FERRING PHARMACEUTICALS

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A phase II trial with response-adaptive allocation

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DSBS 25 years – Kollekolle March 2017

Acknowledgement

Egbert van der Meulen

Scott Berry

Agenda

- Background, Objective and Concept
- Statistical Framework
- Simulations

Background

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- Nocturia is defined as waking from sleep (during the night) **at least once** to urinate
- Ferring Pharmceuticals is currently developing a new compound, a synthetic analogoue of **vasopressin** (a peptide hormone) that allows for **water reabsorbtion** in the kidneys and a more concentrated urine output
- Oral doses tested in Phase I were found to be **safe and tolerable**
- In Phase II efficacy is defined as **reduction in number of nocturnal voids**

- **Maximum sample size 300**

Phase II Trial Design

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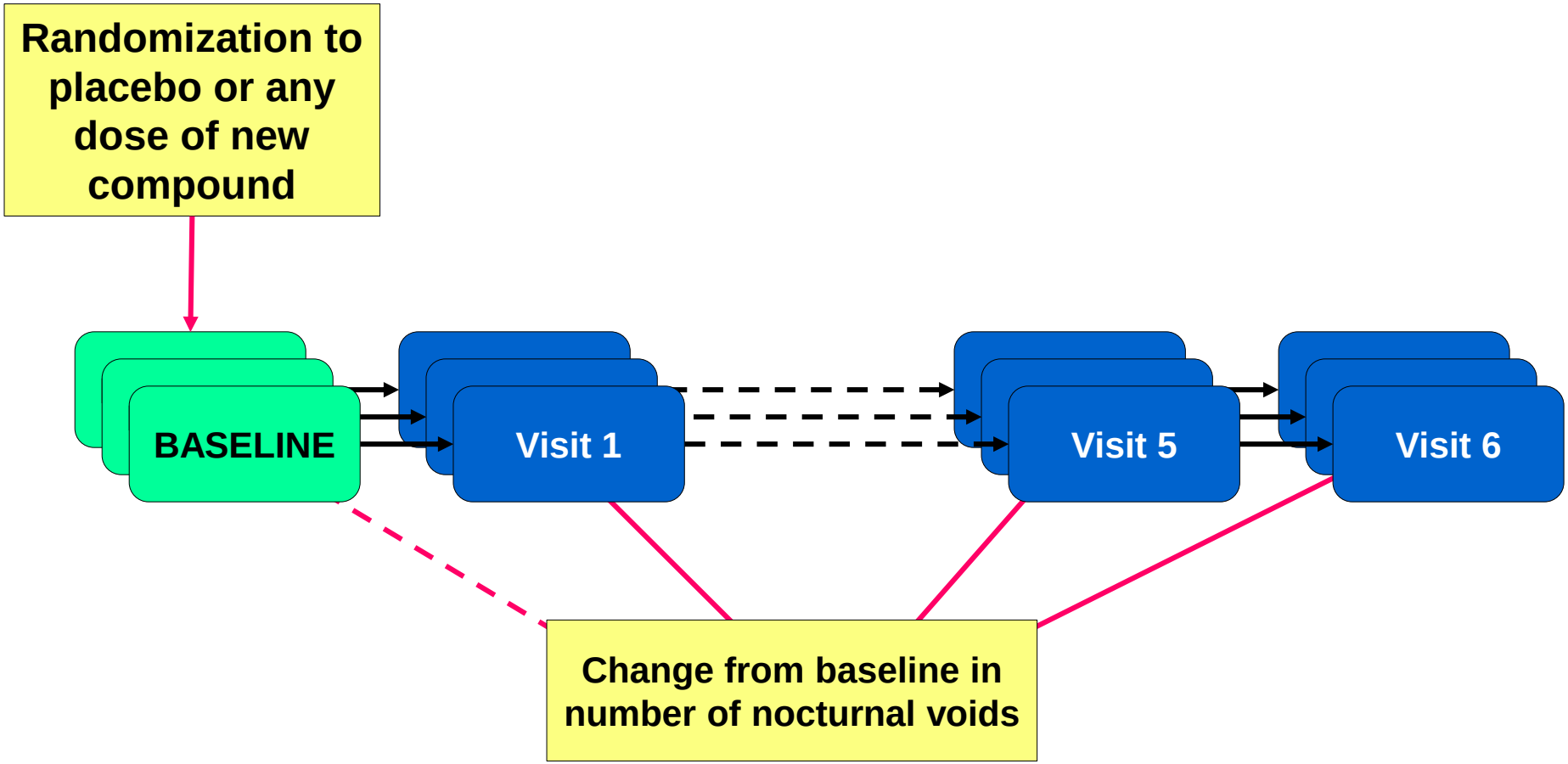

Objectives and Concept for Phase II

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Proof of Concept

- Is the new compound effective?

Test top dose versus placebo

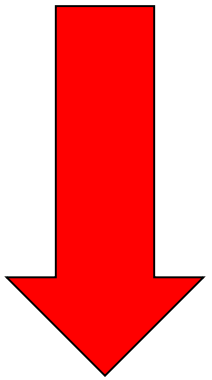
TOP

Estimate Dose-Response Profile

- What doses are likely to achieve target profile?
  - **ED85** = the dose that achives 85% effect of maximum dose
  - **MED** = the dose that has an improvement over placebo of a given threshold

Allocate patients to these doses

DOWN



Implementation of Top-Down Design

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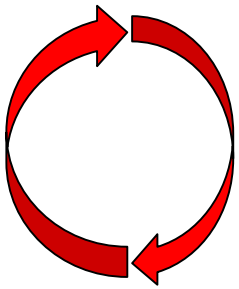
Top

A. Randomize patients to placebo and **top-dose**

B. Plan first interim when 80 patients are randomized and evaluate futility and success criteria



Down

C. Estimate dose-response curve

D. Open randomization to all doses and target ED85 and MED

Repeat B - D every 8 weeks

Agenda

- Background, Objective and Concept
- **Statistical Framework**
- Simulations

Dose-response: Sigmoidal Model

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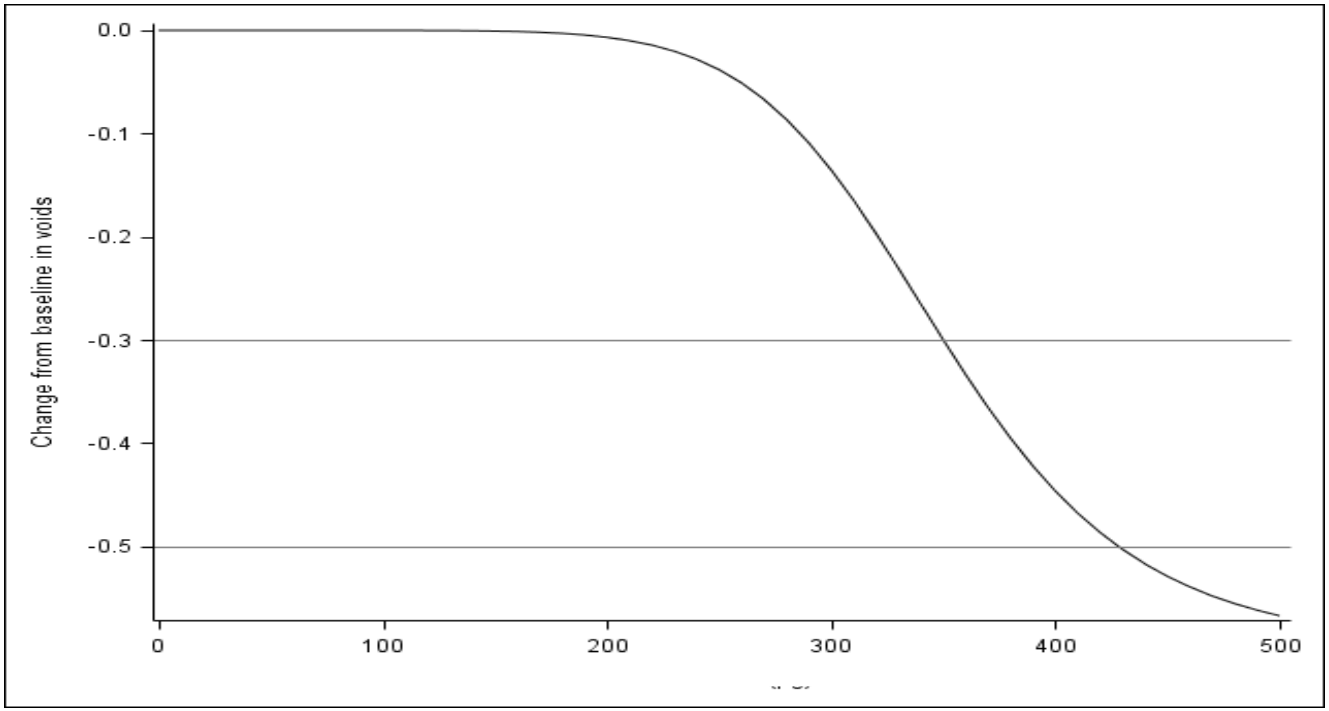
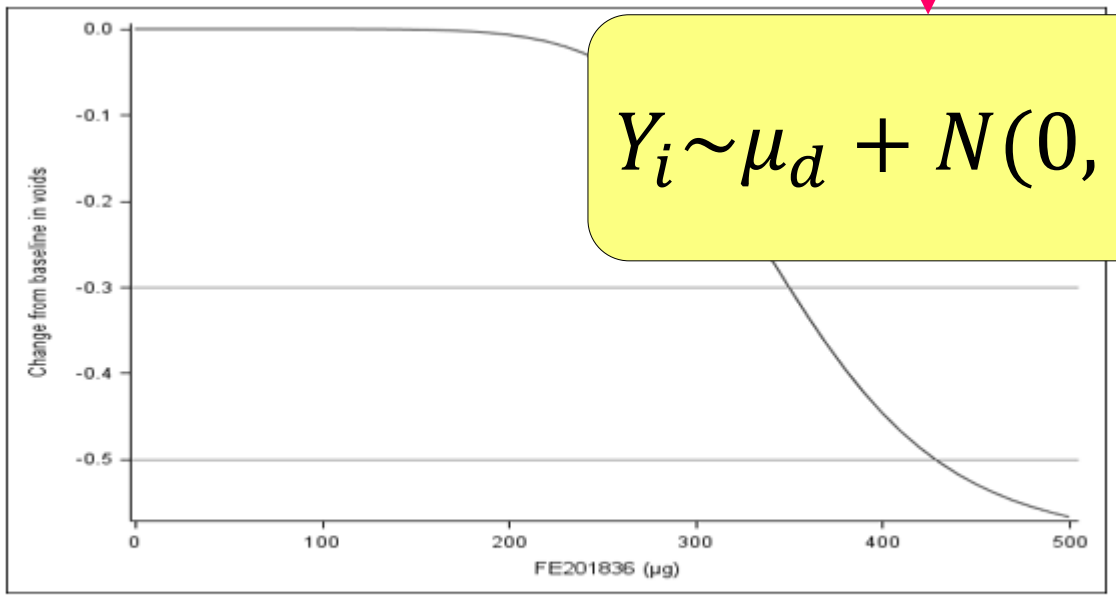


$$\mu_d = \alpha_1 + \frac{(\alpha_2 - \alpha_1)d^{\alpha_4}}{d^{\alpha_4} + {\alpha_3}^{\alpha_4}}$$

Final Endpoint Model

Y_i is the averaged number of voids during treatment

BASELINE → Visit 1 - - - - → Visit 5 → Visit 6



$$Y_i \sim \mu_d + N(0, \sigma^2)$$

$$\mu_d = \alpha_1 + \frac{(\alpha_2 - \alpha_1)d^{\alpha_4}}{d^{\alpha_4} + \alpha_3{}^{\alpha_4}}$$

Final Endpoint… not observed

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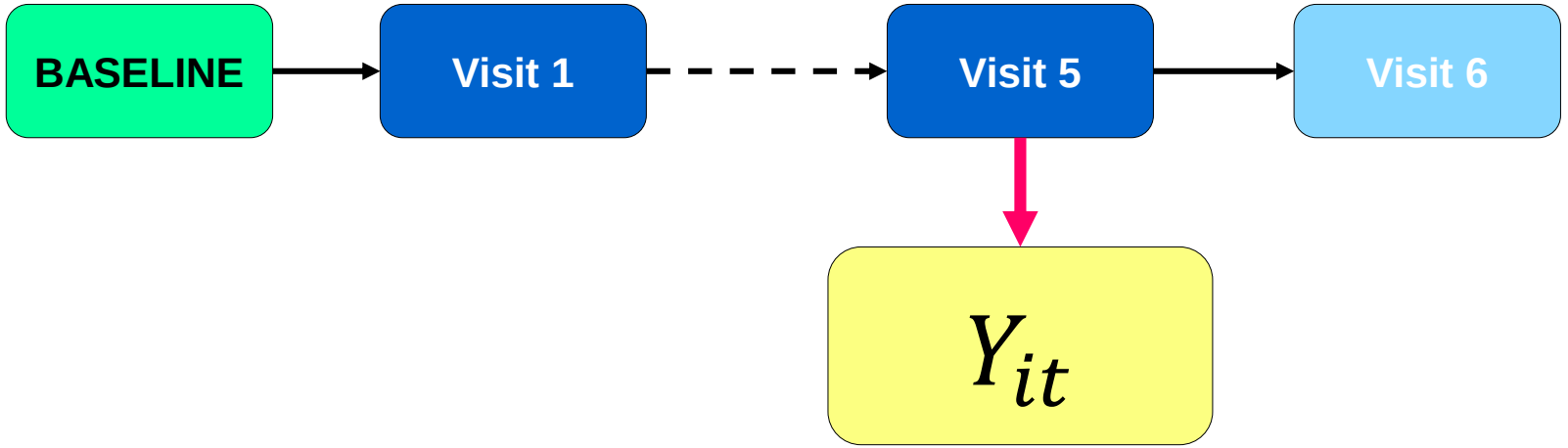

$$Y_{it} \sim e^{\gamma_t}(\mu_d + \delta_i) + N(0, \lambda_t^2) \text{ for t<6}$$

Impute final response as:

$$Y_i \sim \mu_d + \delta_i + N(0, \lambda_T^2)$$

…if yet not observed

Bayesian Framework

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The posterior of the parameters is proportional to the product of…

$$\prod_{i=1}^{n}\prod_{t=1}^{L}[Y_{it}|\gamma_t,\delta_i,\alpha,\lambda_t]$$

Longitudinal data model (used to obtain imputated estimates of final endpoint if subject has not completed trial)

$$\prod_{i=1}^{n}[Y_i|\alpha,\sigma]$$

Dose-response model (observed and imputed data)

$$[\gamma][\delta][\lambda][\alpha][\sigma]$$

Parameter stage

Priors are specified in statistical analysis plan

Sample parameters from their posteriors using Metropolis Hastings or Gibbs sampling (where possible)

Parameter stage:
Samples of the Prior Dose-Response Model

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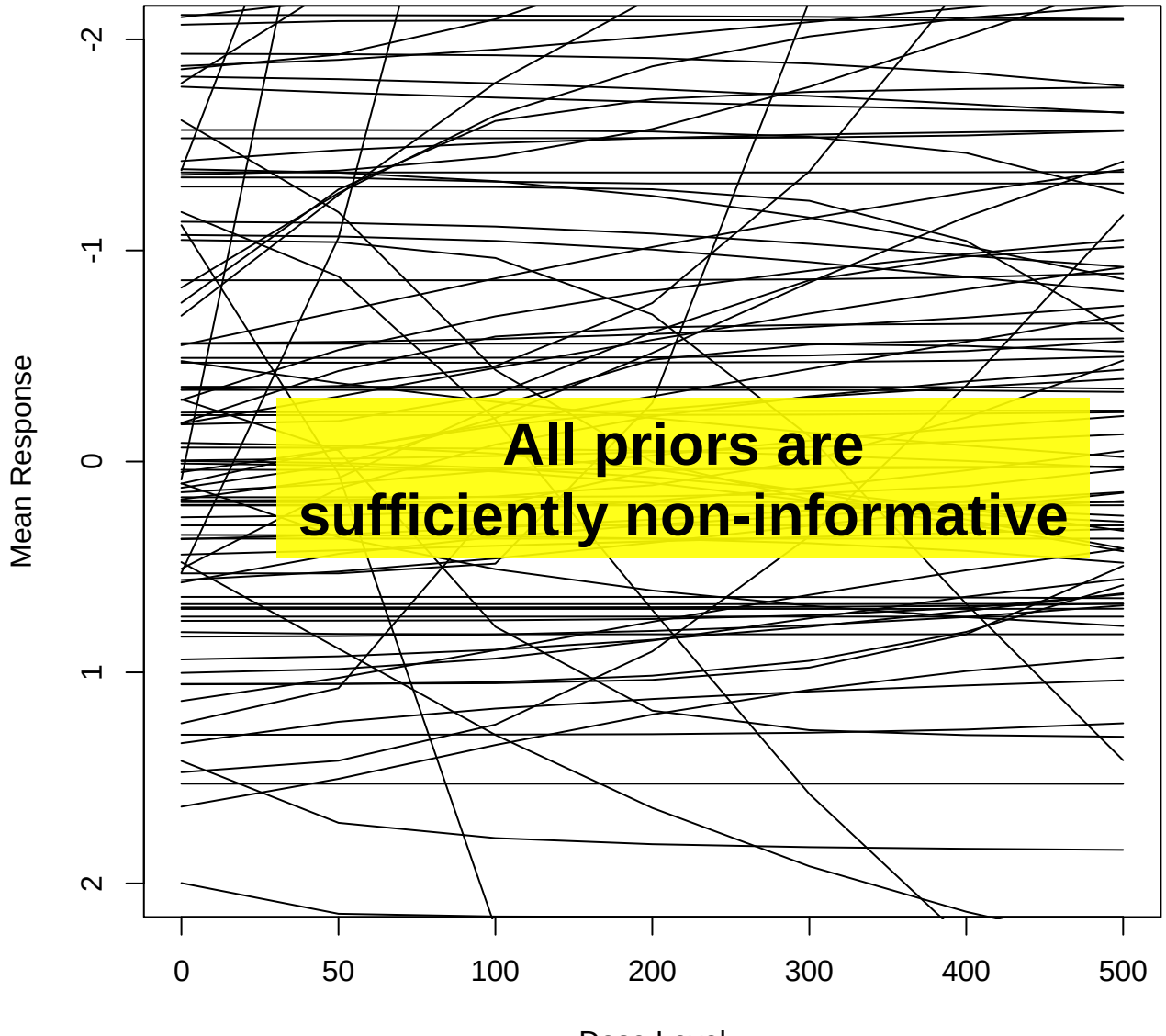

Result of One MCMC Iteration

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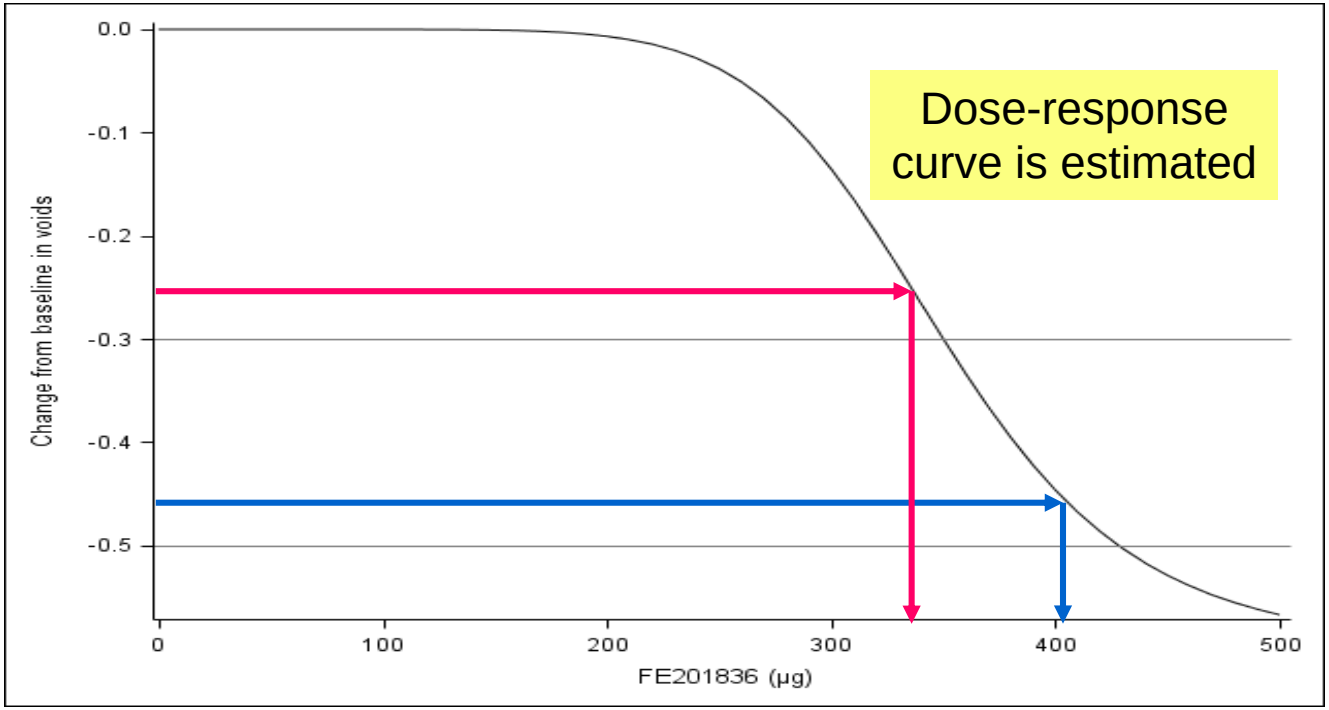

Result of Some More MCMC Iterations

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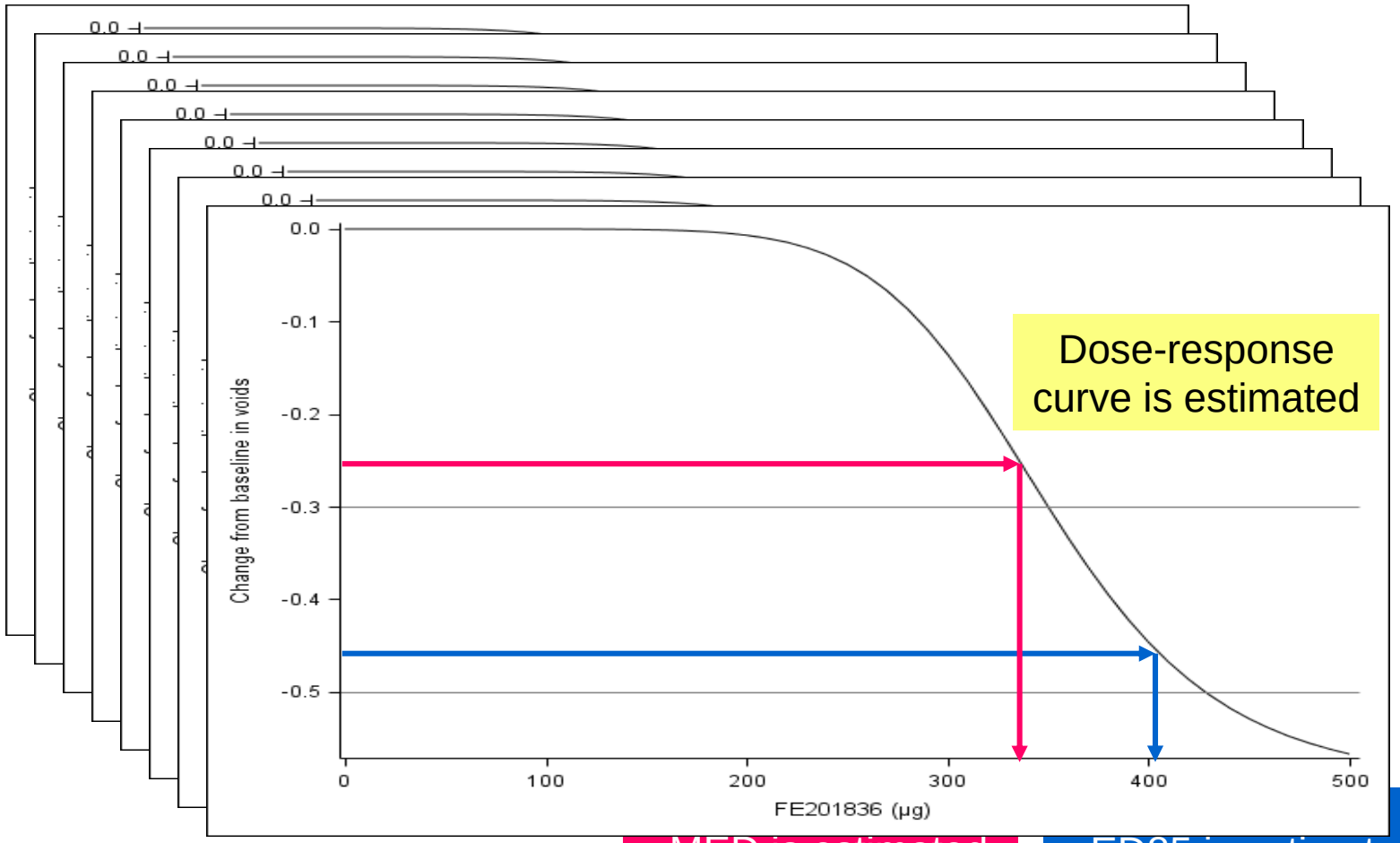

Evaluations at Interim

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POSTERIOR PROBABILITIES

of any quantity of interest are derived…

FUTILITY

If Pr($\mu_{max} - \mu_{Plb} < -\Delta_{MED}$) < *15% (20% at first interim)*

SUCCESS

If Pr(MED) > *50%* AND Pr($\mu_{max} < \mu_{Plb}$) > 97.5%

RESPONSE ADAPTIVE RANDOMIZATION

Allocation probabilities proptional to sum of

Pr(dose d is ED_{85}) and Pr(dose *d* is MED)

Agenda

- Background, Objective and Concept
- Statistical Framework
- **Simulations**

Simulations… easy peacy

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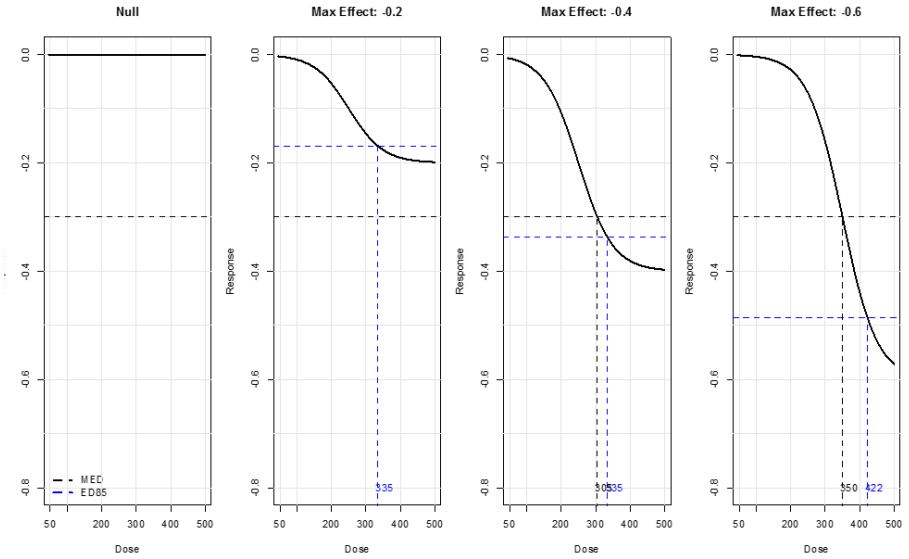
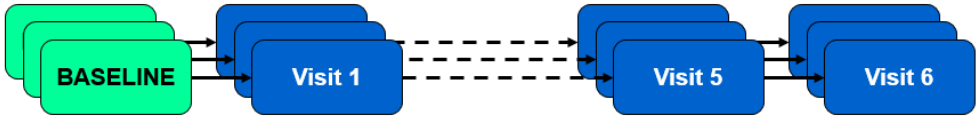
- Specify expected dose-response
- Define allocation and drop-out rates
- Simulate patient outcome





- Apply the top-down design with response adaptive randomization
- Do this many many times…
- Evaluate success rates for different scenarios

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A Futile Trial

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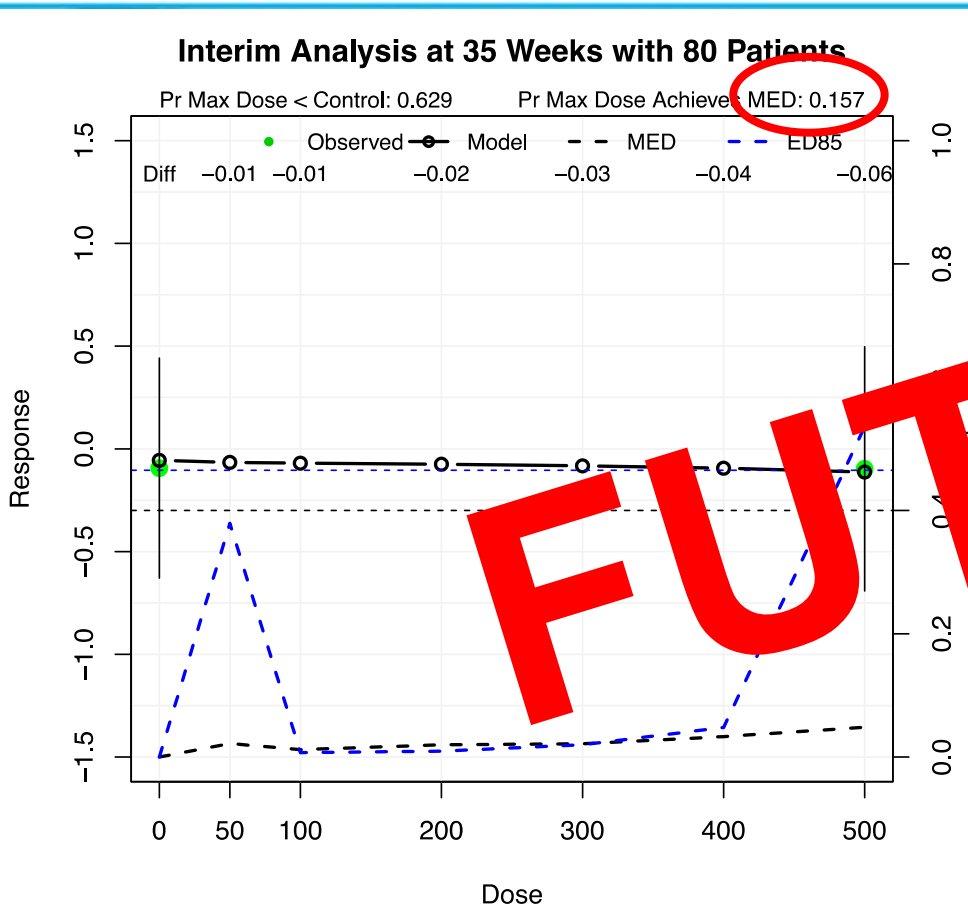
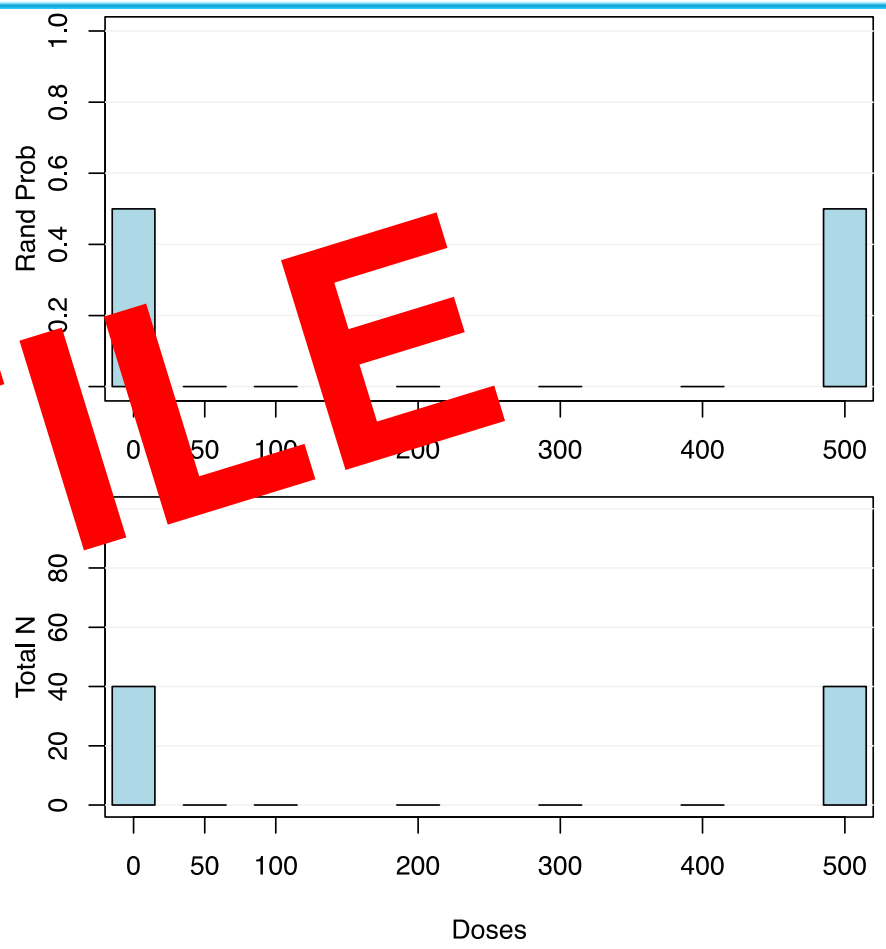


FUTILE



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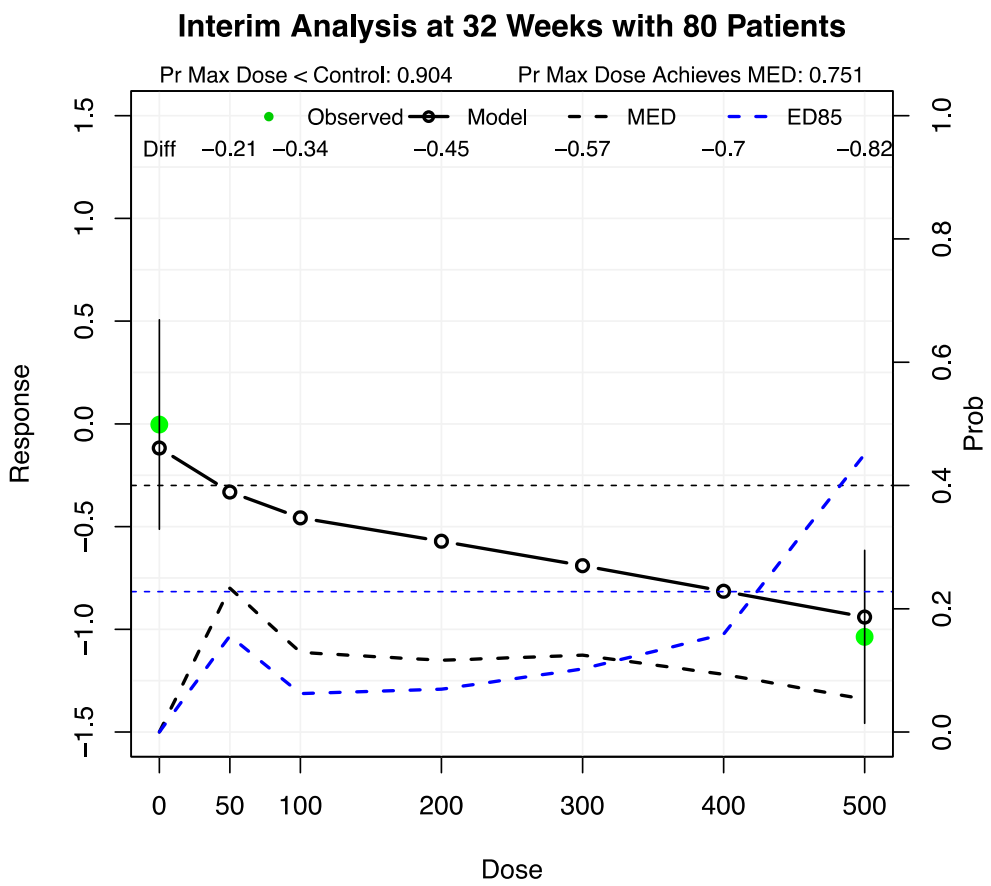
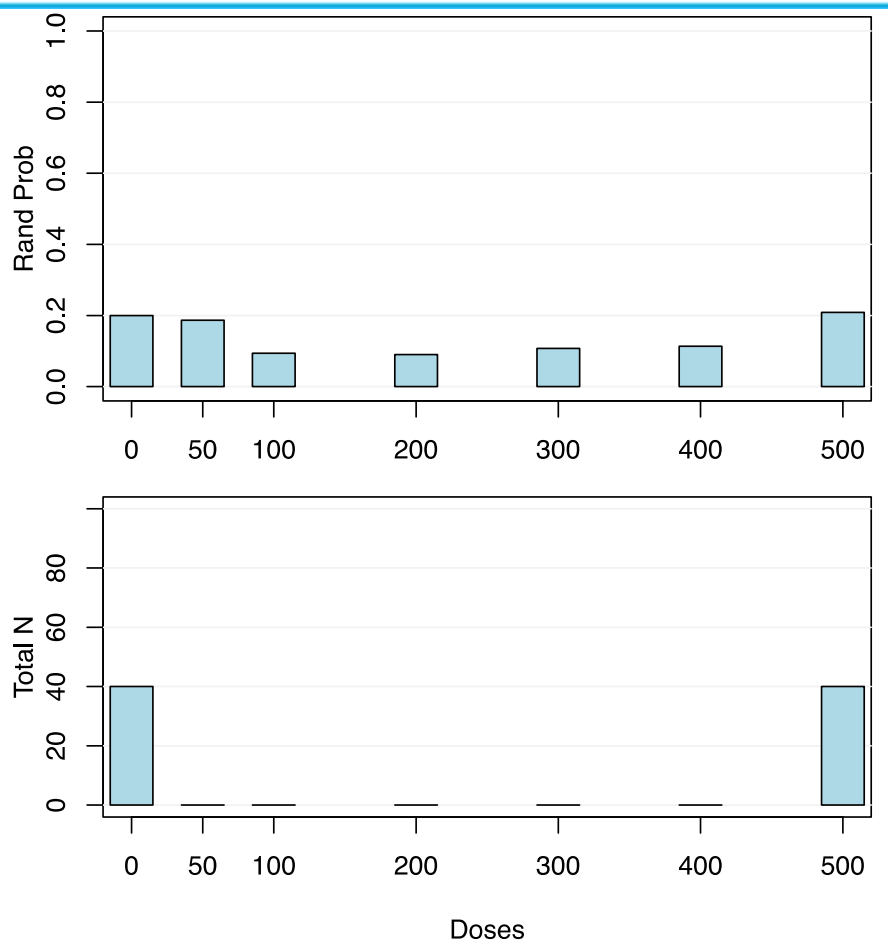
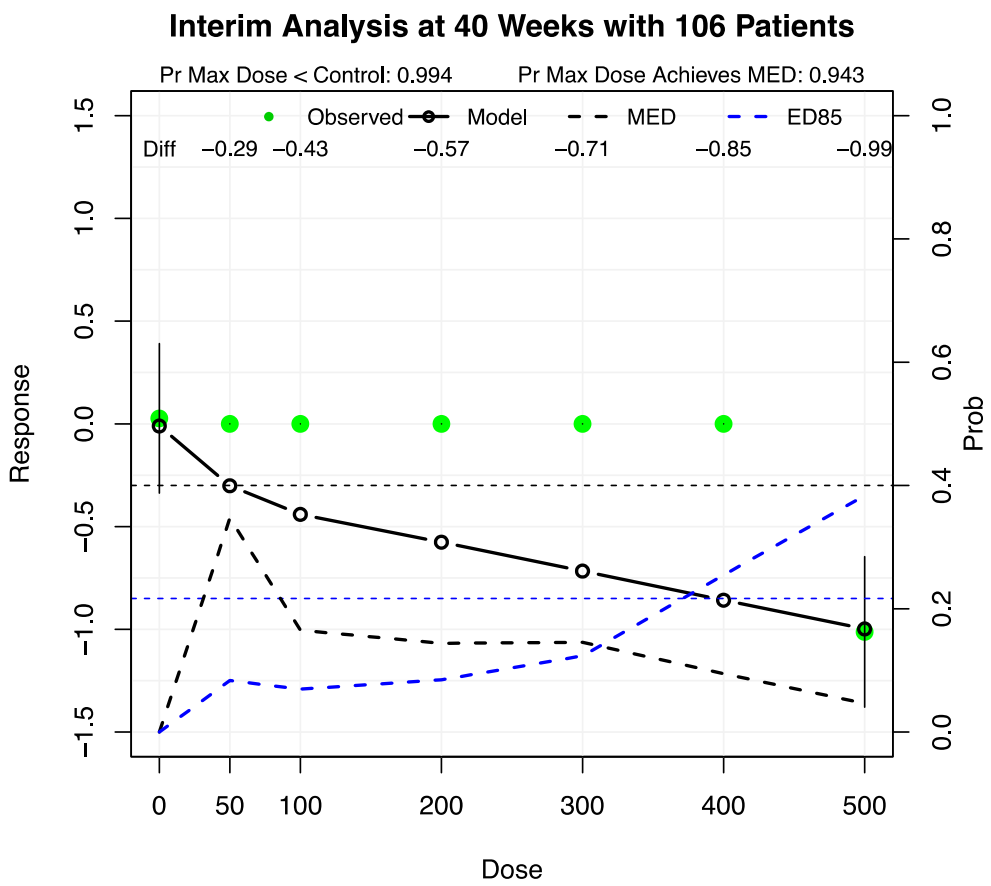
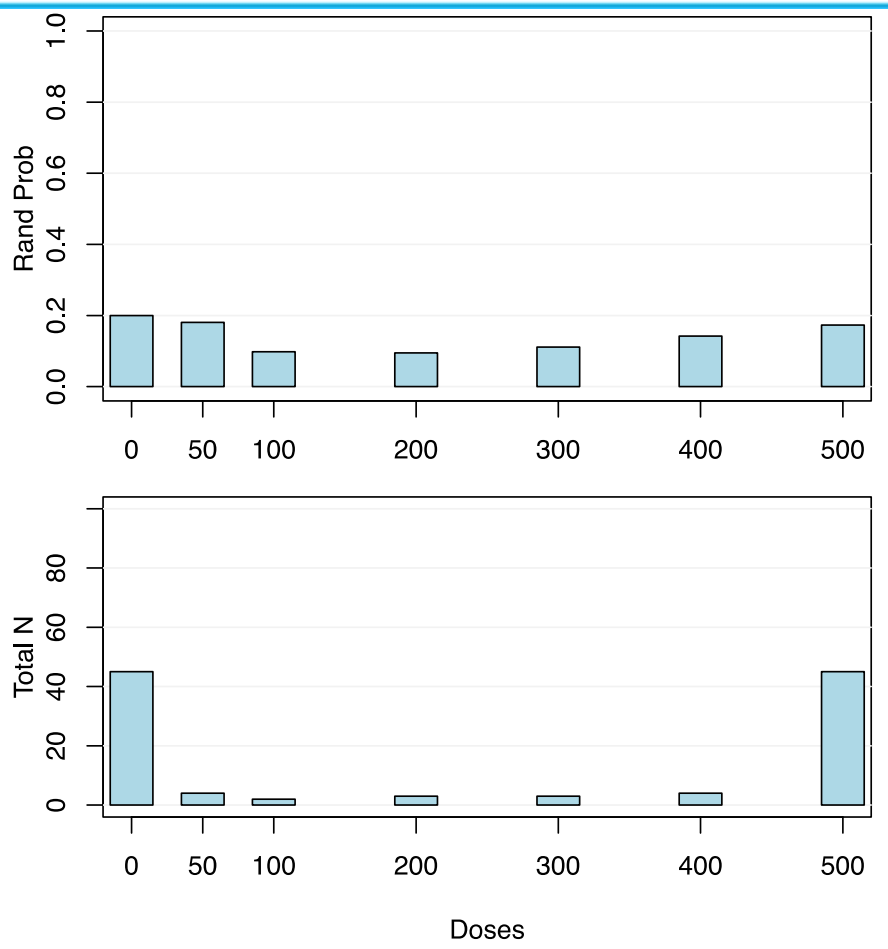
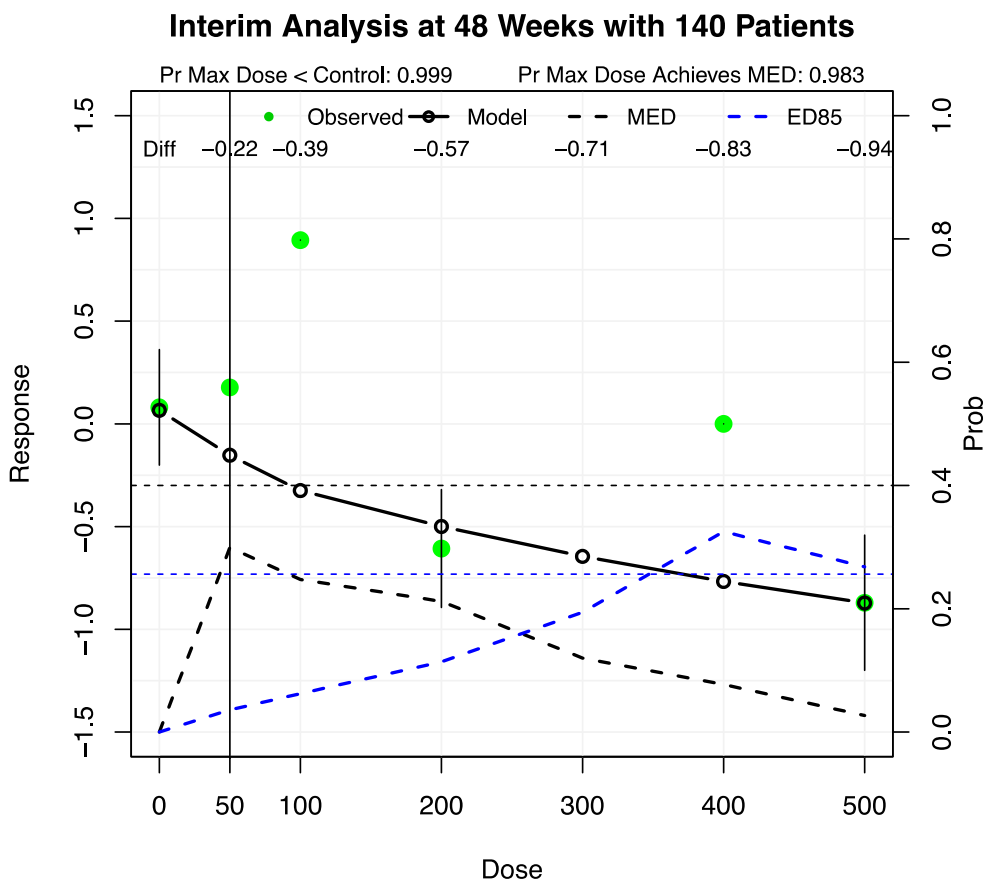
A Successful Trial

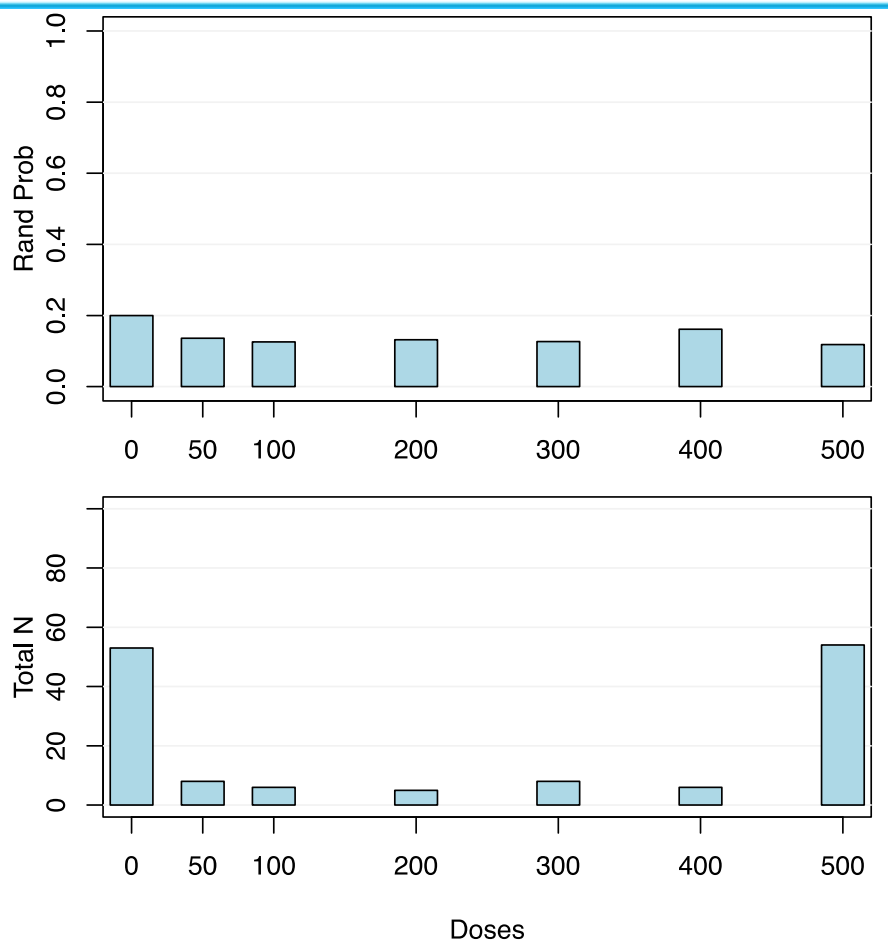

Interim Analysis at 32 Weeks with 80 Patients
Pr Max Dose < Control: 0.904
Pr Max Dose Achieves MED: 0.751
Observed
Model
MED
ED85
Diff −0.21 −0.34 −0.45 −0.57 −0.7 −0.82
Response
Prob
Dose
0 50 100 200 300 400 500
−1.5 −1.0 −0.5 0.0 0.5 1.0 1.5
0.0 0.2 0.4 0.6 0.8 1.0

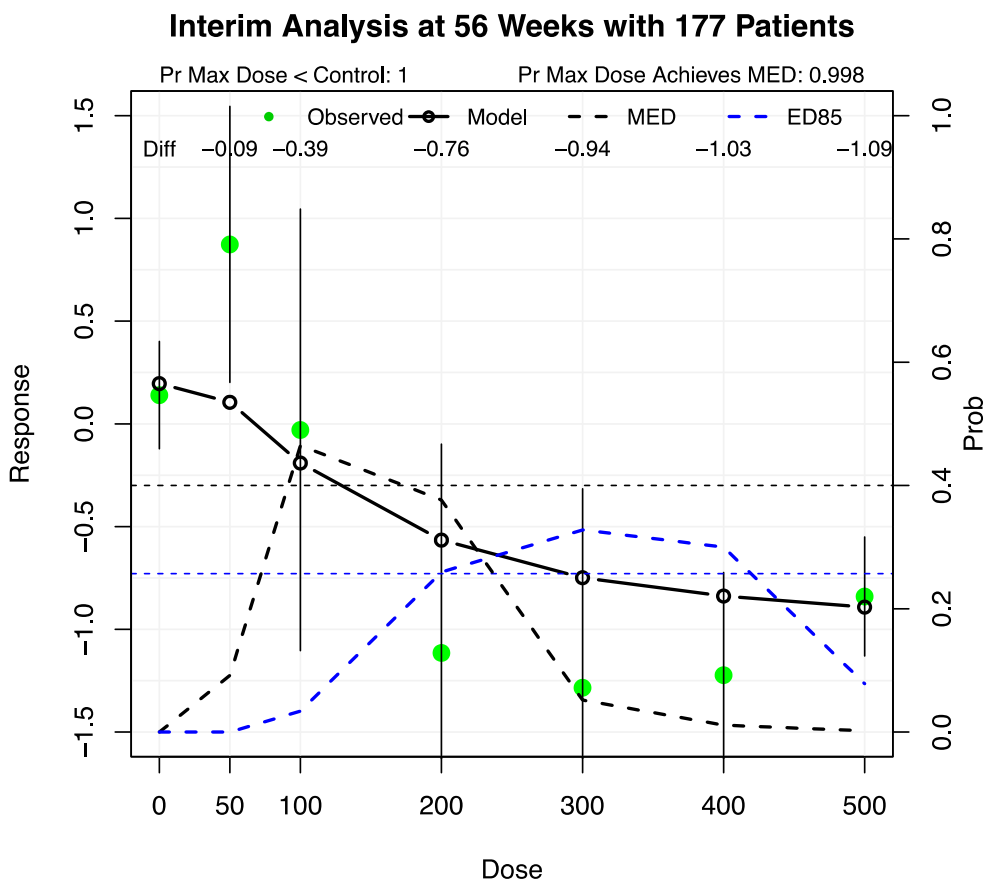

Rand Prob
0.0 0.2 0.4 0.6 0.8 1.0
Total N
0 20 40 60 80
0 50 100 200 300 400 500
Doses

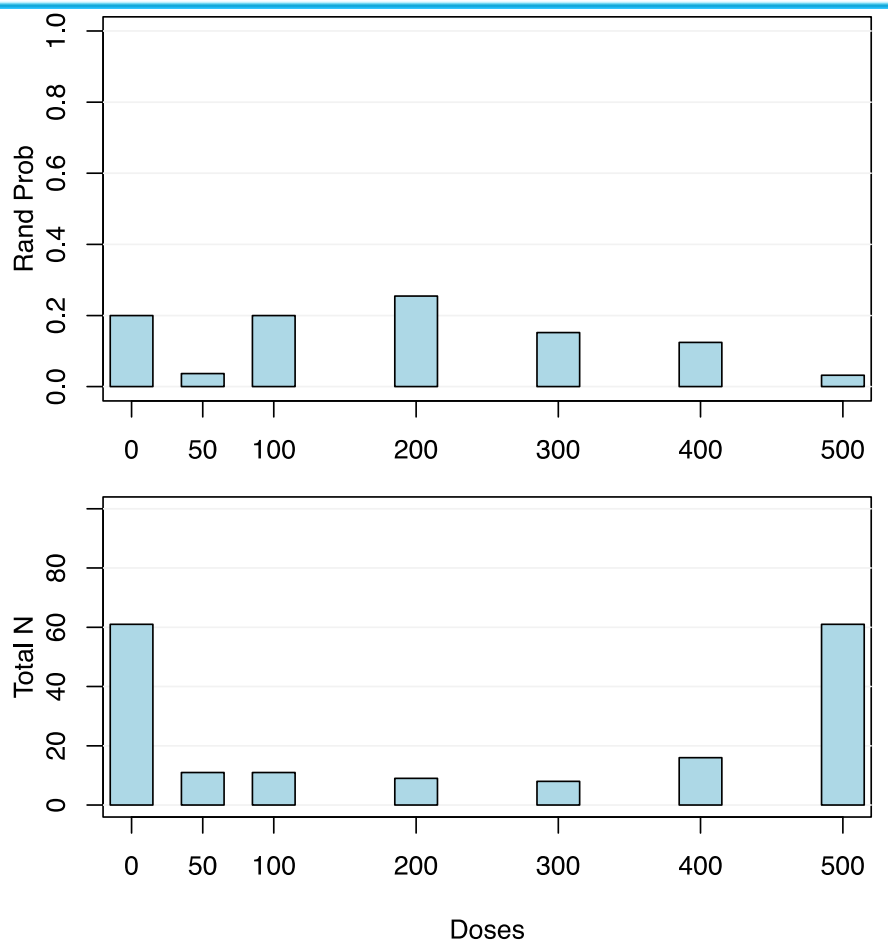

Interim Analysis at 40 Weeks with 106 Patients
Pr Max Dose < Control: 0.994
Pr Max Dose Achieves MED: 0.943
Observed
Model
MED
ED85
Diff −0.29 −0.43 −0.57 −0.71 −0.85 −0.99
Response
Prob
Dose
0 50 100 200 300 400 500
−1.5 −1.0 −0.5 0.0 0.5 1.0 1.5
0.0 0.2 0.4 0.6 0.8 1.0

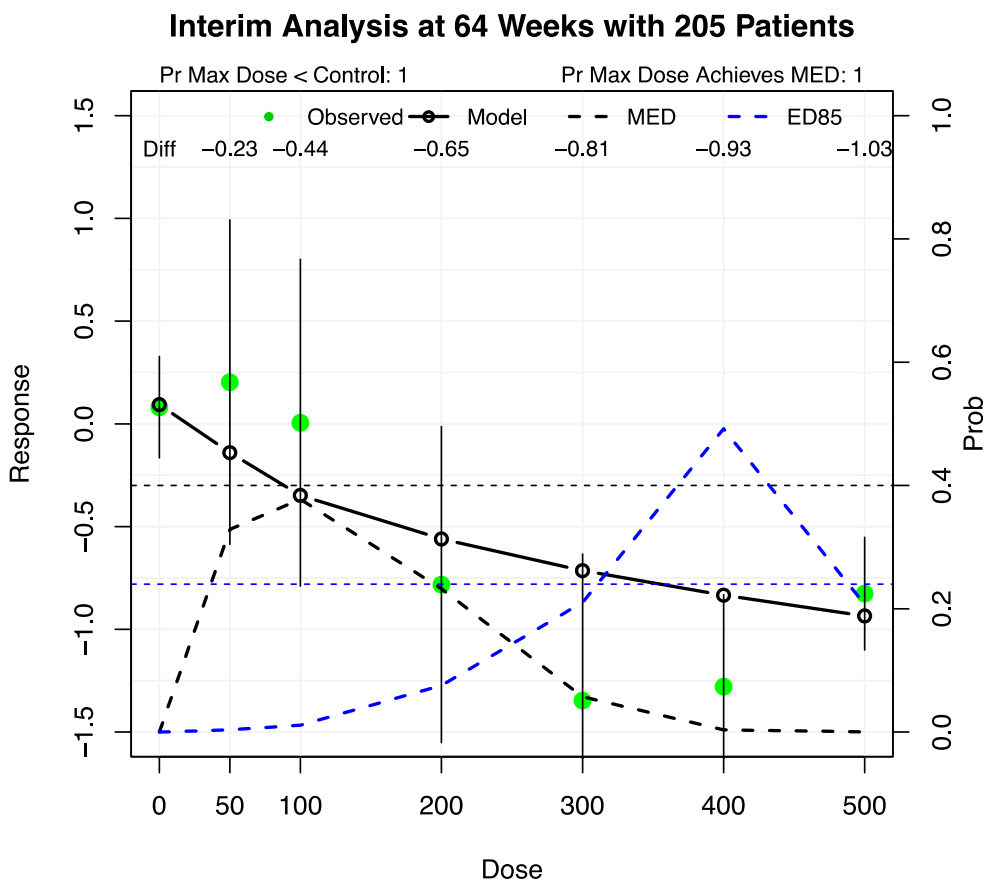

Rand Prob
0.0 0.2 0.4 0.6 0.8 1.0
0 50 100 200 300 400 500
Total N
0 20 40 60 80
0 50 100 200 300 400 500
Doses

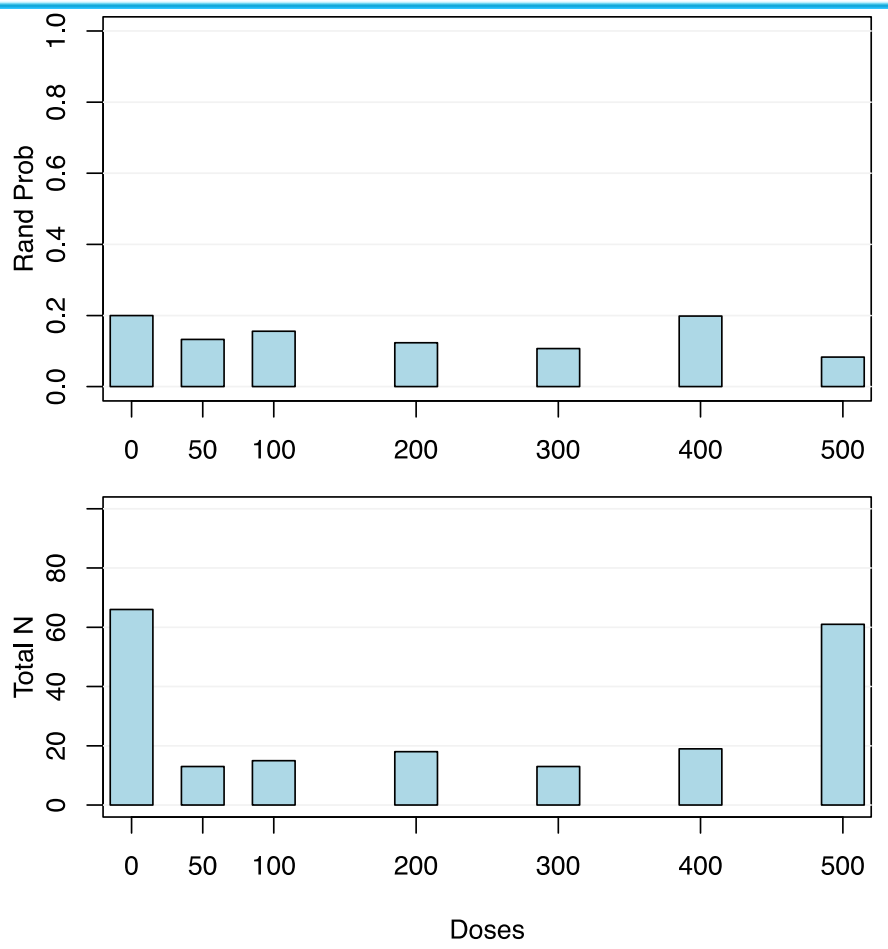

Interim Analysis at 48 Weeks with 140 Patients
Pr Max Dose < Control: 0.999
Pr Max Dose Achieves MED: 0.983
Observed
Model
MED
ED85
Diff −0.22 −0.39 −0.57 −0.71 −0.83 −0.94
Response
Prob
Dose
0 50 100 200 300 400 500
−1.5 −1.0 −0.5 0.0 0.5 1.0 1.5
0.0 0.2 0.4 0.6 0.8 1.0

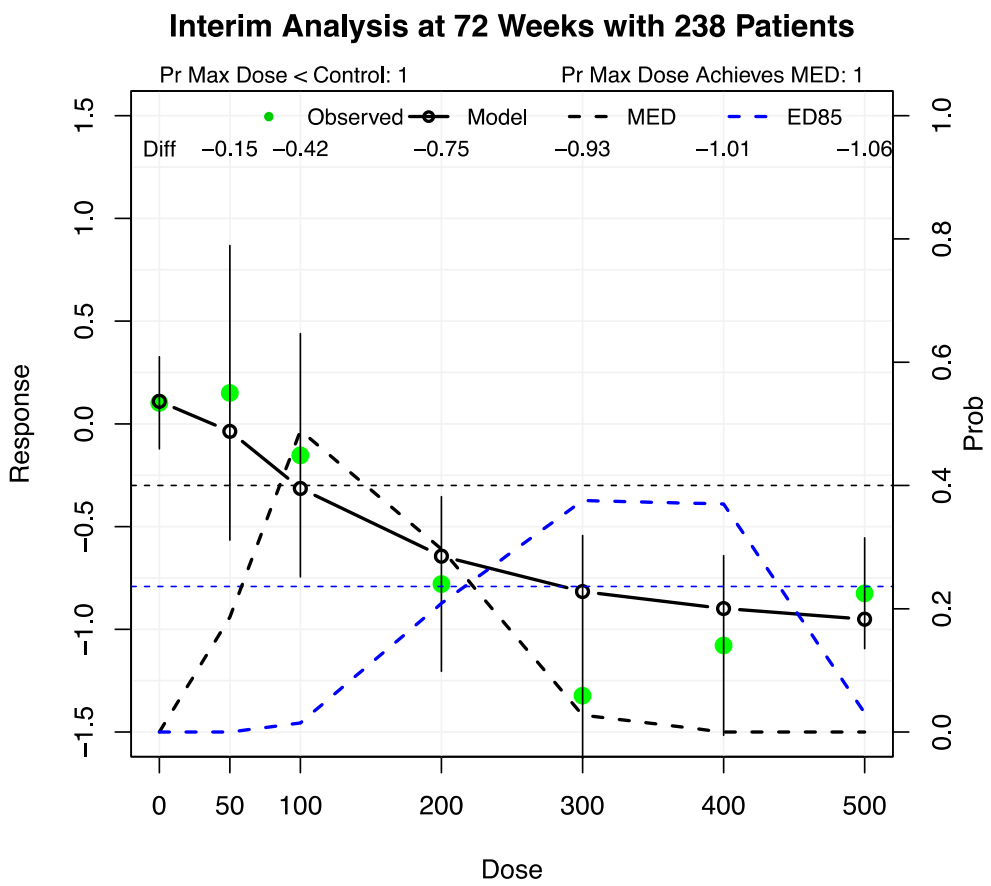

Rand Prob
0.0 0.2 0.4 0.6 0.8 1.0
0 50 100 200 300 400 500
Total N
0 20 40 60 80
0 50 100 200 300 400 500
Doses

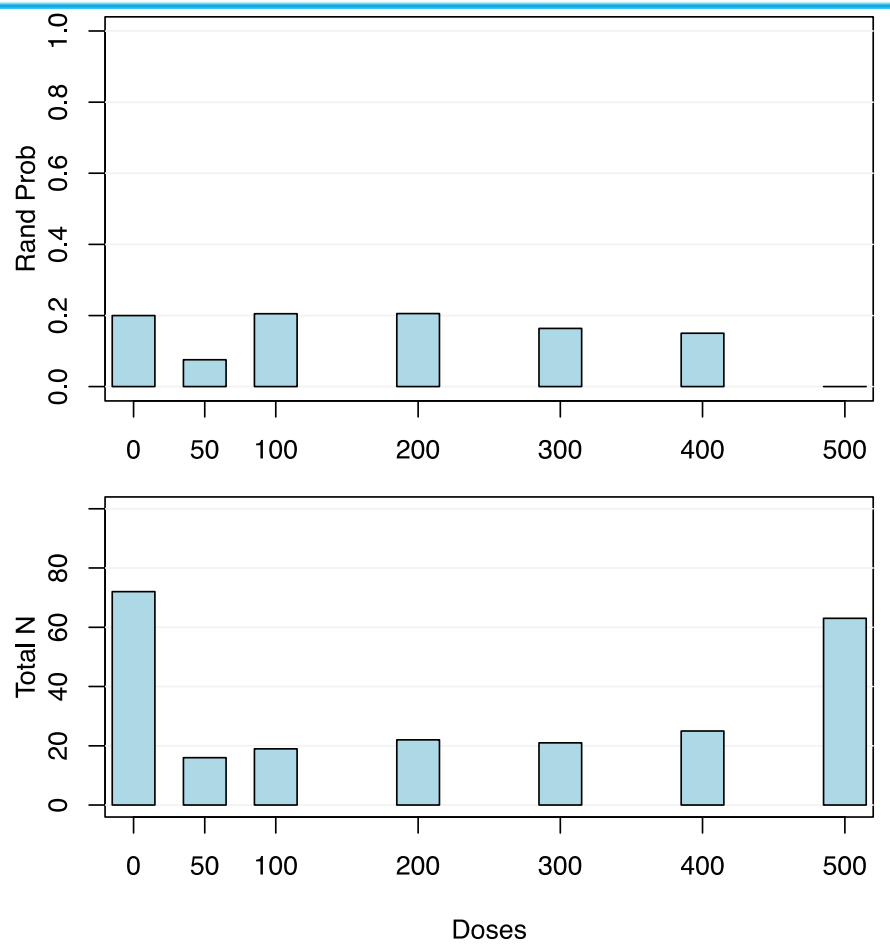

Interim Analysis at 56 Weeks with 177 Patients
Pr Max Dose < Control: 1
Pr Max Dose Achieves MED: 0.998
Observed
Model
MED
ED85
Diff −0.09 −0.39 −0.76 −0.94 −1.03 −1.09
Response
Prob
Dose
0 50 100 200 300 400 500
−1.5 −1.0 −0.5 0.0 0.5 1.0 1.5
0.0 0.2 0.4 0.6 0.8 1.0

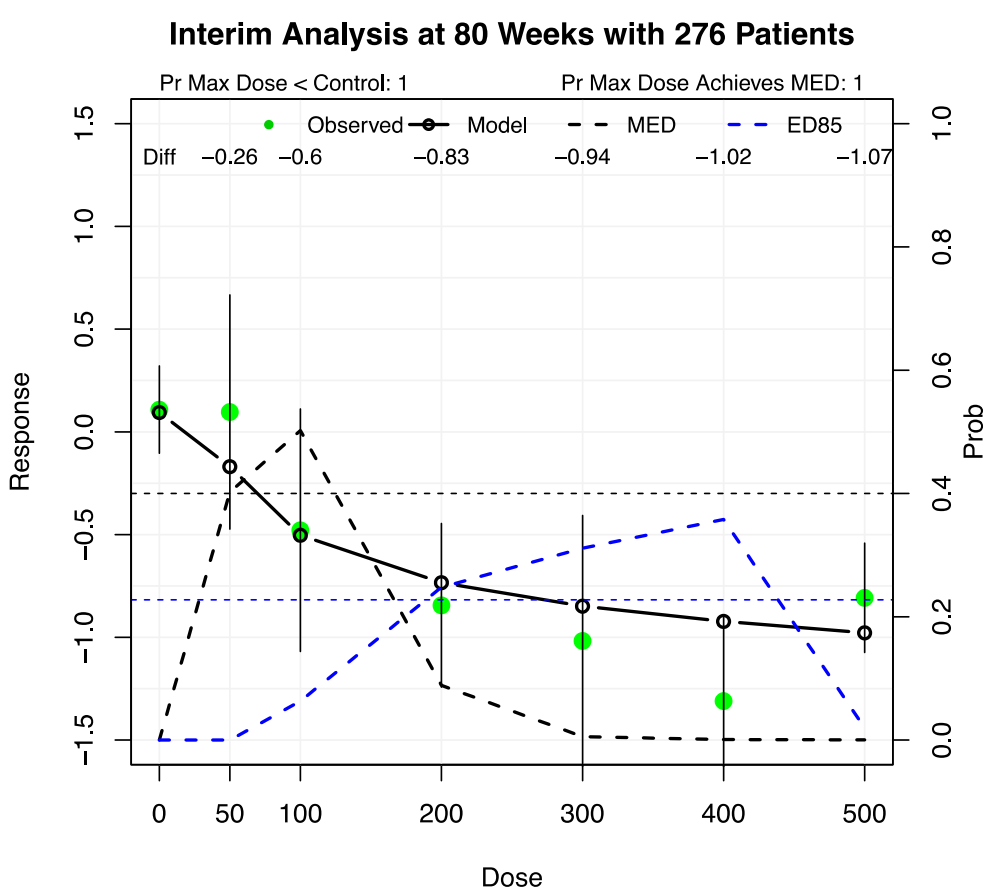

Rand Prob
0.0 0.2 0.4 0.6 0.8 1.0
0 50 100 200 300 400 500
Total N
0 20 40 60 80
0 50 100 200 300 400 500
Doses

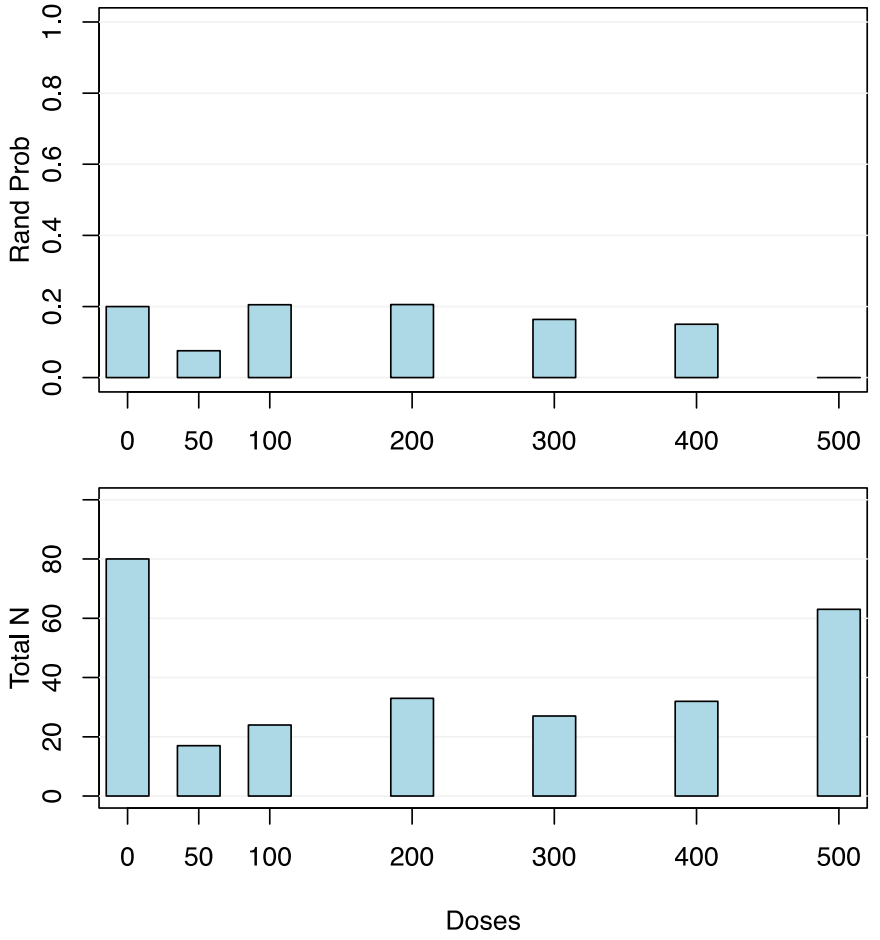

Interim Analysis at 64 Weeks with 205 Patients
Pr Max Dose < Control: 1
Pr Max Dose Achieves MED: 1
Observed
Model
MED
ED85
Diff −0.23 −0.44 −0.65 −0.81 −0.93 −1.03
Response
Prob
Dose
0 50 100 200 300 400 500
−1.5 −1.0 −0.5 0.0 0.5 1.0 1.5
0.0 0.2 0.4 0.6 0.8 1.0


Rand Prob
0.0 0.2 0.4 0.6 0.8 1.0
0 50 100 200 300 400 500
Total N
0 20 40 60 80
0 50 100 200 300 400 500
Doses


Interim Analysis at 72 Weeks with 238 Patients
Pr Max Dose < Control: 1
Pr Max Dose Achieves MED: 1
Observed
Model
MED
ED85
Diff −0.15 −0.42 −0.75 −0.93 −1.01 −1.06
Response
Prob
Dose
0 50 100 200 300 400 500
−1.5 −1.0 −0.5 0.0 0.5 1.0 1.5
0.0 0.2 0.4 0.6 0.8 1.0


Rand Prob
0.0 0.2 0.4 0.6 0.8 1.0
0 50 100 200 300 400 500
Total N
0 20 40 60 80
0 50 100 200 300 400 500
Doses


Interim Analysis at 80 Weeks with 276 Patients
Pr Max Dose < Control: 1
Pr Max Dose Achieves MED: 1
Observed
Model
MED
ED85
Diff −0.26 −0.6 −0.83 −0.94 −1.02 −1.07
Response
Prob
Dose
0 50 100 200 300 400 500
−1.5 −1.0 −0.5 0.0 0.5 1.0 1.5
0.0 0.2 0.4 0.6 0.8 1.0


Rand Prob
0.0 0.2 0.4 0.6 0.8 1.0
0 50 100 200 300 400 500
Total N
0 20 40 60 80
0 50 100 200 300 400 500
Doses

A DOSE IS IDENTIFIED AS MED WITH Probability > 50%

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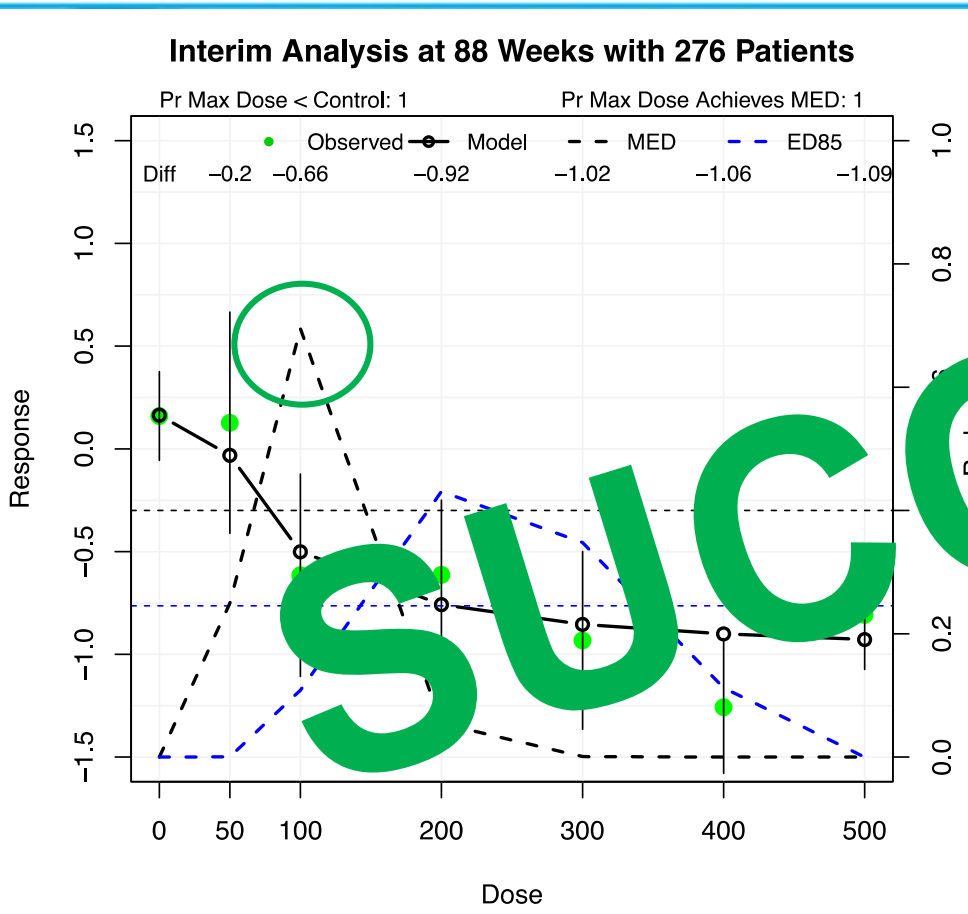

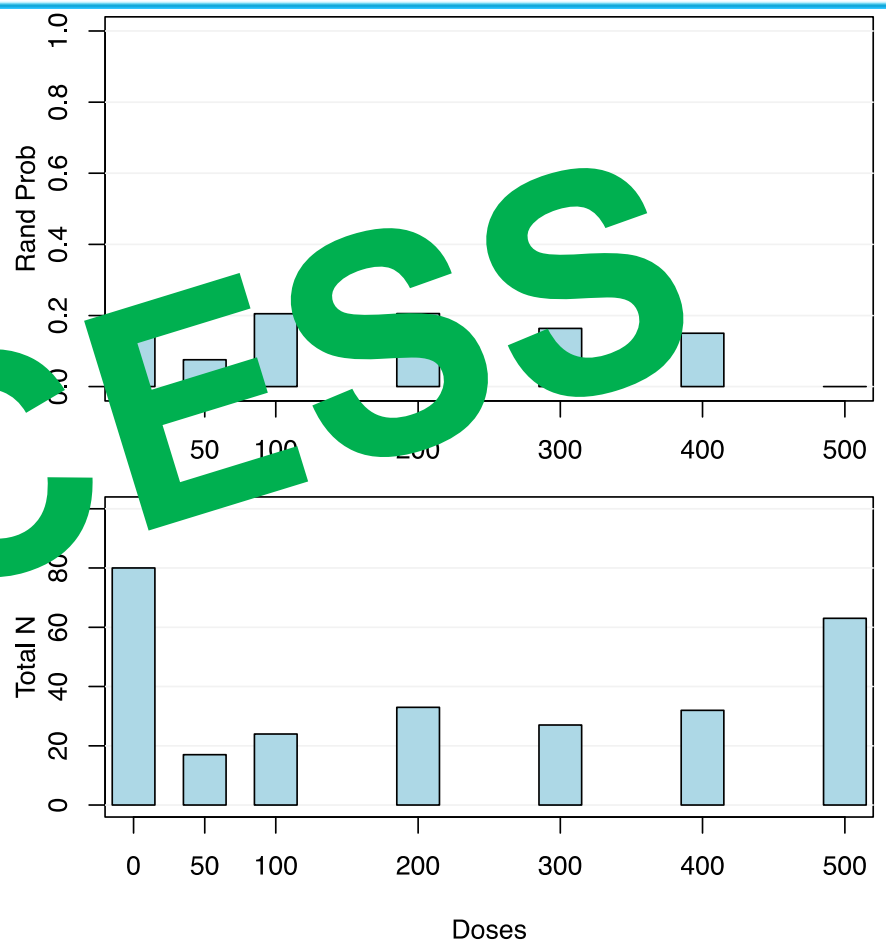

FINAL ANALYSIS WHEN ALL PATIENTS HAVE COMPLETED TRIAL

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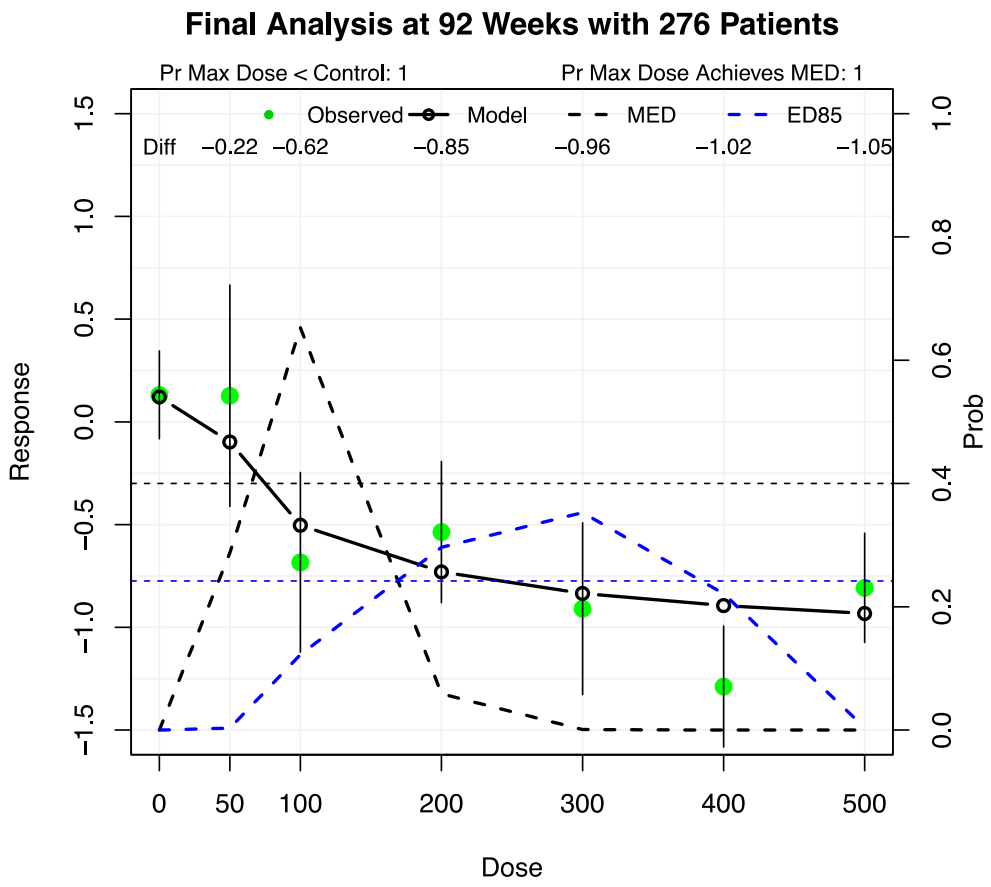

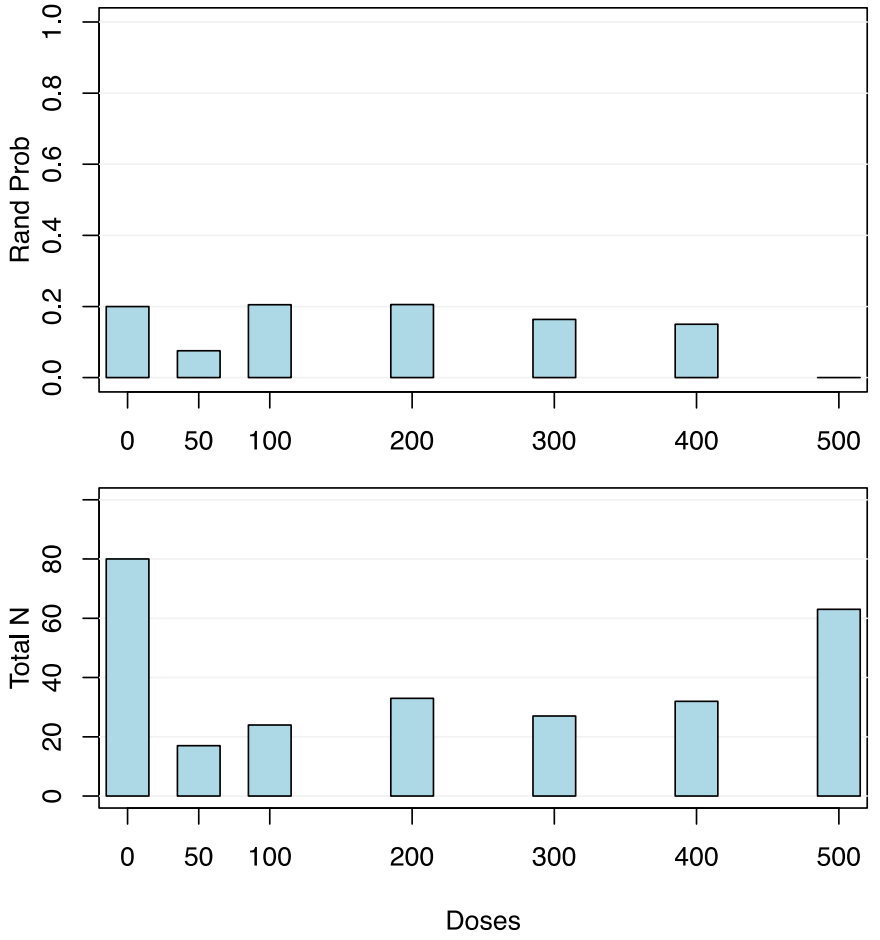

Operating Characteristics

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Dose-Response Scenario		Average Number of Subjects	Futility Stopping at First Interim	Total Futility stopping	**Power** (Total Success)
Null		200	75.8%	97.0%	**3.0%**
I		277	15.7%	47.9%	52.1%
II		288	7.9%	25.1%	74.9%
III		296	2.8%	9.6%	**90.4%**
IV		295	3.4%	15.4%	**84.6%**
V		298	1.4%	2.7%	97.3%

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