Dose finding – is it optimal?

Alun Bedding, Principal Statistical Scientist, Roche Products UK

Why do we look at Dose Response?

Motivating Example

Comparison of Designs – Example

Summary and Conclusions

Dose Response/Finding is done badly in the Pharmaceutical Industry

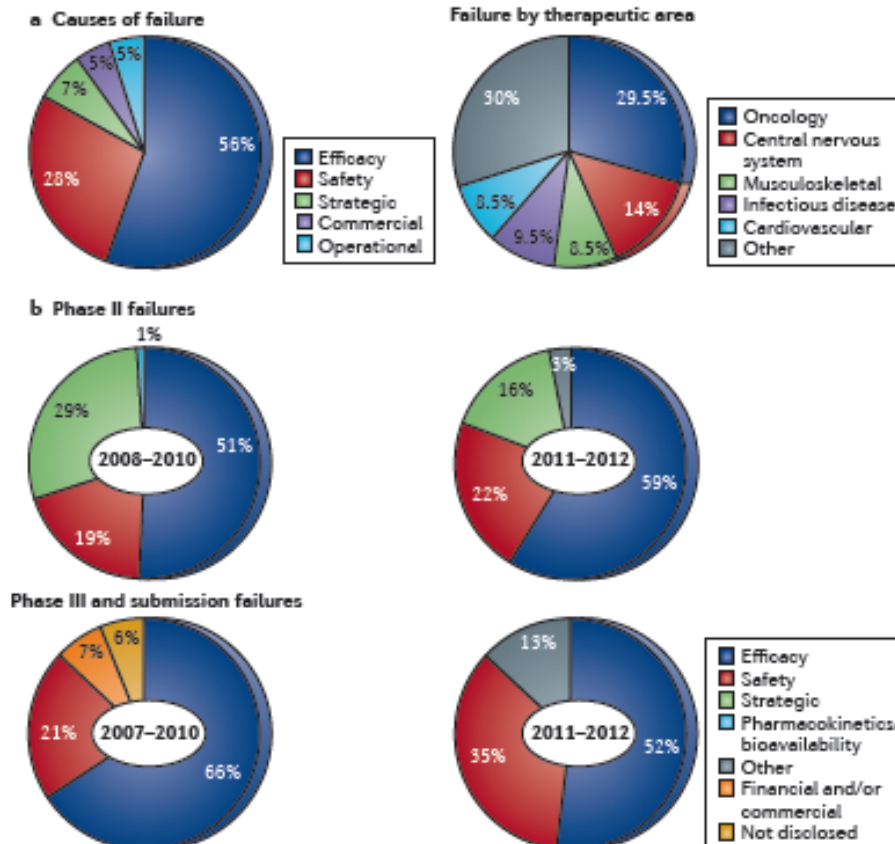# Start with some numbers – lack of efficacy remains the main reason for development failure

Figure 1 | **Trends in attrition rates.** **a** | Of the 148 failures between Phase II and submission in 2011 and 2012, reasons were reported for 105; the majority of failures were due to lack of efficacy, as shown on the left. On the right, the 105 reported failures are broken down according to therapeutic area. **b** | Comparison of the reasons for failures in Phase II and Phase III trials in 2011 and 2012 with those in earlier periods that we reported previously (see main text for details). Data are from Thomson Reuters, *Drugs of Today* © Prous Science S.A.

Arrowsmith & Miller,
Nature Rev Drug Disc
2013;12:569

Why do we look at Dose Response?

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- Knowledge of dose response relationships is important in establishing safe and effective drugs.

- From ICH E4 - Dose-Response Information to Support Drug Registration (1994)

  - Purpose of Dose Response is to have knowledge of the relationships among dose, drug concentration and clinical response

- Could you answer the question "How do you know that lower doses are just as effective and safe?"

What are some of the consequences of poor dose choice?

- 20% of post approval changes are to dose (and this does not include those which have dosage changes whilst in Phase 3)

- This is mainly related to efficacy but could also be related to safety.

- Historically, there have been examples where the dose chosen has turned out to be too high sometimes with adverse consequences (e.g. hypokalemia and other metabolic disturbances with thiazide-type diuretics in hypertension).

- Poor dose finding early on in development could lead to the need for dose finding in a confirmatory study – i.e. take two active doses into Phase 3 and drop one at an interim

- Better to understand as much as possible before going confirmatory – this includes knowledge of the shape and location of the dose response curve.

What Does Knowledge of the Dose Response Curve Give Us?

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- The optimum dose – the dose which best addresses the objectives

- The minimal effective dose

- The dose producing the maximum effect

- Allows for adjustment of doses beyond what dose would there be no benefit or be unsafe

- Allows us to understand the therapeutic window
  - For this we need knowledge of DR for both desirable and undesirable effects

Dose Response Curve
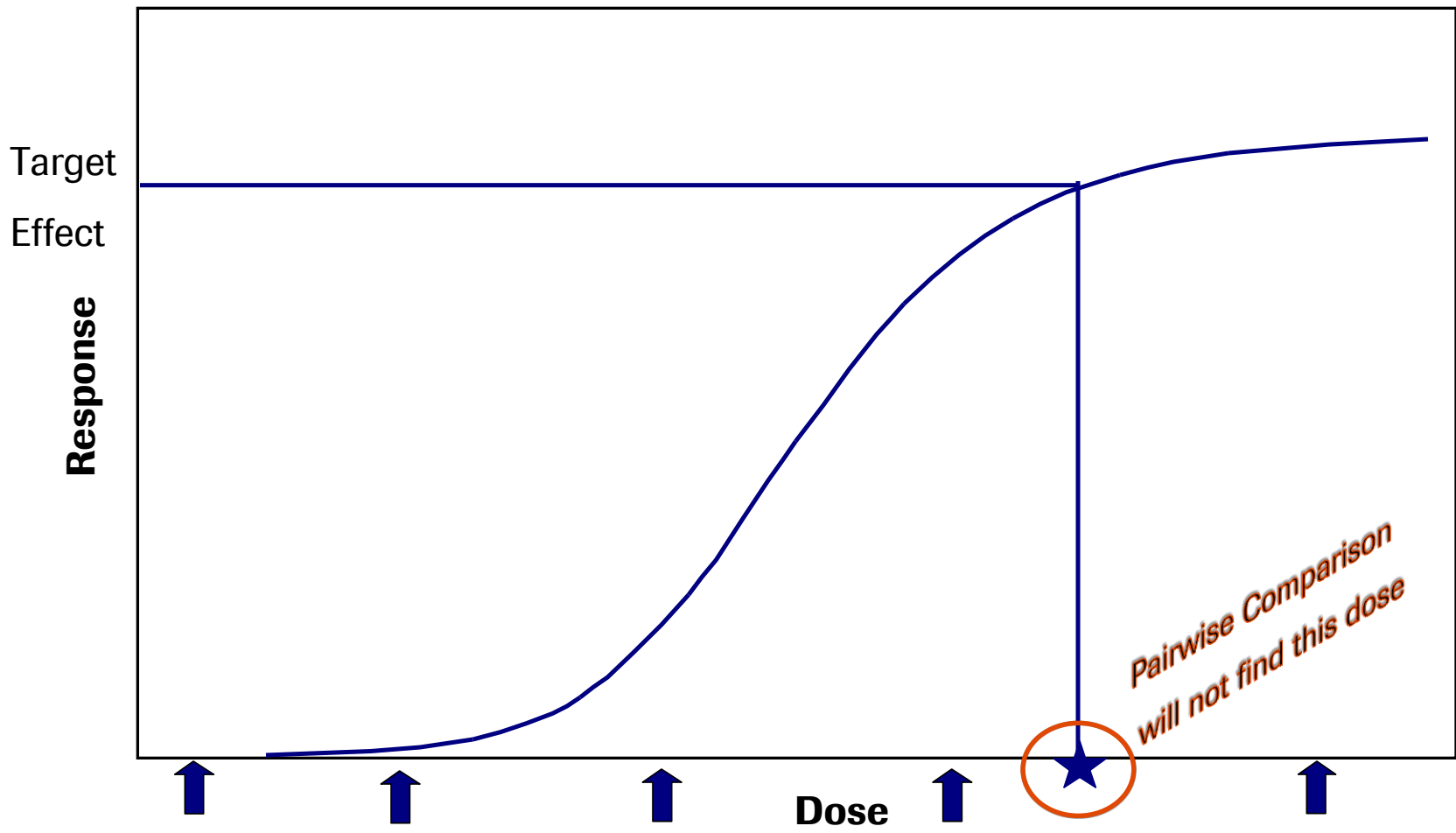
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Taylor & Francis
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AN ADAPTIVE OPTIMAL DESIGN FOR THE E_{max} MODEL AND ITS APPLICATION IN CLINICAL TRIALS

Sergei Leonov[1] and Sam Miller[2]

[1]GlaxoSmithKline Pharmaceuticals, Research Statistics Unit, Collegeville, Pennsylvania, USA
[2]GlaxoSmithKline Pharmaceuticals, Drug Development Sciences, Harlow, UK

A project team working on a compound to treat Alzheimer's disease is carrying out a first-time-in-human dose-escalation study in patients. The team wished to maximize the efficiency of the study by using doses targeted at maximizing information about the dose-response relationship within certain safety constraints. We have developed an adaptive optimal design tool to recommend doses when the response follows an E_{max} model, with functionality for pretrial simulation and in-stream analysis. We present the results of a simulation to investigate the operating characteristics of the applied algorithm.

First Time in Human Study in Alzheimer's Patients

- Objective was to evaluate safety, tolerability, PK, PD and immunogenicity

- Single dose, single blind, parallel group

- Traditional dose escalation design would have equally spaced ascending doses

- Aim to determine the dose that "inhibits" plasma biomarker

- Inhibition = Percentage decrease in the biomarker at day 21 post-dose compared with baseline (pre-dose)

    - $100 * (B_{pre} - B_{post}) / B_{pre}$

- Used to adaptively guide dose escalation (in conjunction with safety, tolerability and pharmacokinetic endpoint)

Modelled inhibition over time

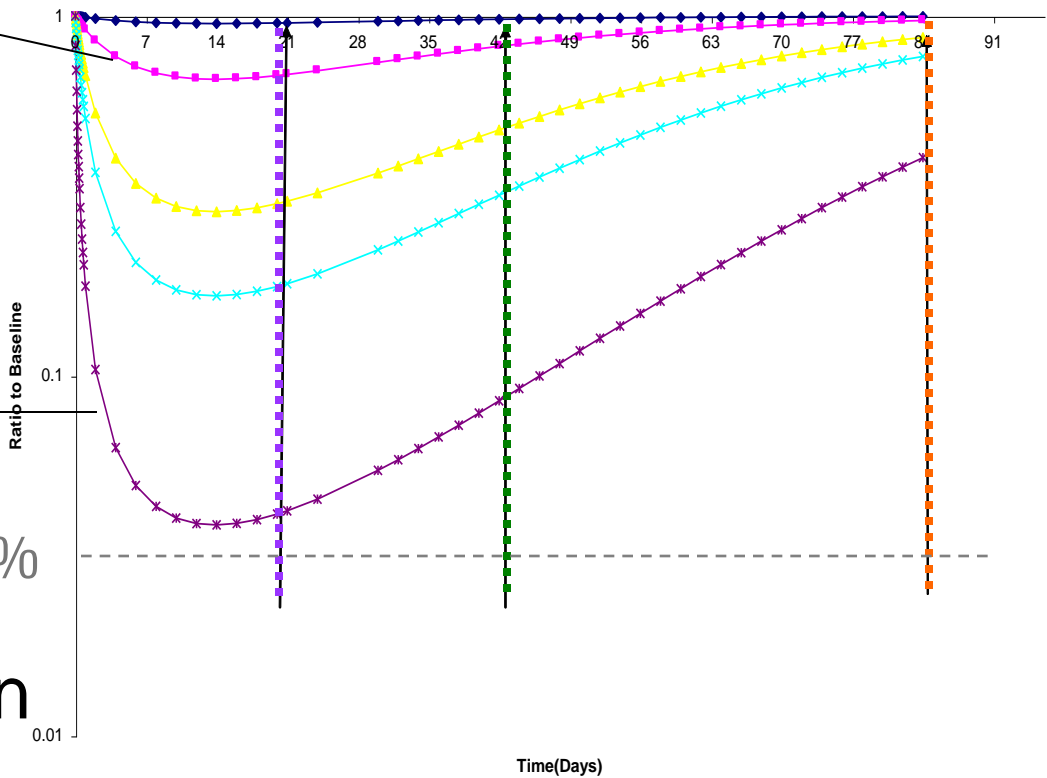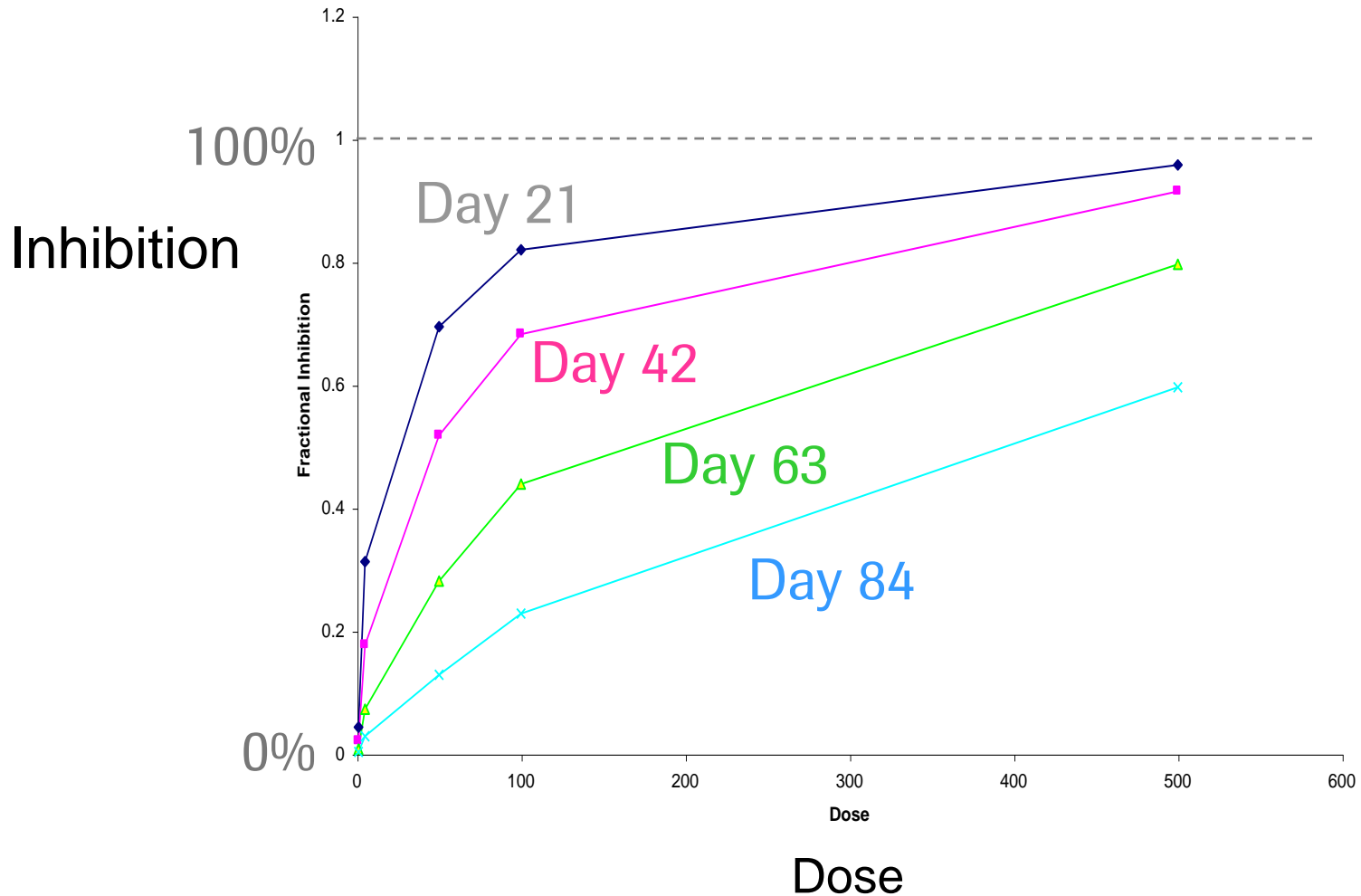# Modelled inhibition as function of dose

Simulated Inhibition as function of dose: Emax model
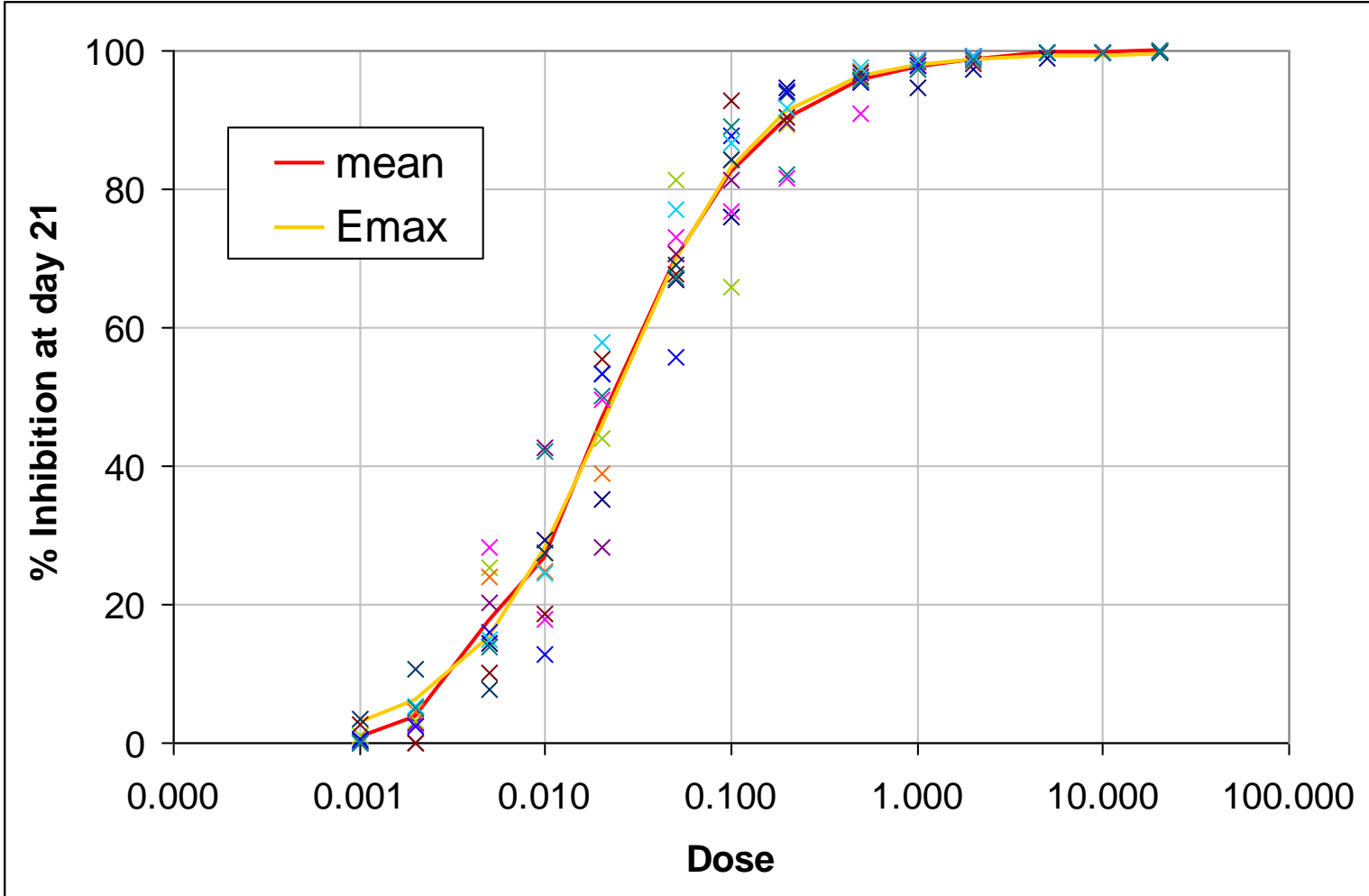
Doses

- Dose range
  - Defined using animal studies
  - Dose for the first cohort: 0.001
  - Maximum dose: 20

- Doses for subsequent cohorts
  - May be altered based on accumulating data (subject to limits)
    » 10-fold while dose has "small PD effect"
    » 5-fold once a PD effect is observed
  - Nominal doses to use as defaults if necessary
    – 0.001, 0.005, 0.02, 0.08, 0.4, 2, 10 and 20

Model

Measurements: $Y_i = f(d_i, \beta) + \varepsilon_i$, $i = 1, \ldots, N$

- f – response function:

$$f(d, \beta) = \frac{E_{max}\, d^{\gamma}}{ED_{50}^{\gamma} + d^{\gamma}} = \frac{E_{max}}{1 + (ED_{50}/d)^{\gamma}}$$

- d_i – dose for patient i, N - number of patients

- Response parameters $\beta = (E_{max}, ED_{50}, \gamma)$:
  - E_{max}: maximal response (limit as dose increases)
  - ED_{50}: dose at which the response is half of E_{max}
  - γ: slope parameter (how steep/flat the curve is)

Model **(cont.)**

- Errors: Gaussian i.i.d. ε_i with zero mean

- Variance models (with additive and multiplicative components)
  - $S = \text{Var } \varepsilon_i = \sigma^2_A + \sigma^2_M \, f_i, \;\; f_i = f(d_i, \beta)$
  - (variance increases with dose)
  - $S = \sigma^2_A + \sigma^2_M \, f_i \, (E_{max} - f_i)$
  - (variance is the largest in the middle near ED_{50})

- $\theta = (E_{max}, ED_{50}, \gamma; \; \sigma^2_A, \sigma^2_M)$: combined vector of parameters

Goal

Find dose ED_{90} which attains 90% of max response

- Interplay of model-based design and estimation techniques

- Optimal design: search for doses that allow for "best" estimation of:

  - All model parameters → D-criterion, det [Var(θ)]

  - Dose ED_{90} → C-criterion, Var(ED_{90})

- For each cohort, search for "optimal" doses given current estimates of model parameters → adaptive approach

  Box and Hunter (1965), Fedorov and Leonov (2005)

Applying this more widely

- Could we apply this in a different dose finding scenario?

- Could it be used with MCPMOD?

- Could it be used in an adaptive trial?

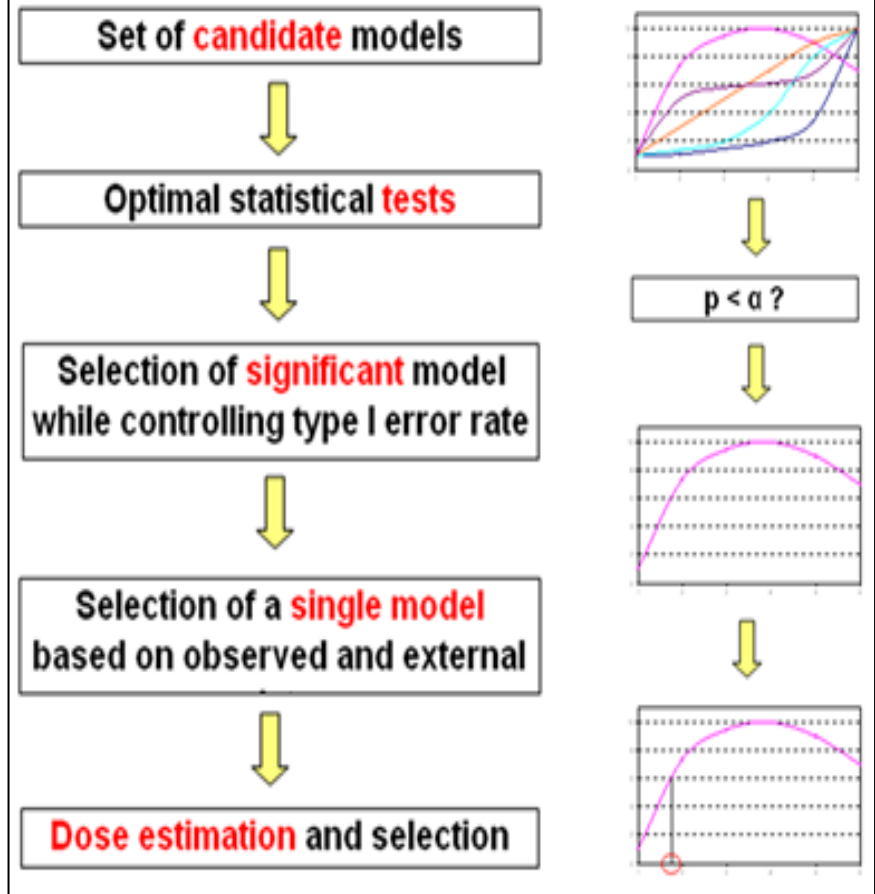- How could it be used in an adaptive trial?

A Word About MCPMOD

European Medicines Agency — SCIENCE MEDICINES HEALTH

23 January 2014
EMA/CHMP/SAWP/757052/2013
Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

Draft agreed by Scientific Advice Working Party	5 September 2013
Adopted by CHMP for release for consultation	19 September 2013[1]
Start of public consultation	15 October 2013[2]
End of consultation (deadline for comments)	24 November 2013[3]
Adoption by CHMP	23 January 2014

Keywords	Qualification, Dose Finding, Regulatory, Modelling

Set of **candidate** models

↓

Optimal statistical **tests**

↓

Selection of **significant** model while controlling type I error rate

↓

Selection of a **single model** based on observed and external

↓

Dose estimation and selection

$p < \alpha$?

Why do we look at Dose Response?

Motivating Example

Comparison of Designs – Example

Summary and Conclusions

Comparison of Designs - Example

- Simple Example
    - Phase IIb dose finding trial in respiratory
    - Objective – Find the dose that produces an improvement in FEV1 of 130 mL over placebo
    - Five doses levels and placebo
        - 100, 250, 500, 1000, 2000 mg
    - Placebo response assumed to be = 150 mL
    - SD = 400 mL
    - One-sided alpha level of 2.5%
    - Max sample size = 480 (interim at 240)
    - Endpoint available 1 week after dosing
    - Recruitment rate = 4 per week
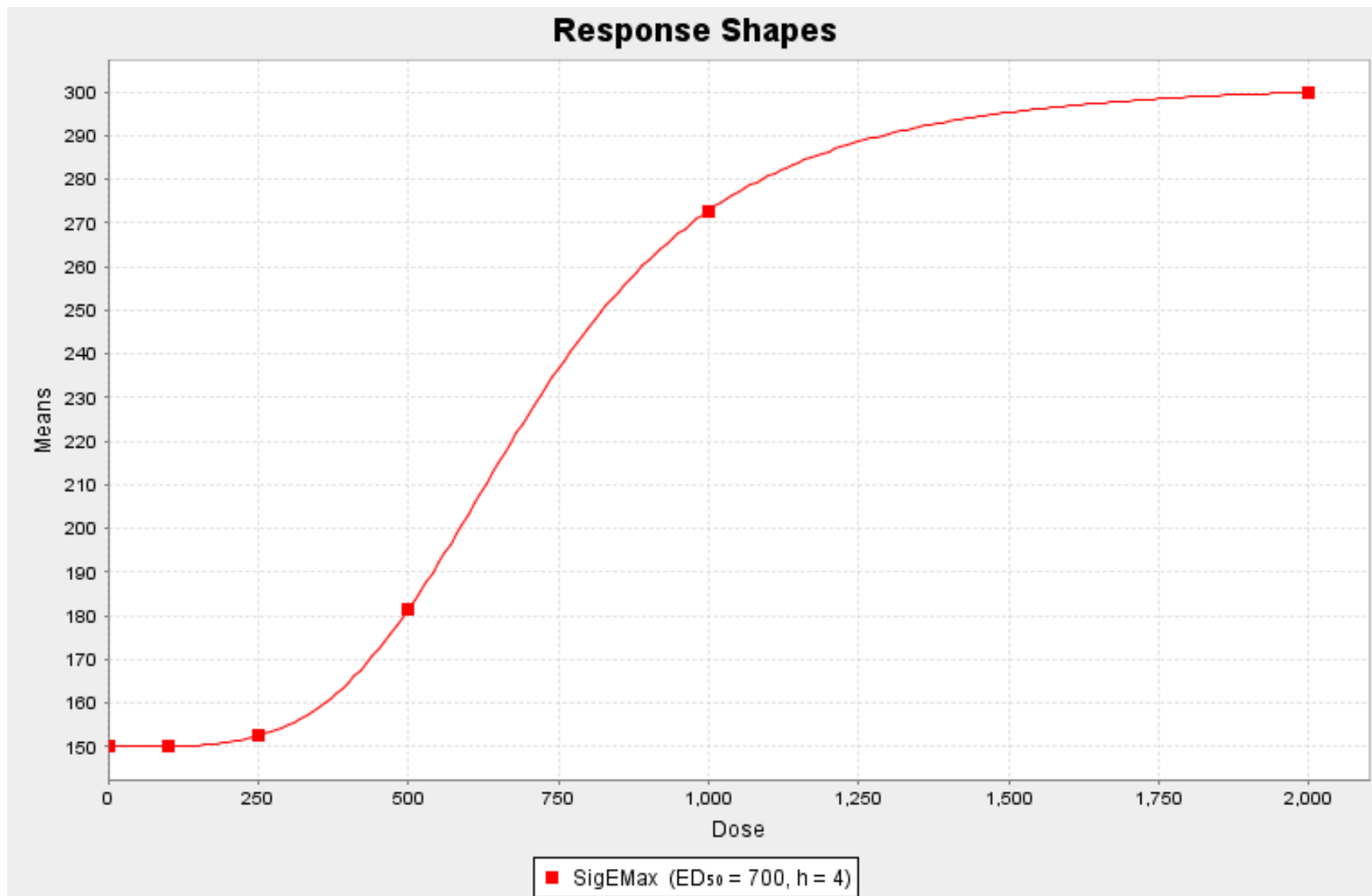
Compare Three Approaches

- MCP-Mod Only
  - No interim and equal randomisation
  - Analysis at the end of the study using MCP-Mod

- Optimal MCP-Mod
  - Interim carried out at 240 subjects and then use D and C Optimality to determine the randomisation of the next subjects
  - Analysis at the end of the study using MCP-Mod (even though you have a good idea of the dose response)

- Adaptive Design – Best Intention
  - Interim carried out at 240 subjects
  - Allocate remaining subjects according to what dose has the highest probability of being the target dose.
  - Analysis at the end Bayesian Pr(delta > 0)

- Then for interest compare to Dunnett contrasts and model based contrasts

Candidate Models for MCP-Mod
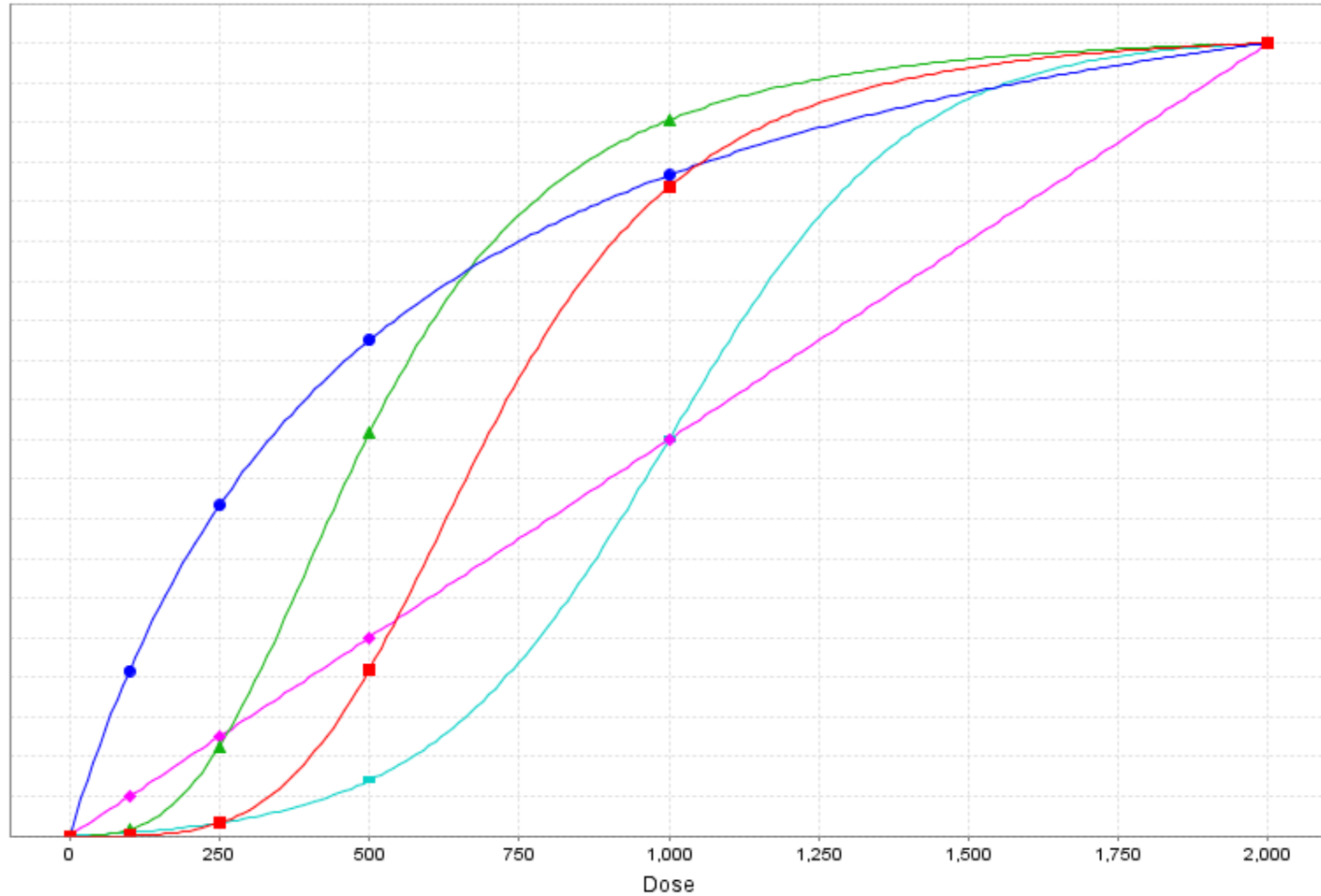
Legend:
- SIG_E_MAX (ED_50 = 700.0, H = 4.0)
- E_MAX (ED_50 = 500.0)
- SIG_E_MAX (ED_50 = 500.0, H = 3.0)
- LINEAR
- LOGISTIC (ED_50 = 1000..., DELTA = 200.0)

X-axis: Dose (0, 250, 500, 750, 1,000, 1,250, 1,500, 1,750, 2,000)

Assumed Response Shape

Response Shapes

Means vs Dose

SigEMax (ED_{50} = 700, h = 4)

Assumed Response Shape

- Sigmoid Emax

  - $E_0 = 150$ (Placebo effect)

  - $E_{max} = 150$ (maximum effect over placebo)

  - $ED_{50} = 700$ (Dose which produces 50% of maximum effect)

  - Hill parameter = 4

Sample Sizes for Each Dose Under the Three Designs – Maximum Sample Size = 480

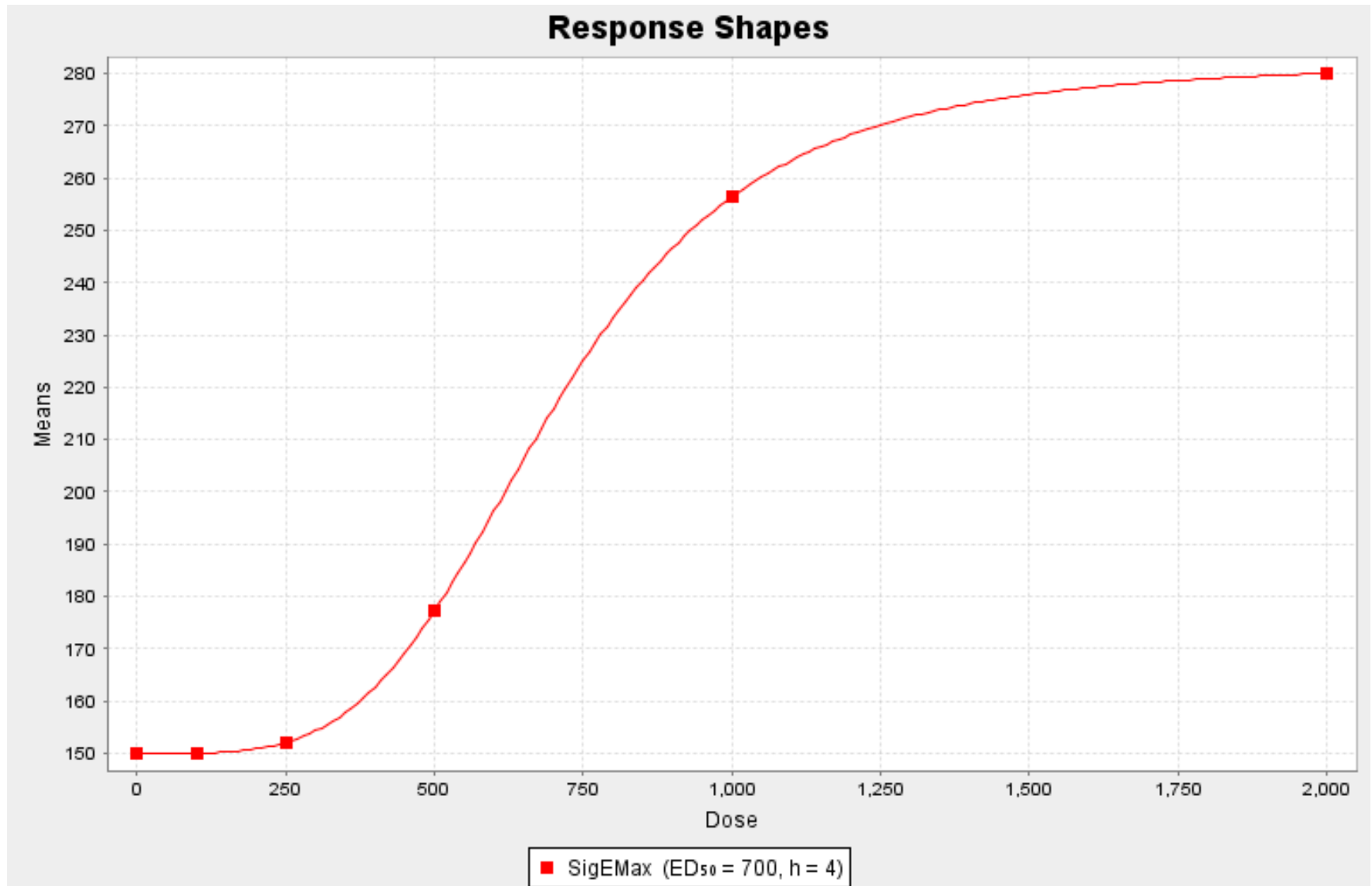| Design	Placebo	100 mg	250 mg	500 mg	1000 mg	2000 mg
MCP-Mod	80	80	80	80	80	80
Optimal MCP-Mod	131	40	40	71	123	75
Best Intention	164	51	41	43	55	126

- Do we want/need equipoise?

- What is our objective in Phase II – find appropriate dose for Phase III and optimise shape of the dose response curve

Power Under the Three Designs (and Dunnett or Model Based Contrasts)

- Power – to detect at least one dose significantly different to placebo

Design	Power	Type I error
MCP-Mod	95%	4.1%
Optimal MCP-Mod	96%	4%
Best Intention	95%	2.4%
Dunnett	65%	5%
Model Based Contrasts	93%	5%

Assumed Response Shape

Assumed Response Shape

- Sigmoid Emax

  -

    E_0 = 150 (Placebo effect)

  - E_{max} = 130 (maximum effect over placebo)

  -

    ED_{50} = 700 (Dose which produces 50% of maximum effect)

  -

    Hill parameter = 4

Sample Sizes for Each Dose Under the Three Designs – Maximum Sample Size = 480

Design	Placebo	100 mg	250 mg	500 mg	1000 mg	2000 mg
MCP-Mod	80	80	80	80	80	80
Optimal MCP-Mod	130	40	40	70	70	130
Best Intention	155	70	41	42	49	123

Power Under the Three Designs (and Dunnett or Model Based Contrasts)

- Power – to detect at least one dose significantly different to placebo

Design	Power
MCP-Mod	90%
Optimal MCP-Mod	94%
Best Intention	81%
Dunnett	53%
Model Based Contrasts	85%

Not the whole story – find a dose which gives 130mL increase over placebo
Maximum effect – 150mL

Design	True Dose	
MCP-Mod	1088	944
Optimal MCP-Mod	1088	1029
Best Intention	1088	1000

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Summary and Conclusions

- We have to change the paradigm of dose finding

    - Stop pairwise comparisons – fit a model

- MCP-Mod provides a good model based way of fitting a model to the data

- Use of adaptive designs can provide a flexible framework for modifying the allocation

- The use of optimal designs can provide allocation where it is most informative

- Using a combination of adaptive then allocating to the optimal doses can be even more powerful

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Doing now what patients need next