Applications of robust MAP priors in quantitative trial design

B Magnusson, H Schmidli

Statistical Methodology and Consulting
Novartis Pharma AG

Bayes Pharma – 21 May 2015

NOVARTIS

Introduction

Methodology and overview

- **Context**:
  - Planning Novartis early development clinical trials
  - Desire to incorporate historical control information
- **Methodology**:
  - MAP priors commonly used to obtain equivalent sample size (Neuenschwander et al. 2010)
  - Concerns about prior-data conflict and analytical intractability
  - Mixture priors of conjugate distributions are appealing in this setting (Schmidli et al. 2014)
- **Application**:
  - Case study from infectious disease proof of concept study design
  - Mixture prior approach fully implemented in design and analysis

Case study: Phase 2a efficacy study

Overview

- New compound intended to treat an infection and its resulting disease
  - Infection is common (>50% world-wide)
  - Latent infection – immune system fails to clear the virus
- Most infections are asymptomatic or mild but significant disease can appear in at-risk persons
  - Bacterial and fungal infections
  - Deafness/blindness
  - Mental retardation
  - Death
- Currently available therapies are efficacious, but also associated with serious toxicities
  - Neutropenia, thrombocytopenia, seizures, anemia
  - Carcinogenicity/teratogenicity in animals

Disease prevention and treatment

Treatment strategies for patients at risk

- Due to mortality and morbidity associated with infection/disease, most common strategy is preventative treatment
- Prophylaxis:
  - Therapy given during period of highest risk to prevent virus growth
- Preemptive:
  - Therapy initiated after virus is detected (viral load exceeds given threshold) but before disease develops
- Prophylaxis more efficacious than preemptive strategy, but also associated with increased risk of toxicity

ABC123

Background and high-level study design

- Novel compound (ABC123) has the potential to be used in a prophylaxis setting
  - Well tolerated in preclinical toxicity studies at 10 times highest (expected) human dose
  - Well tolerated in first-in-human healthy volunteer study
- First clinical study in patients – randomized, double-blind, placebo-controlled
  - Evaluate efficacy, safety and PK of ABC123 when given as a prophylaxis
  - Recruit patients that are at relatively high risk of infection
  - Goal is to prevent infection, i.e. prevent viral loads from reaching a pre-defined threshold
  - If this threshold is reached, then treat patients with standard-of-care
  - Placebo-controlled study is ethical in this setting

ABC123 patient study

Key statistical aspects of study design

- Primary endpoint is binary (infection yes/no)
  - Efficacy represented in terms of relative risk p_T/p_C
- Use beta-binomial (conjugate) model for analysis
  - Non-informative Beta(1/3,1/3) prior for p_T
  - Informative prior on p_C based on historical data (details to follow)
  - Prior mean 0.41 and 90% CI (0.21,0.64) – Effective sample size 42
- 3:1 randomization ratio in favor of ABC123 with total N = 64
- Quantitative PoC criteria:
  1. Posterior probability that p_T/p_C <1 is at least 0.9
  2. Posterior probability that p_T/p_C <0.5 is at least 0.5
- Outcomes
  - 1) and 2): “Positive result”
  - Neither 1) nor 2): “Negative result”
  - 1) or 2), not both: “Indeterminate”

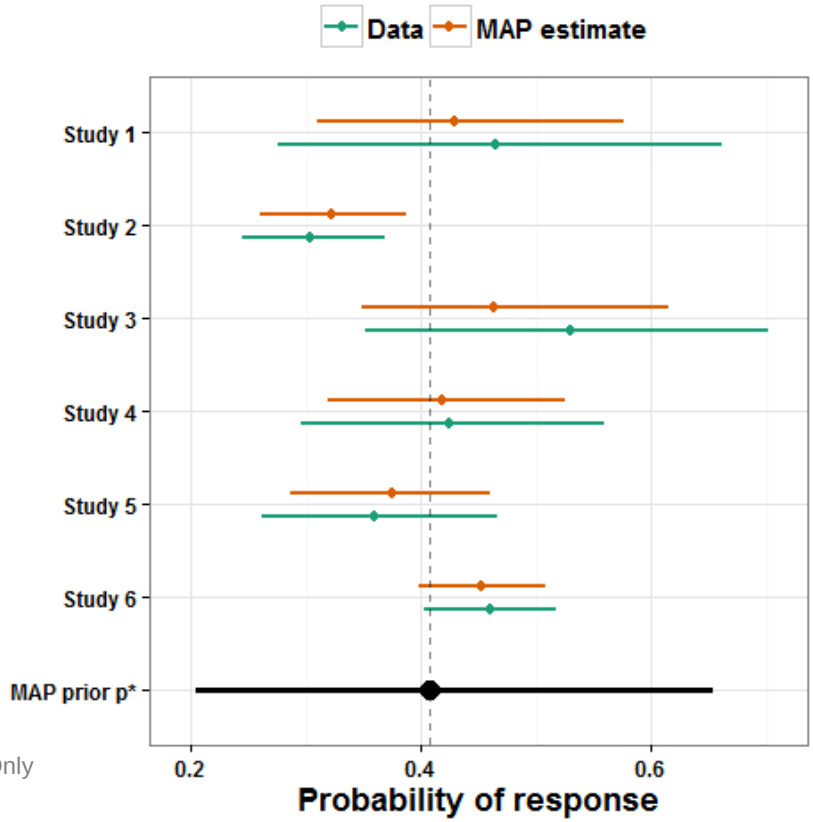
Meta-analysis for the placebo arm

Mathematical model

- Mathematical setup for H historical studies:

$$\text{Model: } r_h \sim \text{Binomial}(p_h, n_h),\ \text{logit}(p_h) \sim N(\mu, \tau^2),\ h = 1, \ldots, H$$
$$\text{Priors: } \mu \sim N(0, 1e10) \text{ and } \tau \sim \text{Half-Normal}(0, 1)$$
$$\text{Prediction for this study: } \text{logit}(p^*) \sim N(\mu, \tau^2)$$

- 6 similar historical studies with 747 total placebo patients
  - Pooled mean event rate = 40%
- JAGS used to simulate draws from prior predictive distribution of p*
- Forest plot shows results of this analysis



Meta-analysis for the placebo arm

Robust mixture priors

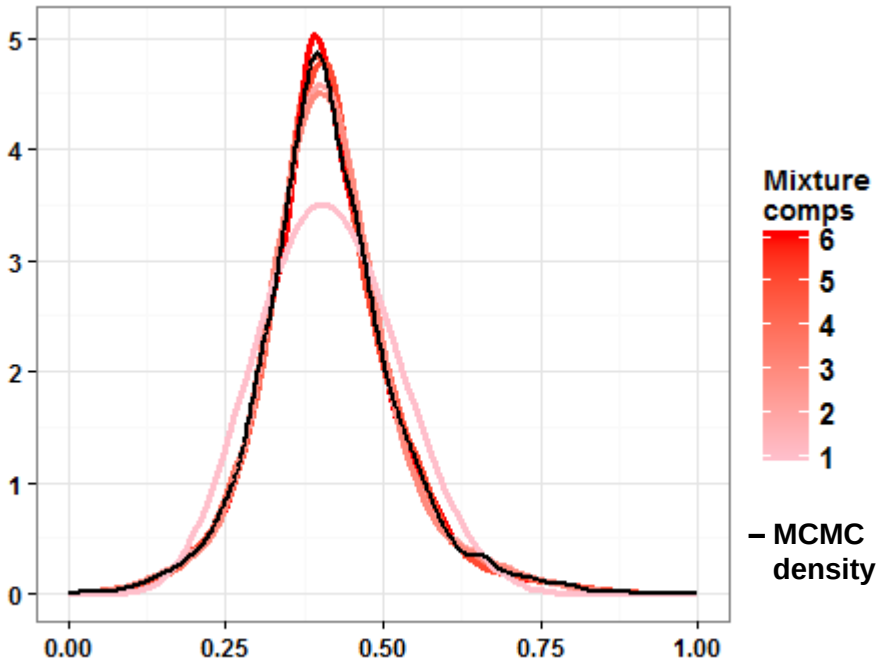
$$w_i^* = \frac{w_i C_i}{\sum_j w_j C_j}$$

$$C_j = \frac{B(a_j + y_C, b_j + n_C - y_C)}{B(a_j, b_j)}$$

- Distribution for p* approximated with a mixture of beta priors
- Reasonably good approx. with ≥2 components

$$p_C \sim \sum_{i=1}^{3} w_i \text{Beta}(a_i, b_i)$$

$$\Rightarrow p_C | Y_C = y_c \sim \sum_{i=1}^{3} w_i^* \text{Beta}(a_i + y_C, b_i + n_C - y_C)$$



NOVARTIS

Meta-analysis for the placebo arm

Robust mixture priors

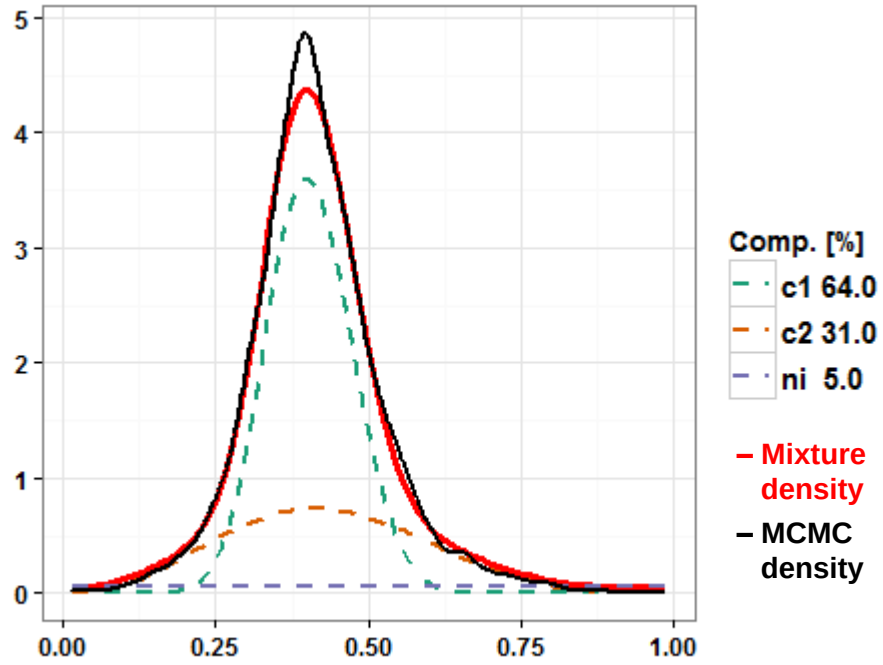
$$w_i^* = \frac{w_i C_i}{\sum_j w_j C_j}$$

$$C_j = \frac{B(a_j + y_C, b_j + n_C - y_C)}{B(a_j, b_j)}$$

- Distribution for p* approximated with a mixture of beta priors
- Reasonably good approx. with ≥2 components
- Final prior is 3-component beta mixture:
  - 0.64*Beta(19.49,28.80) + 0.31*Beta(3.88,5.11) + 0.05*Beta(1,1)
  - 'Simpler' prior chosen at the time for pragmatic reasons
  - Extra weakly-informative component added for 'robustification'

$$p_C \sim \sum_{i=1}^{3} w_i \text{Beta}(a_i, b_i)$$

$$\Rightarrow p_C | Y_C = y_c \sim \sum_{i=1}^{3} w_i^* \text{Beta}(a_i + y_C, b_i + n_C - y_C)$$

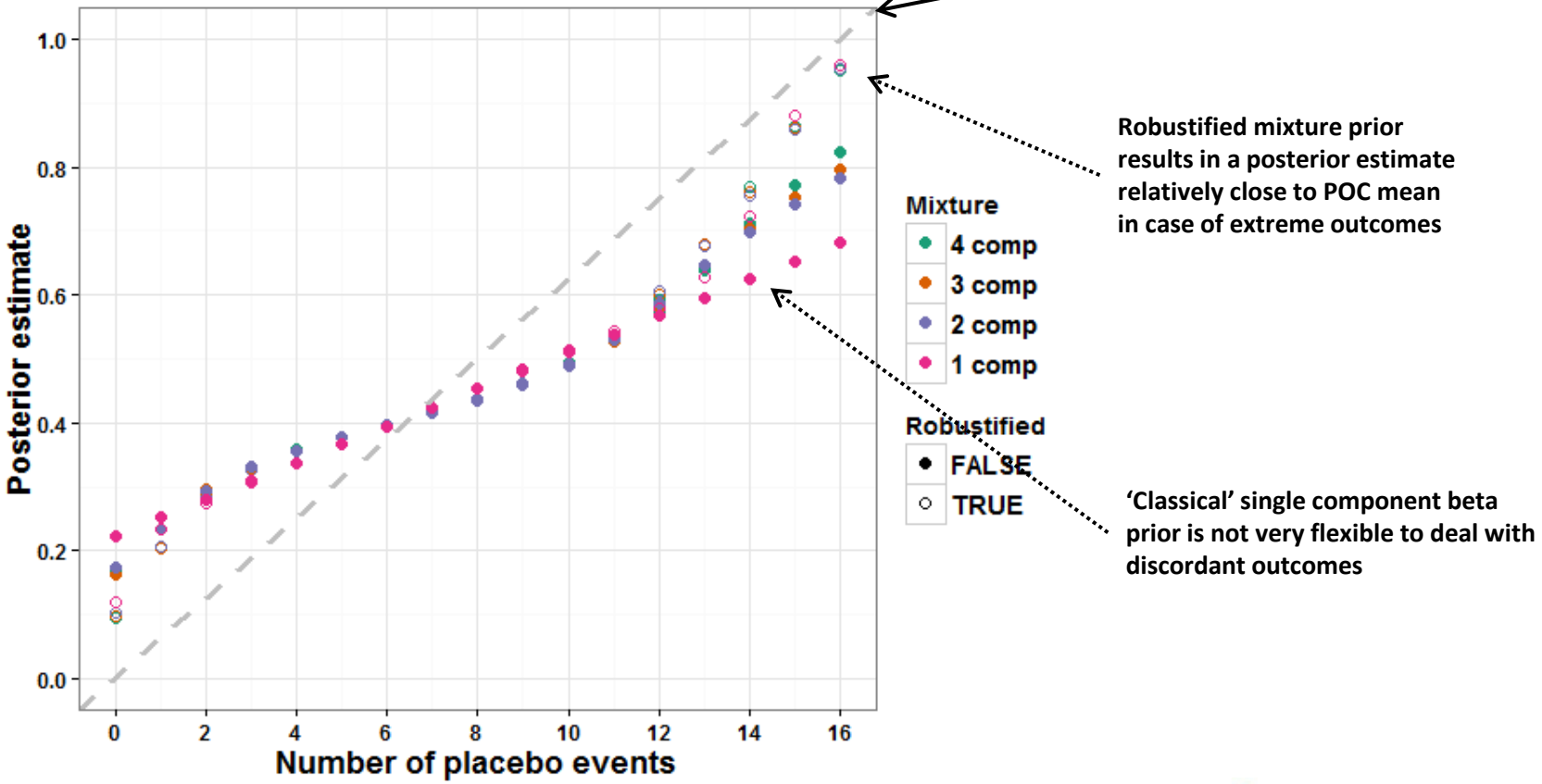


NOVARTIS

Meta-analysis for the placebo arm

Robusness

- 'Robustified' MAP prior responds with greater flexibility to prior data conflicts
- Number of components not too influential in this context (as long as ≥2)

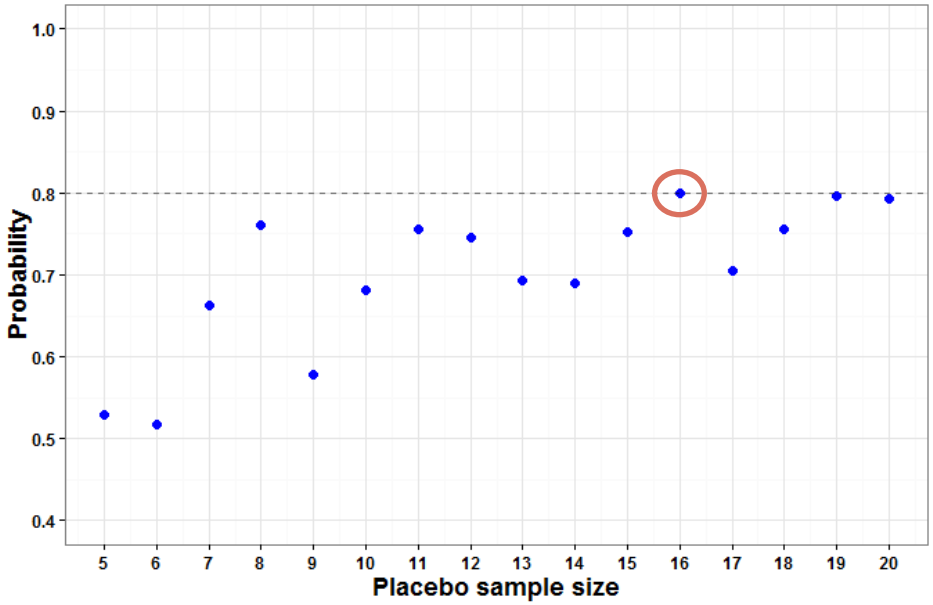


NOVARTIS

Meta-analysis for the placebo arm

Placebo sample size

- Effective sample size of prior computed as in (Morita et al. 2008)
  - ESS = Sample size such that expected information of the posterior under a non-informative prior is the same as the information of the robust MAP prior
  - In our case = 42
- Considerable information for placebo
- Decision: 16 placebo patients
  - Allow meaningful comparison on secondary endpoints and safety
  - Maximize prior predictive probability of observing a placebo event rate in the 90% predicted interval for p*



NOVARTIS

Primary analysis

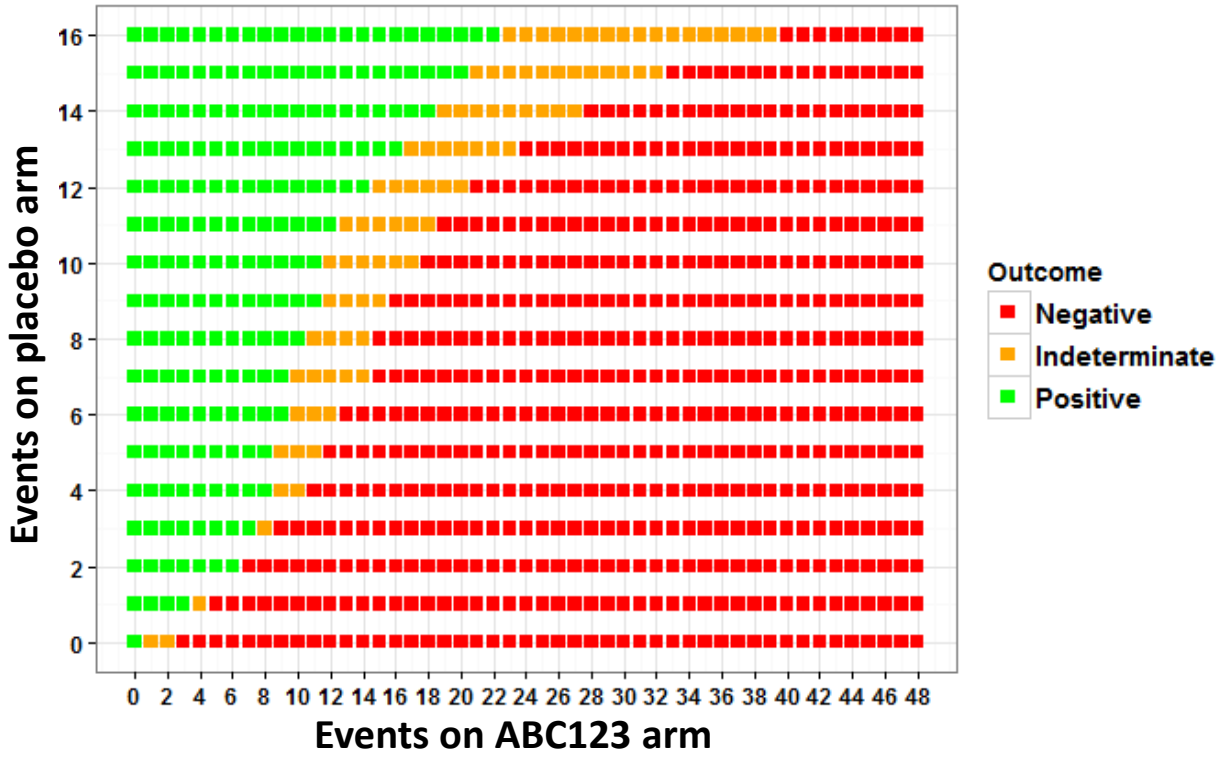
Statistical model and PoC criteria

- Primary endpoint is binary (infection yes/no)
  - Efficacy represented in terms of relative risk pT/pC
- Use beta-binomial model for analysis
  - Non-informative Beta(1/3,1/3) prior for p_T
  - Informative prior on p_C based on historical data (details to follow)
  - Prior mean 0.41 and 90% CI (0.24,0.64) – Effective sample size 42
- 3:1 randomization ratio in favor of ABC123 with total N = 64
- Quantitative PoC criteria:
  1. Posterior probability that p_T/p_C <1 is at least 0.9
  2. Posterior probability that p_T/p_C <0.5 is at least 0.5
- Outcomes
  - 1) and 2): “Positive result”
  - Neither 1) nor 2): “Negative result”
  - 1) or 2), not both: “Indeterminate”

Trial outcomes

Visualizing outcome vs. success/failure

- With a binary endpoint we can tabulate (or plot) trial outcomes ahead of time
- Quantitative success criteria can be fine-tuned via visualization
- This illustration quite useful for clinical colleagues as a ‘gut-check’ of success criteria

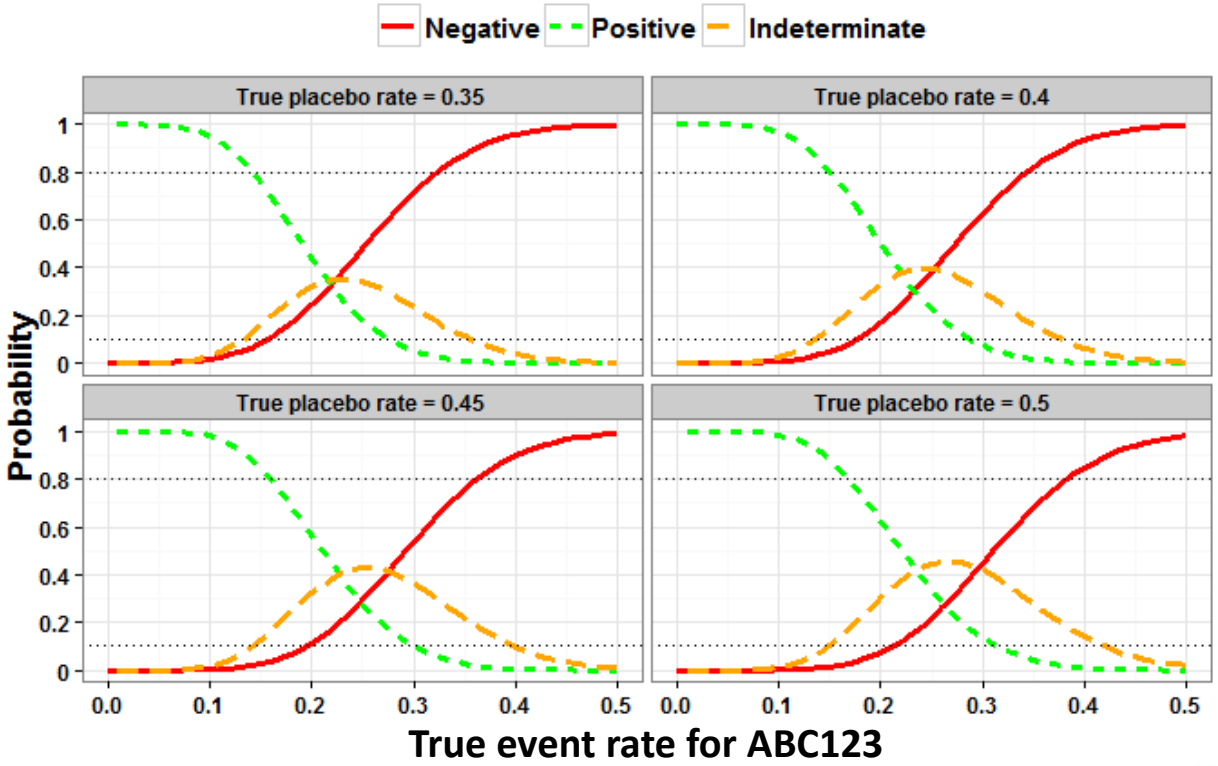


NOVARTIS

Operating characteristics

3:1 randomization – 64 total evaluable subjects

- Probability of negative result is usually <0.2 (at ABC123 ≤0.2)
- Probability of positive result usually >0.8 (at ABC123≤0.15)
- Robust OC for range of true placebo event rates (0.35-0.5)

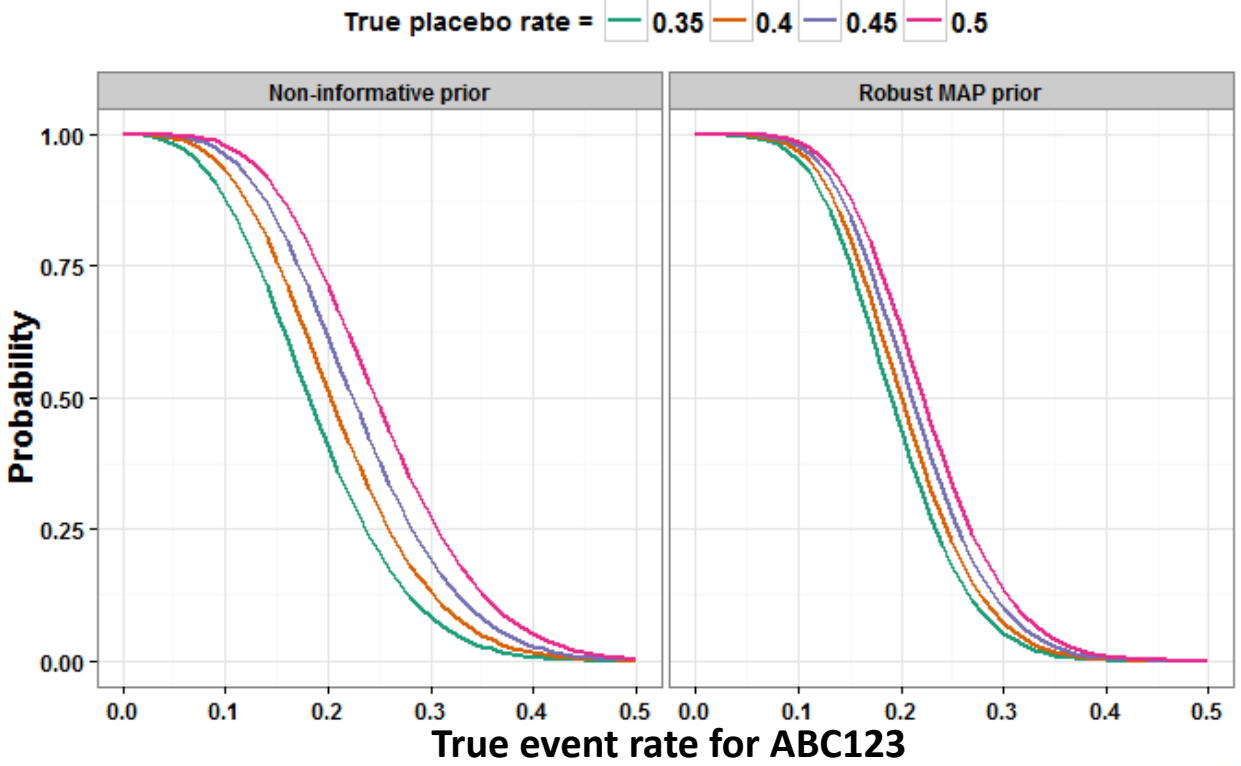


NOVARTIS

Operating characteristics

3:1 randomization – 64 total evaluable subjects

- Probability of negative result is usually <0.2 (at ABC123 ≤0.2)
- Probability of positive result usually >0.8 (at ABC123≤0.15)
- Robust OC for range of true placebo event rates (0.35-0.5)



NOVARTIS

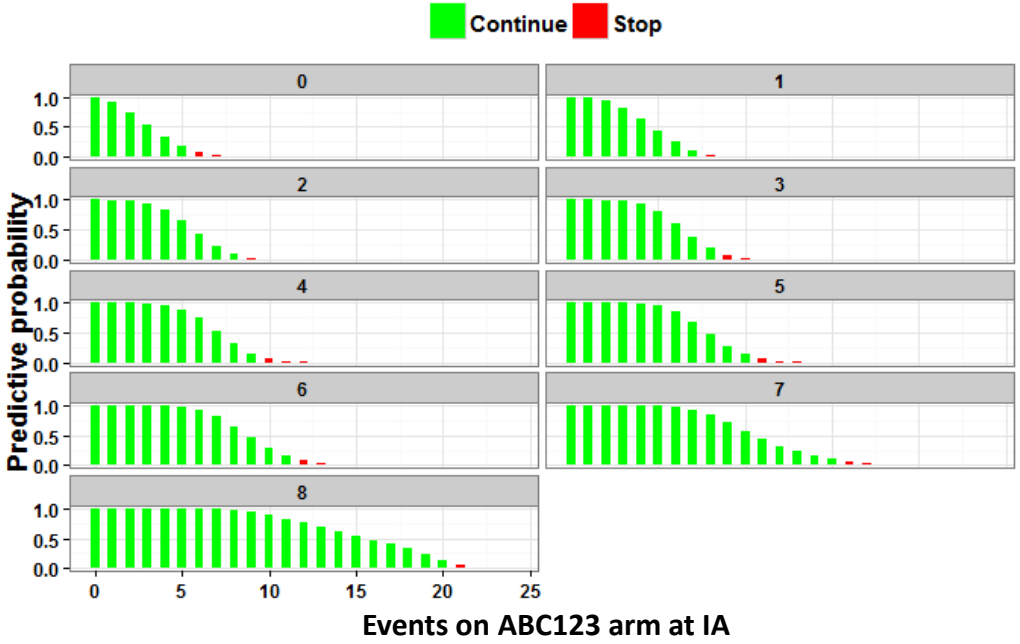
Interim analysis

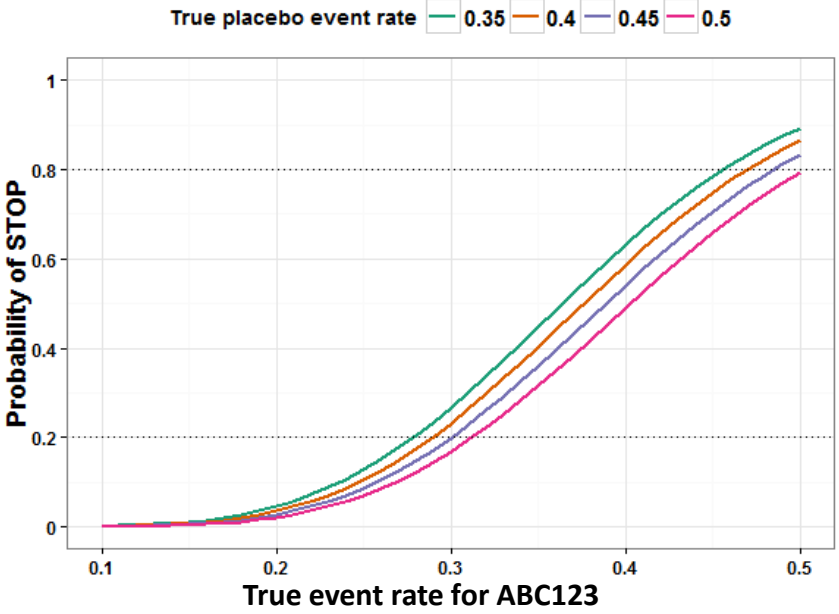
Quantitative futility criterion

$$\Pr\left(\text{Pos or Ind} \mid \text{data}\right) = \int \Pr\left(\text{Pos or Ind} \mid \theta\right) p(\theta|\text{data}) d\theta$$

$$\theta = (p_C, p_T)$$

- Team desired IA with option to terminate study based on futility
  - Analysis conducted with 50% planned sample size
- Futility defined as <0.1 predictive probability of achieving positive or indeterminate trial result





NOVARTIS

Conclusion & discussion

- Clinical trial team was enthusiastic about the methodology
  - “Bayesian” seems popular
  - Saving placebo patients was an attractive option
- MCMC distribution can be approximated with few (≥2) mixture components
- Additional possibilities not included in final design
  - IA readout for efficacy
  - Re-estimation of placebo sample size at IA
- Choosing the placebo sample size was not straightforward
  - Some confusion about “confirming” the meta analysis
- Usefulness of graphs for illustration
  - Trial outcomes, predictive power, etc.

References

- Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B (2014) Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics* 70(4):1023-1032.
- Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ (2010) Summarizing historical information on controls in clinical trials. *Clinical Trials* 7, 5-18.
- Morita S, Thall PF, Müller P (2008) Determining the effective sample size of a parametric prior. *Biometrics* 64, 595-602.