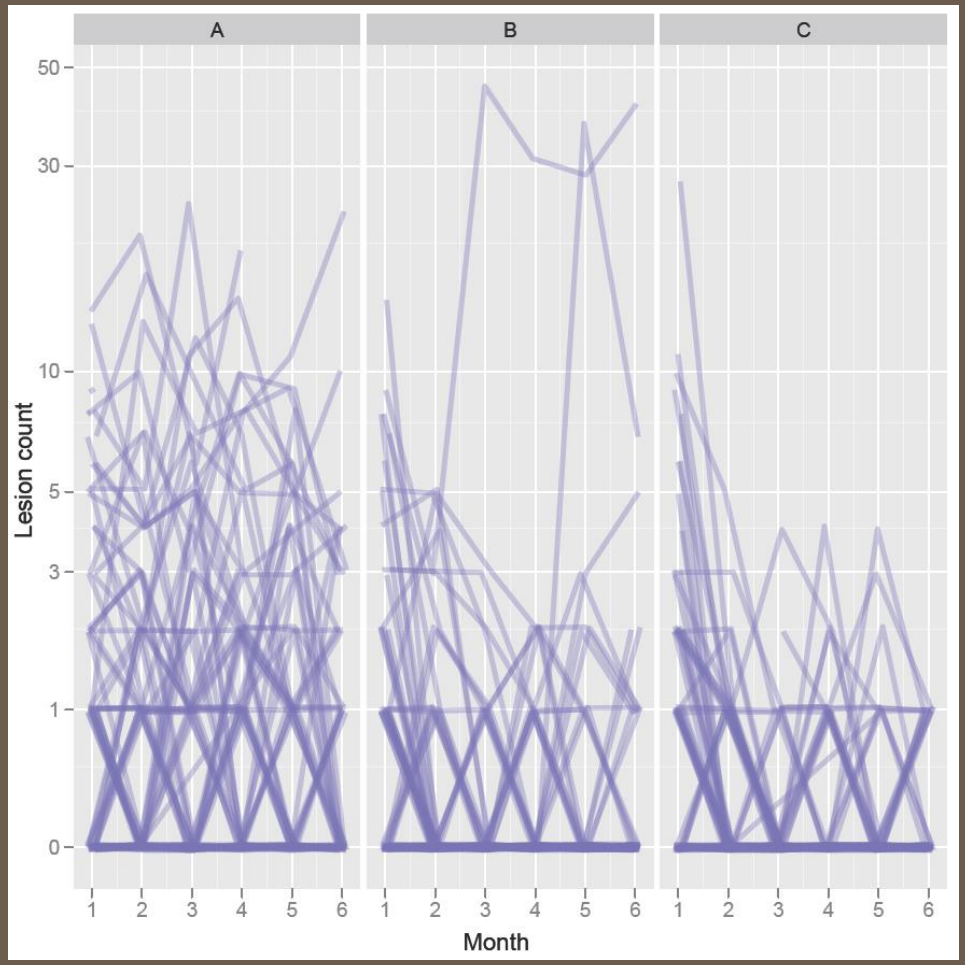
$$\log(\text{count}) = \mu(\text{dose}) + \beta \times \text{time}$$

  - time assumed to have linear effect on log(count) – based on modeling of previous compound in same class
  - dose response model represented by μ(dose) – multiplicative effect in original scale (can be interpreted as % reduction in lesion count)
- Uncertainty *a-priori* about shape of μ(dose)

Methodological challenges

Time course of lesion count

- Individual time profiles of new GdE lesion count from previous compound in same class



Methodological challenges
C+D

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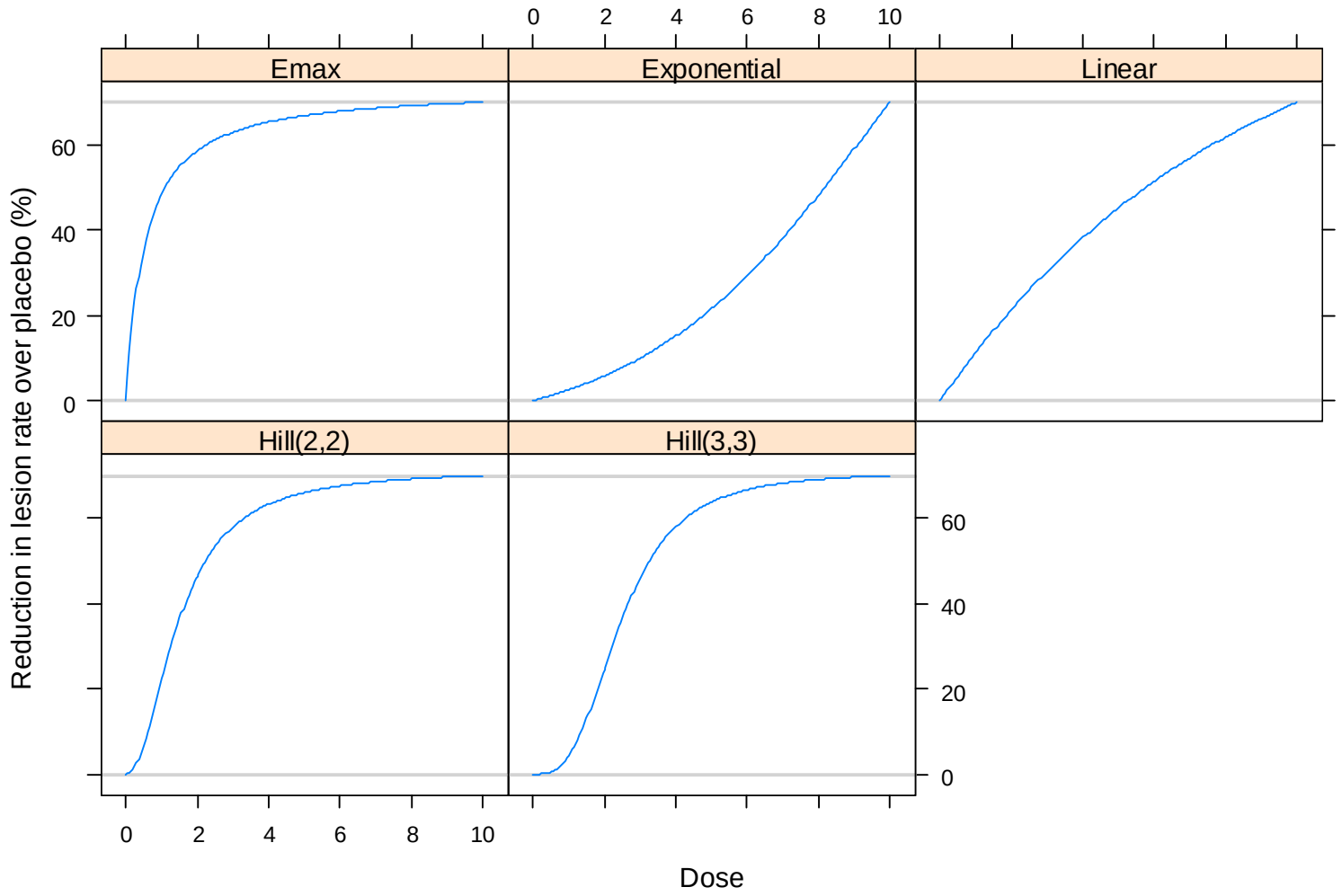
Methodological challenges
MCP-Mod approach

- Combination of multiple comparison procedure (MCP) and modeling (Mod) for
  i. testing DR signal,
  ii. estimating DR model
  iii. selecting appropriate dose for ph3
- Incorporates model uncertainty by using set of candidate DR models, instead of assuming DR shape known *a-priori*
- DR signal tested via contrast tests derived from candidate models – correcting for multiplicity
- If DR signal significant, “best” model (among candidate DR models) representing observed data is selected and fitted to data,
- Final model is used to estimate target doses (i.e., producing a desired clinical effect)
- Original MCP-Mod developed for normal response – needed to be adapted to longitudinal count data for this study

Methodological challenges

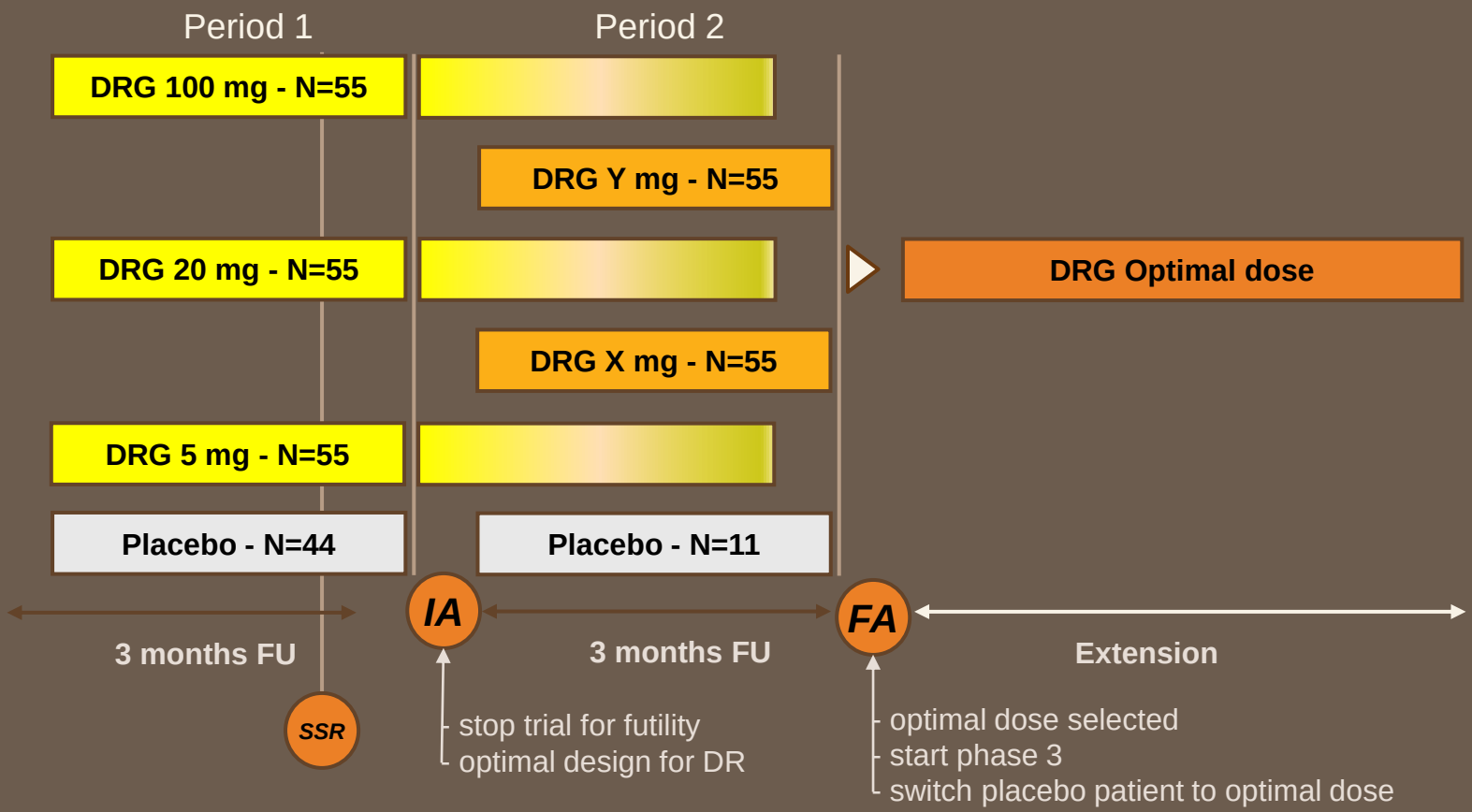
Candidate DR models considered



Methodological challenges

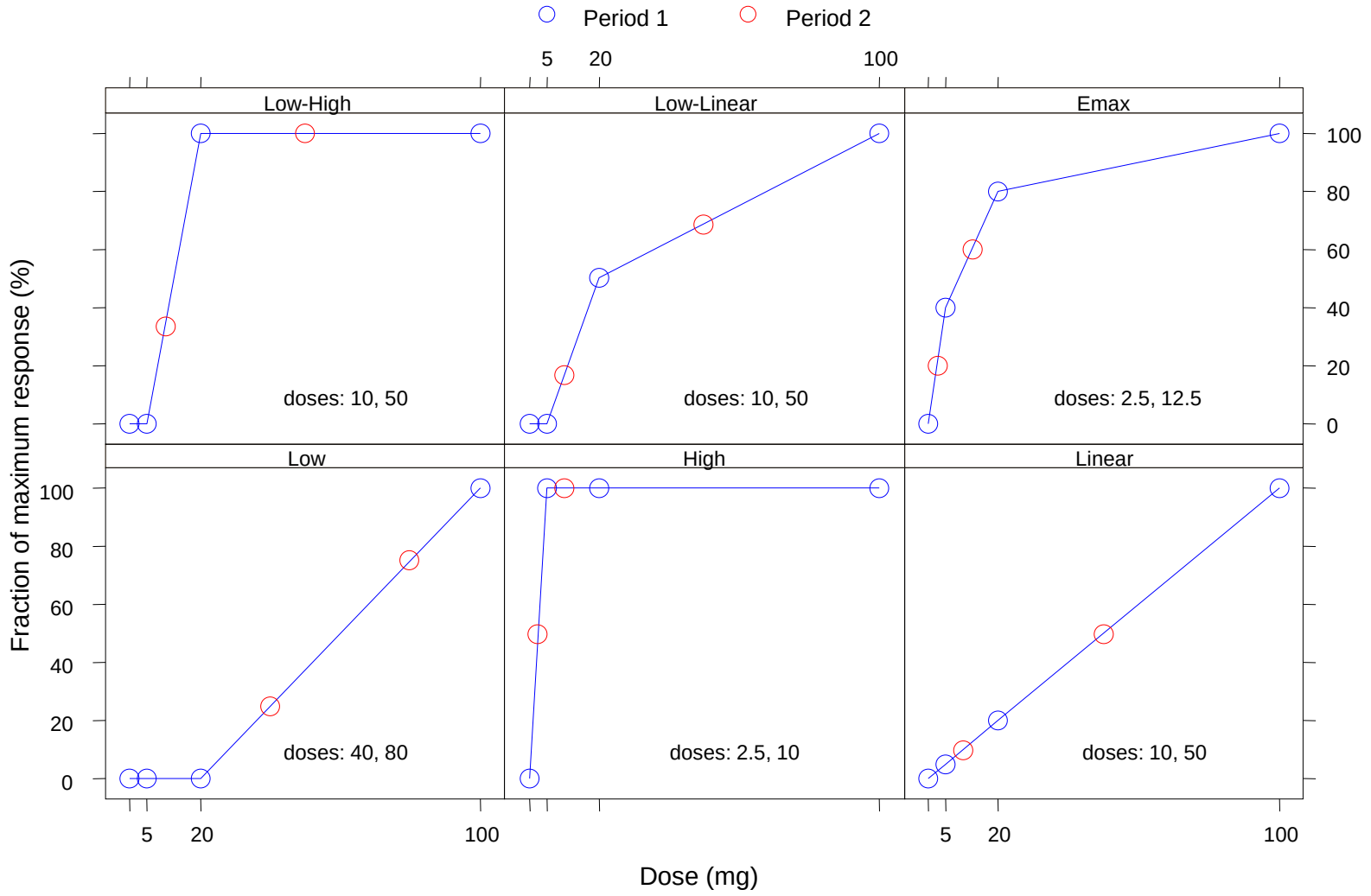
Adaptive dose-ranging study design

- Motivation: learn about DR from data in Period 1 and select most informative doses for Period 2 at interim analysis (IA)



Methodological challenges

Decision rule for dose to introduce in Period 2



Methodological challenges
E

A. Primary endpoint, number of new Gd-enhanced and new/newly enlarged T2 lesions is a count variable: traditional statistical analysis methods (e.g., ANCOVA model) can not be used

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D. Unclear what dose range is more informative for learning about DR

E. Need to make decision on continuing/stopping trial based on interim data (stop for futility)

Methodological challenges
Futility rule

- Motivation: allow stopping at IA after Period 1, if highly unlikely that clinically relevant response will be attained
- Bayesian rule used: stop trial if $p(\exp(\mu_x)/\exp(\mu_0)<0.65)<0.20$, for any dose $x>0$.
- Simulations used to evaluate operational characteristics of futility rule (and to define probability and effect thresholds)
- Small reduction in power for clinically relevant effects and over 50% chance of stopping when no DR effect present

Methodological challenges

Sample size reassessment

- Motivation: Allow assessment of assumptions regarding NB parameters (derived from analysis of lesion counts with previous compound in same class) utilized in sample size calculation
- Sample size re-calculated on the basis of revised NB parameter estimates (μ_0, β, θ) derived from observed month-2 data for Period 1 patients
- SSR requires unblinding data (for fitting NB model), but is based on parameters with no information about treatment effect (placebo rate and overdispersion)
- If the parameter estimates suggest a power<80% under any of the candidate models, N per group (for both Period 1 and 2) is then increased in order to ensure a minimum power of 80% (up to an extra 20 patients/arm)

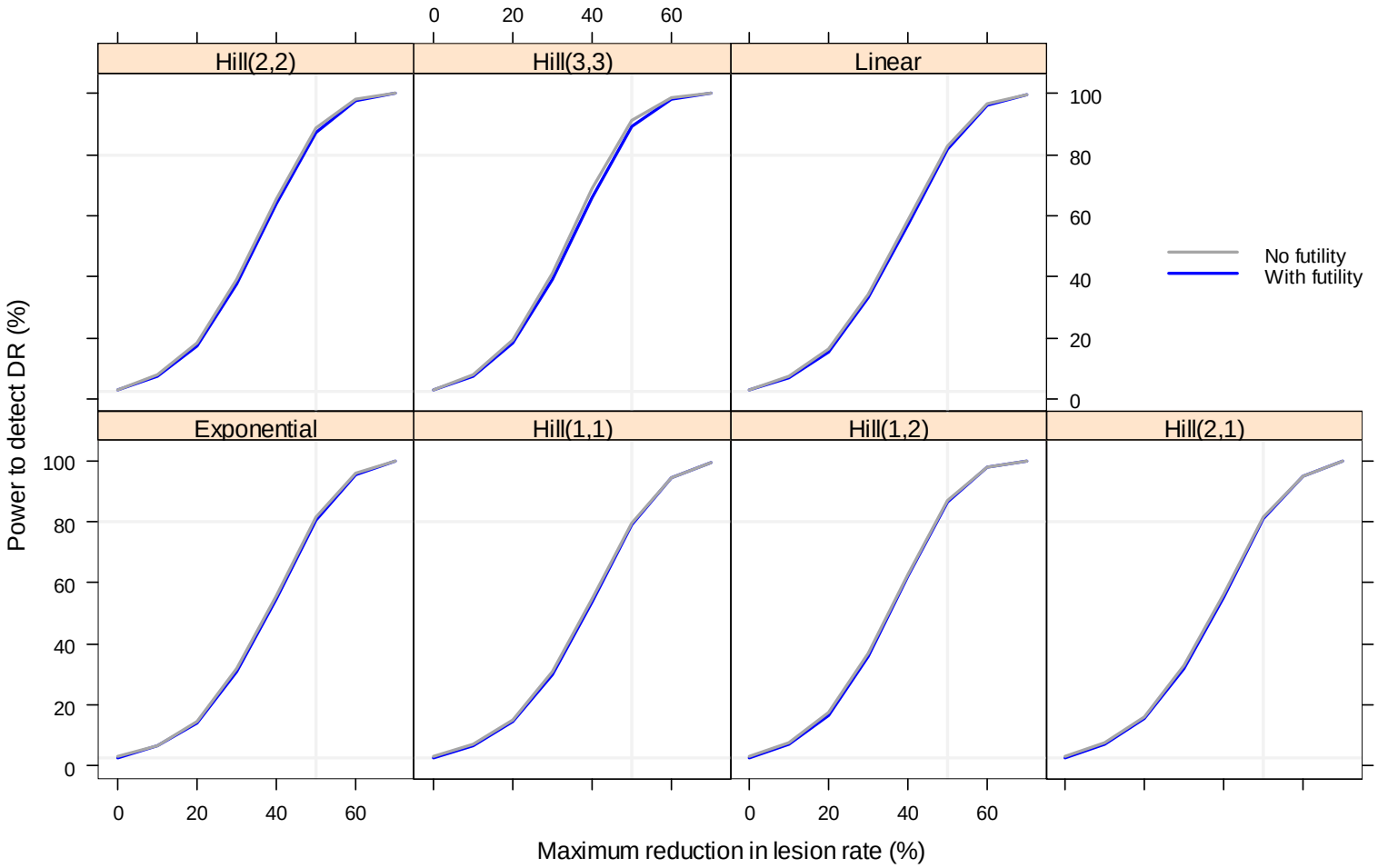
Simulations to support study design

Plan

- Evaluate operational characteristics of design and analysis methods, including:
  - power to detect DR signal
  - precision of target dose estimate
  - precision of target response at estimated dose
- Decisions to take: adaptive vs. non-adaptive, Period 1 vs. Period 2 doses, sample size, and calibrate rules (e.g., thresholds for futility rule)
- Different scenarios: DR models (including models not in candidate set), max reduction in lesion rate (up to 70%), drop-out rate (5, 7, and 10%)
- 10,000 simulated trials for each scenario

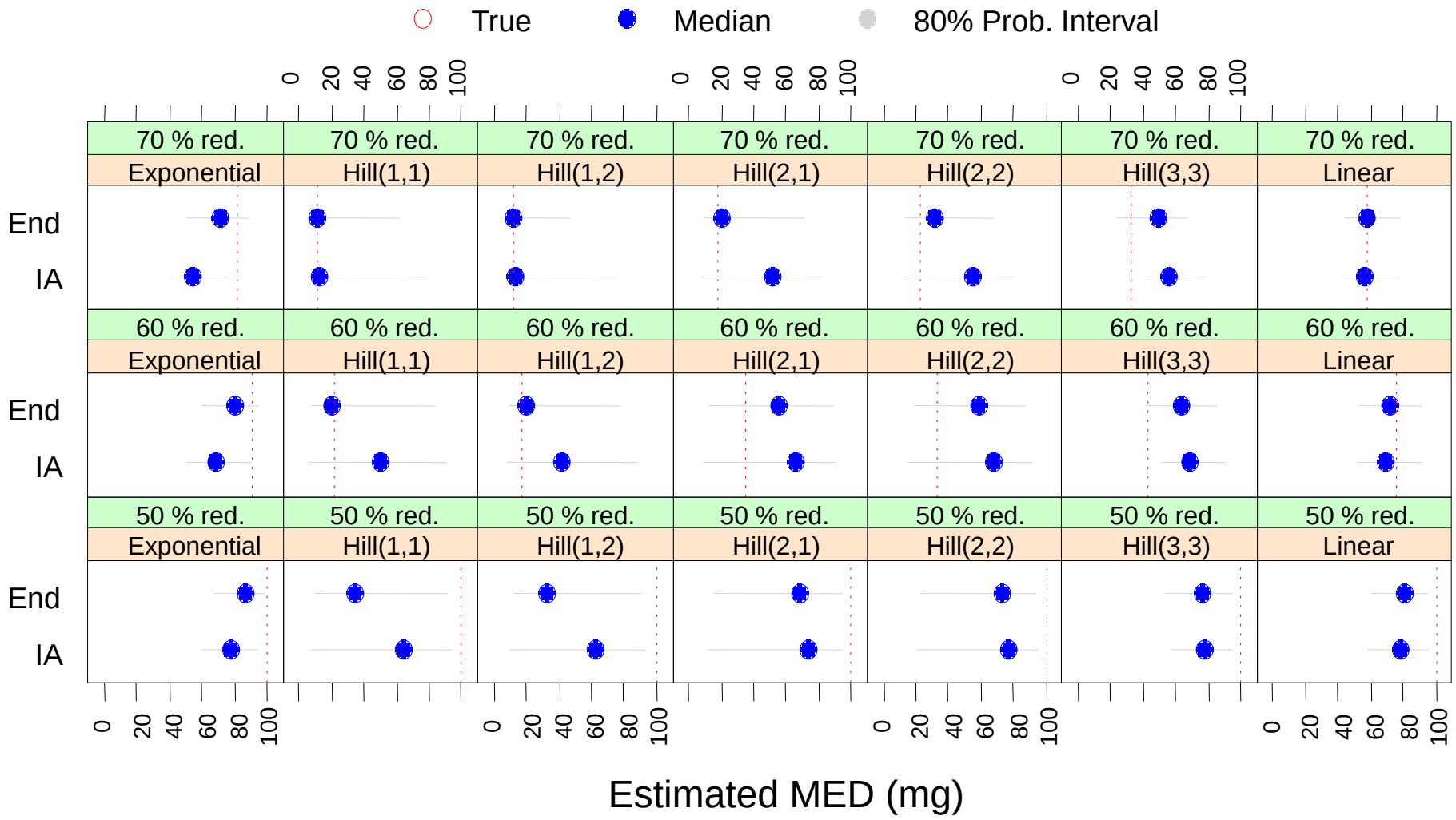
Simulations to support study design

Power to detect DR



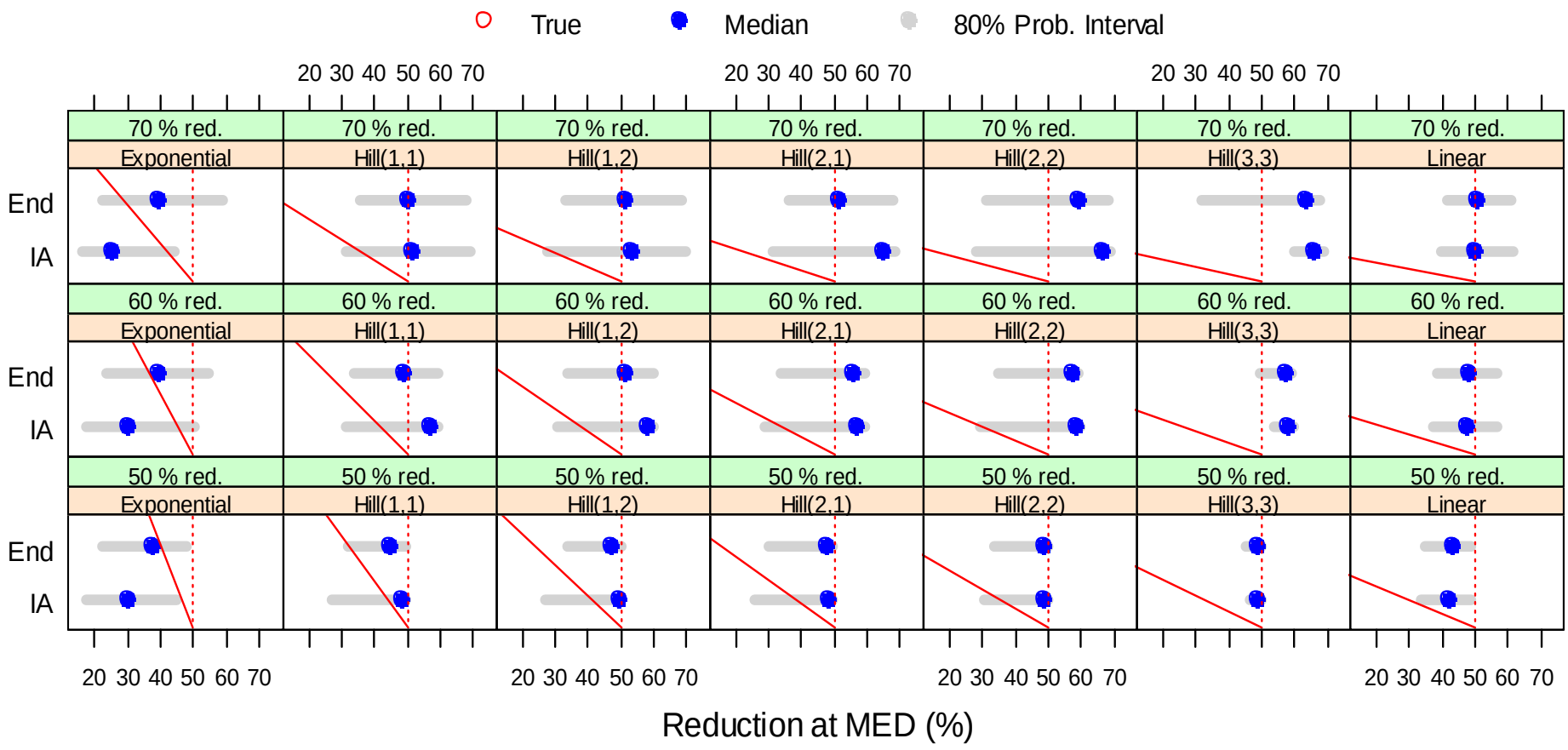
Simulations to support study design

Precision of MED – 50% target reduction



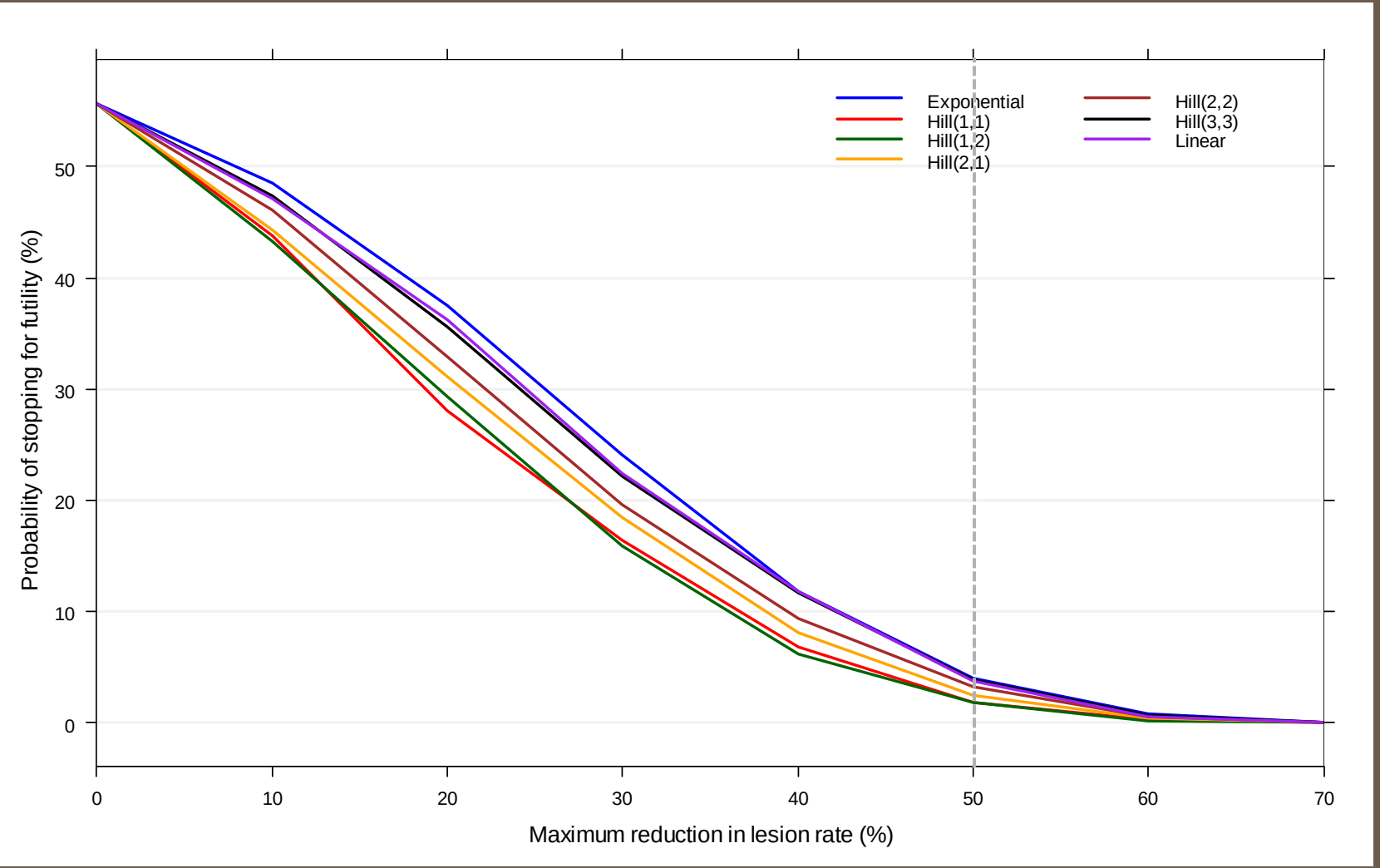
Simulations to support study design

Response @ MED – 50% target reduction



Simulations to support study design

Probability of stopping for futility



Conclusion

- Short, small and efficient adaptive dose-ranging trial design to test DR signal and select appropriate dose for phase 3
- Adaptive design allows to focus dose range on more informative region of DR, learning from interim data
- Futility rule let study be stopped if it appears to be unlikely that the compound works – prevents unnecessary exposure of patients to drug
- MCP-Mod handles uncertainty about DR shape
- Technical difficulties associated with analysis of count data have been overcome via Negative Binomial model
- Benefit from experience and data from previous compound in the same class
- Excellent collaboration with clinical team

Acknowledgements

- David Ohlssen, Erika Rochotte, from Novartis - Statistics
- Olivier Luttringer from Novartis - Modeling and Simulation
- Erik Wallstroem, Frank Dahlke from the Novartis - Clinical Neuroscience

BACK-UP

Why still a placebo ?

- To provide a clear efficacy, safety and tolerability profile
- To control for regression to the mean effects, alternating periods of disease activity/inactivity and placebo effects,
- To simplify comparisons across trials