

For the sake of the patient – reducing placebo exposure by using historical controls

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Motivation for considering the use of historical controls

- During drug development, frequently a part of the study population is exposed to (ineffective) placebo, a burden for the patient and the Sponsor
- Recent advances in evidence synthesis offer a possibility to reduce this burden by using historical control information instead of actually exposing patients to placebo
- Historical controls have already been successfully used for PoC trials (e.g., reduction of 24 placebo patients to 6 by using historical control information: PoC in ankylosing spondylitis, Lancet 2013).

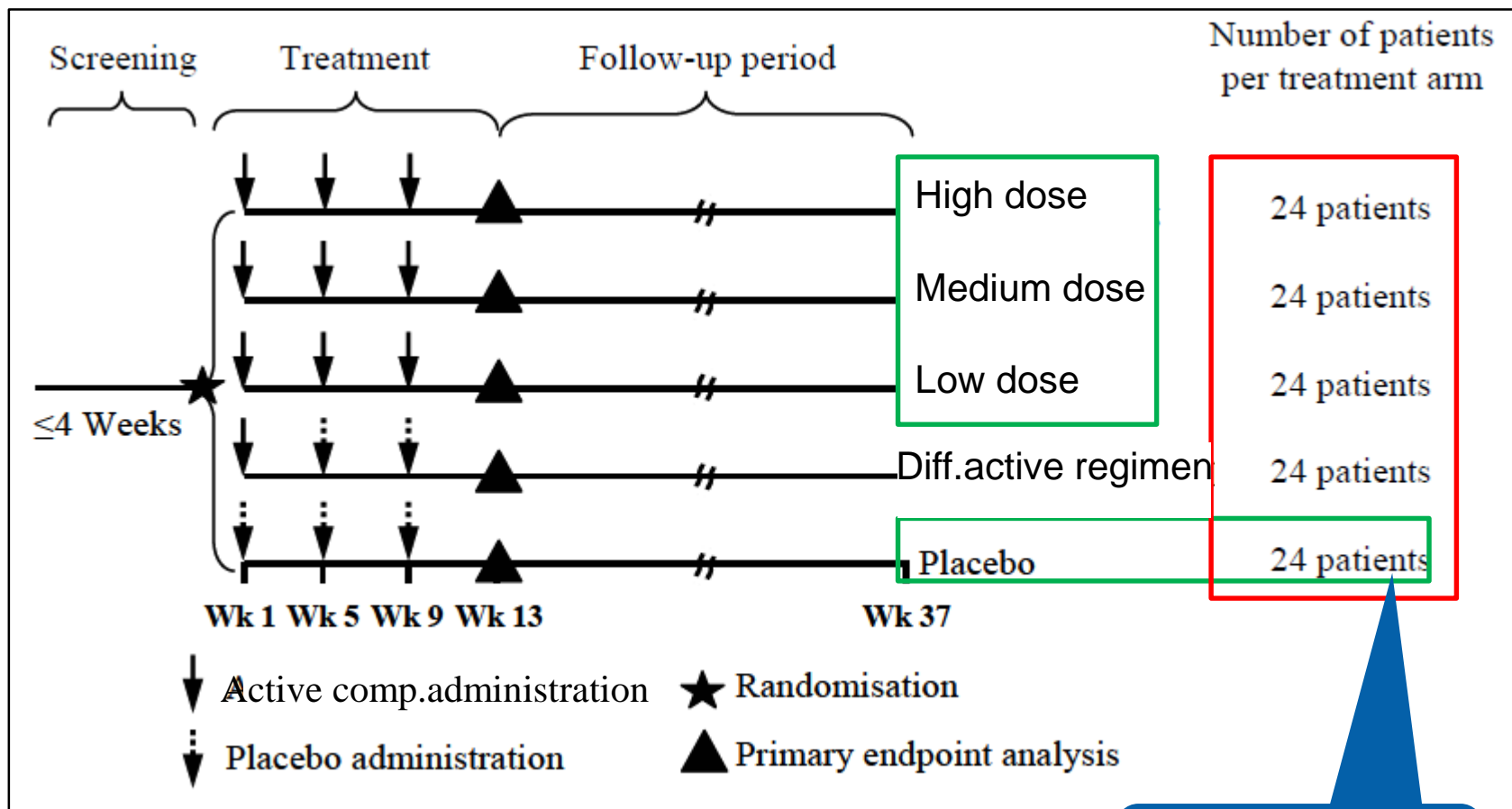
Case study:

Psoriasis dose finding study

- We assessed whether by using historical data, the dose finding program for a compound in psoriasis could have been implemented with **fewer or no subjects on placebo** at little or no loss of accuracy– using only information available at the time
- This was assessed specifically for a dose ranging study.
- Objective: “Select dose such that we are 80% sure that PASI75* response rate is at least 55% better than placebo”

*Psoriasis Area and Severity index reduction $\geq 75\%$

Case Study design



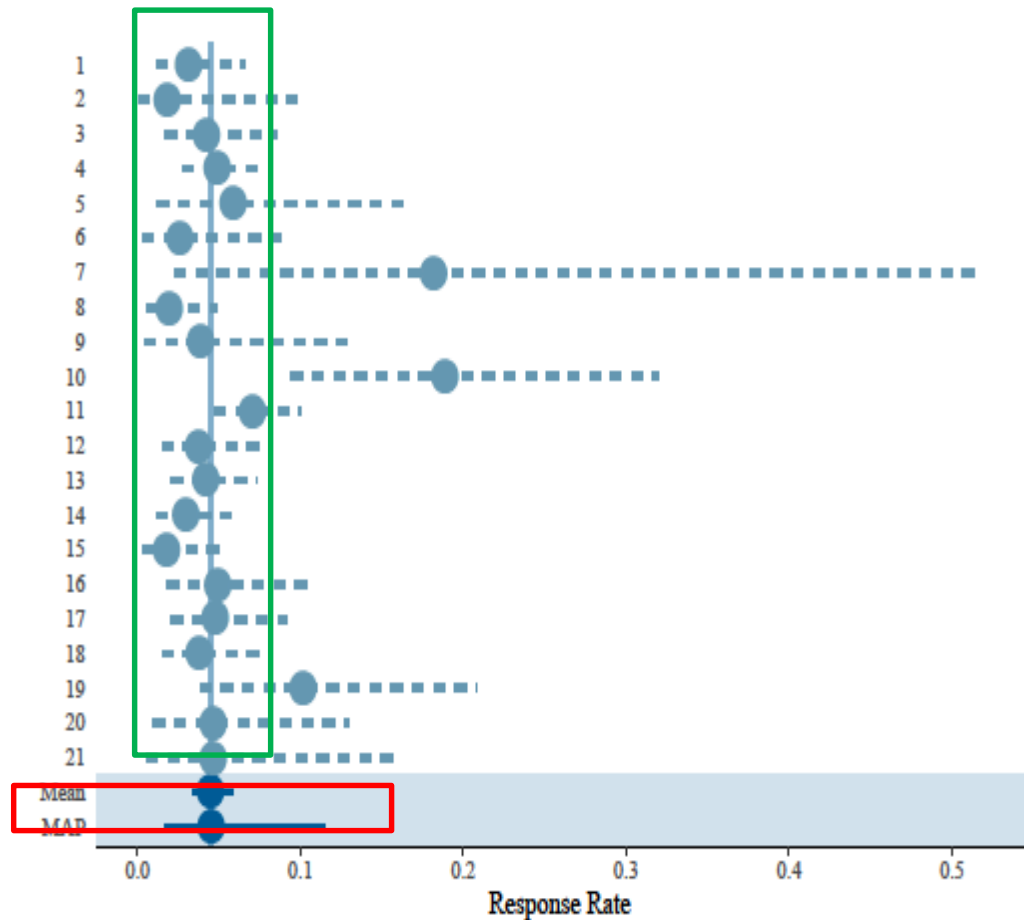
Note balanced randomization

Historical placebo response rates

- 21 historical randomized controlled clinical studies in psoriasis, with 3,071 pbo subjects
- Note that most studies show similar response rates

Prediction of response rate in new study (mean = 0.05 95% Credible Interval 0.017, 0.115)

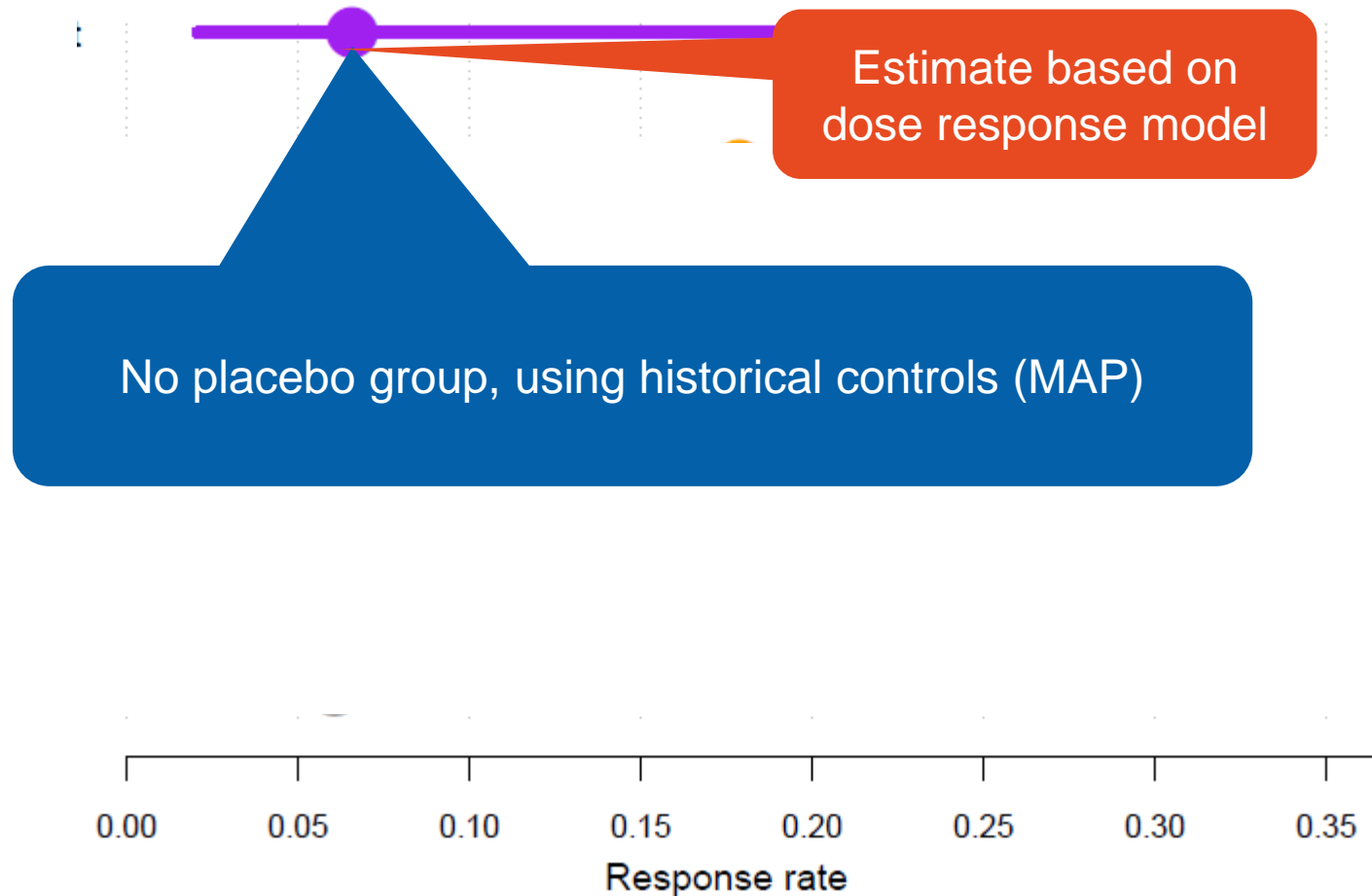
Bansbeck N et al, 2009



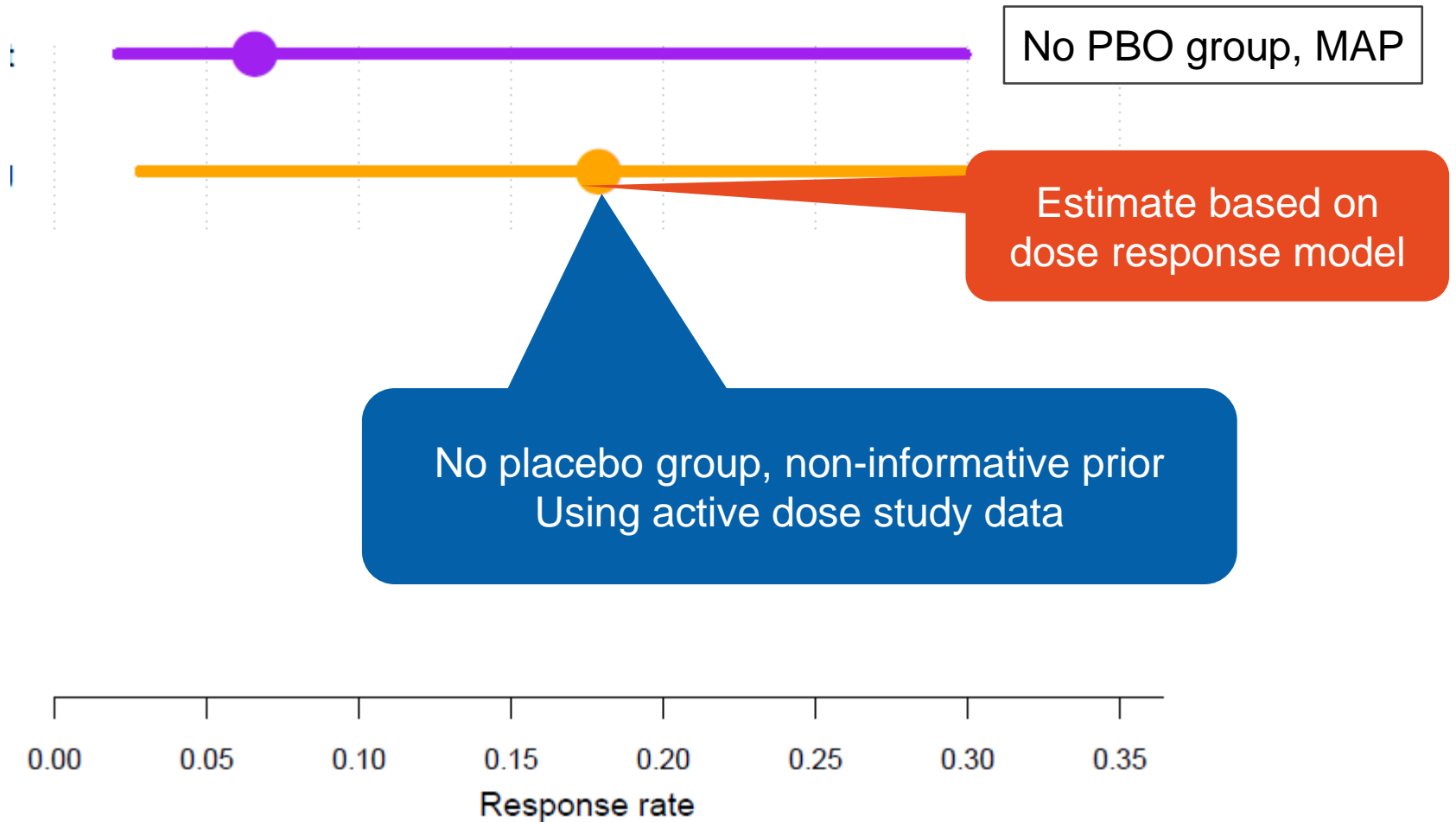
Possible outcomes

- **Predicted** placebo response rate in the new study of 5%, Credible Interval (CI) 1.7% to 11.5%
- **The study was evaluated using a Bayesian approach to estimate a dose-response model (sigmoid Emax model)**
 - With the full placebo group and a non-informative prior (NIP)
 - With 0 placebo patients and no historical data
 - With 0 placebo patients and using historical controls (MAP)
- If using historical support, will the outcome of «no placebo scenarios» be **similar** to the full study data scenario?

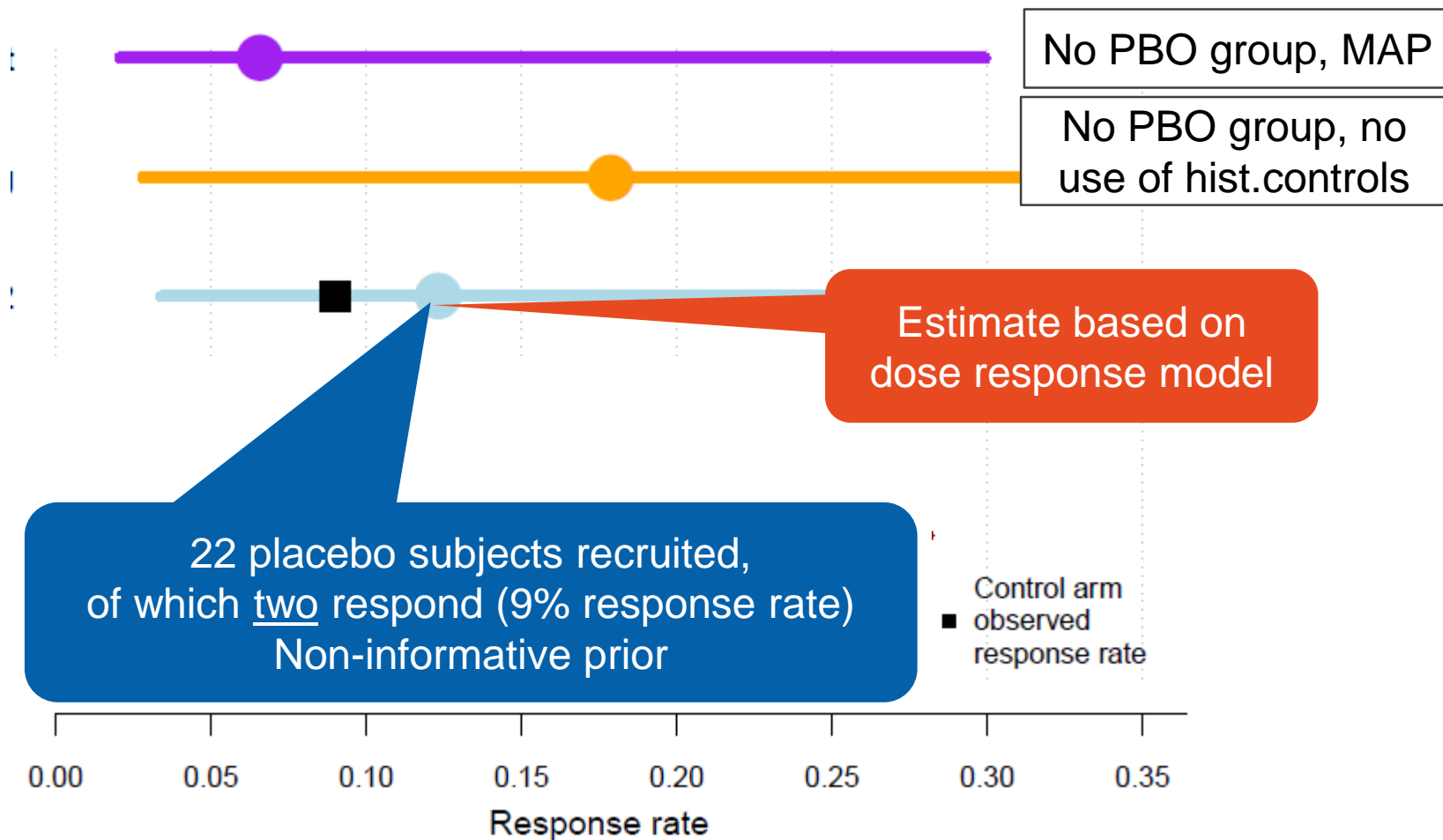
Observed and estimated, based on dose response model, PBO response



Observed and estimated, based on dose response model, PBO response



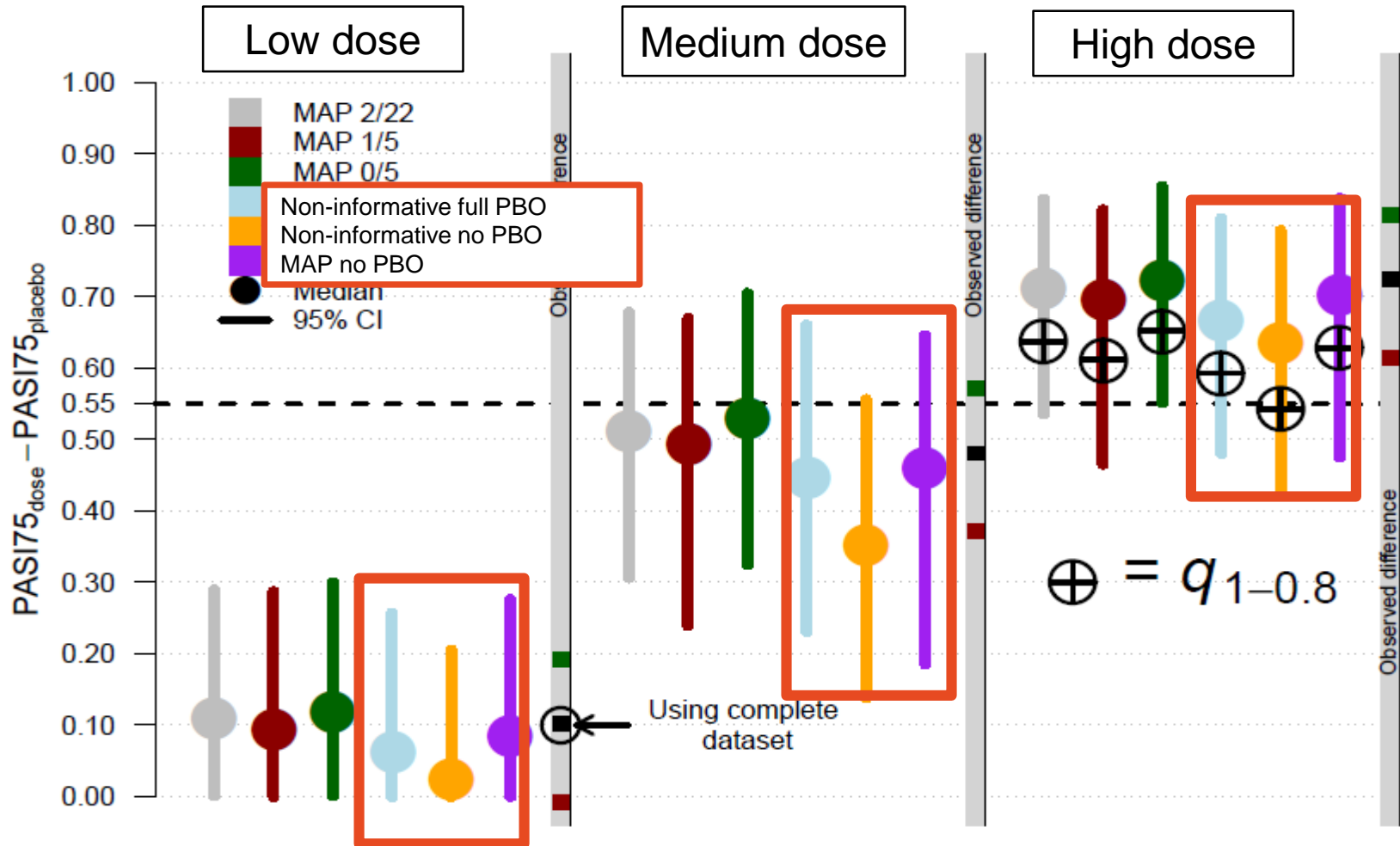
Observed and estimated, based on dose response model, PBO response



What we wanted to find out

- In the original study, **22 subjects received placebo**, of which 2 (9%) had a PASI 75 response at Week 12
- What would have happened if we had exposed **no** subjects to placebo?
 - ...and had taken into account historical information?
 - ...and had ignored historical information?
- Other scenarios evaluated, not discussed here– 5 PBO patients with 0/1 responders

Results Difference vs placebo per dose



- Only the high dose fulfills the selection criterion
- Same decision reached with no patients on placebo, using historical controls
- No dose selected if a non-informative prior is used (without historical controls)

Summary and Discussion

- Had we taken into account historical data into the planning of the analysis, we could have exposed **fewer (e.g. 5) or even no instead of 22** subjects to placebo – and have come to the **exact same conclusion!** (provided response rates for the active doses remained very similar if 5 or no patients had been randomised to placebo, and the placebo response level is stable over time)
- Further research is required to gain insight into how the size of the placebo group can influence the level of response
- Usually, placebo data do not only provide information on the dose (primary) response curve but also on secondary variables and safety. These data would not be available without a placebo group.

Summary and Discussion

- More experience is needed with applications of the approach discussed here (MAP based on a meta-analysis and functional uniform priors for Bayesian dose response estimation) – planning ongoing

References

1. Björn Bornkamp. Practical considerations for using functional uniform prior distributions for dose-response estimation in clinical trials. *Biometrical Journal*, 56(6):947962, 2014.
2. Nick Bansback, Sonia Sizto, Huiying Sun, Steven Feldman, Mary Kaye Willian, and AslamAnis. Ecacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. *Dermatology*, 219(3):209218, 2009
3. Heinz Schmidli, Sandro Gsteiger, Satrajit Roychoudhury, Anthony O'Hagan, David Spiegelhalter and Beat Neuenschwander. Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, 70(4):10231032, 2014.