Bayesian borrowing of adult efficacy data in paediatric drug development: A Case Study

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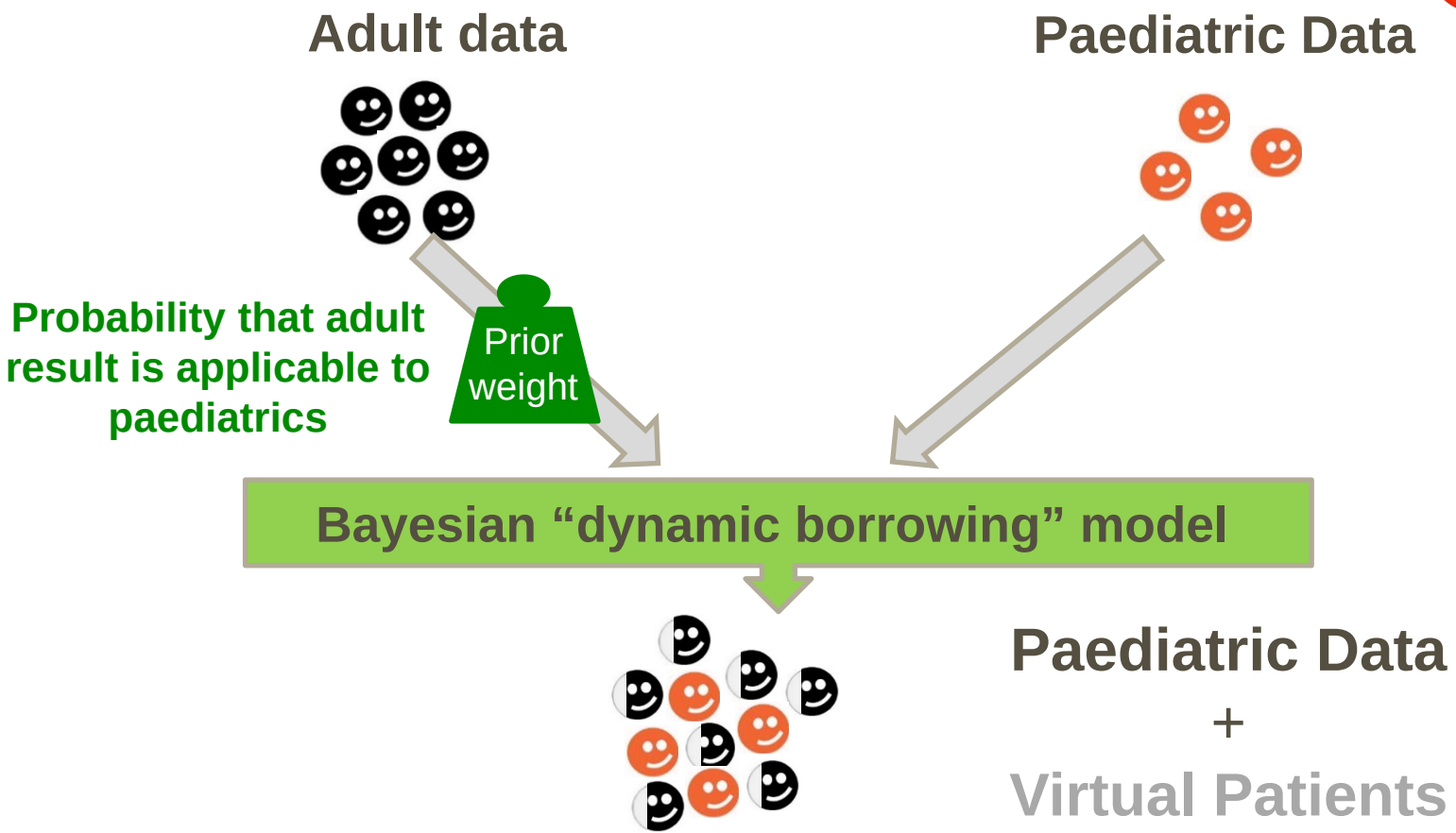
Case study: Benlysta for SLE in paediatric patients

- Intravenous Benlysta® (Belimumab) is approved for the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) , which was supported by two pivotal Phase 3 studies (C1056 and C1057).
- The PLUTO study was carried out in children aged 5-17 with SLE as part of the paediatric post-marketing requirement.
- Paediatric lupus is very rare, and shares the same pathophysiology and disease manifestations as adult SLE.
  - A fully powered study with a large sample size was not feasible.
  - Consideration should be given to avoid exposing children to placebo-controlled trials unnecessarily.
  - Study was designed using a bridging strategy to show directional consistency in efficacy and safety with adults, and was not powered for any hypothesis testing.
  - It was agreed with regulators to collect data from ~90 subjects and summarise results descriptively.

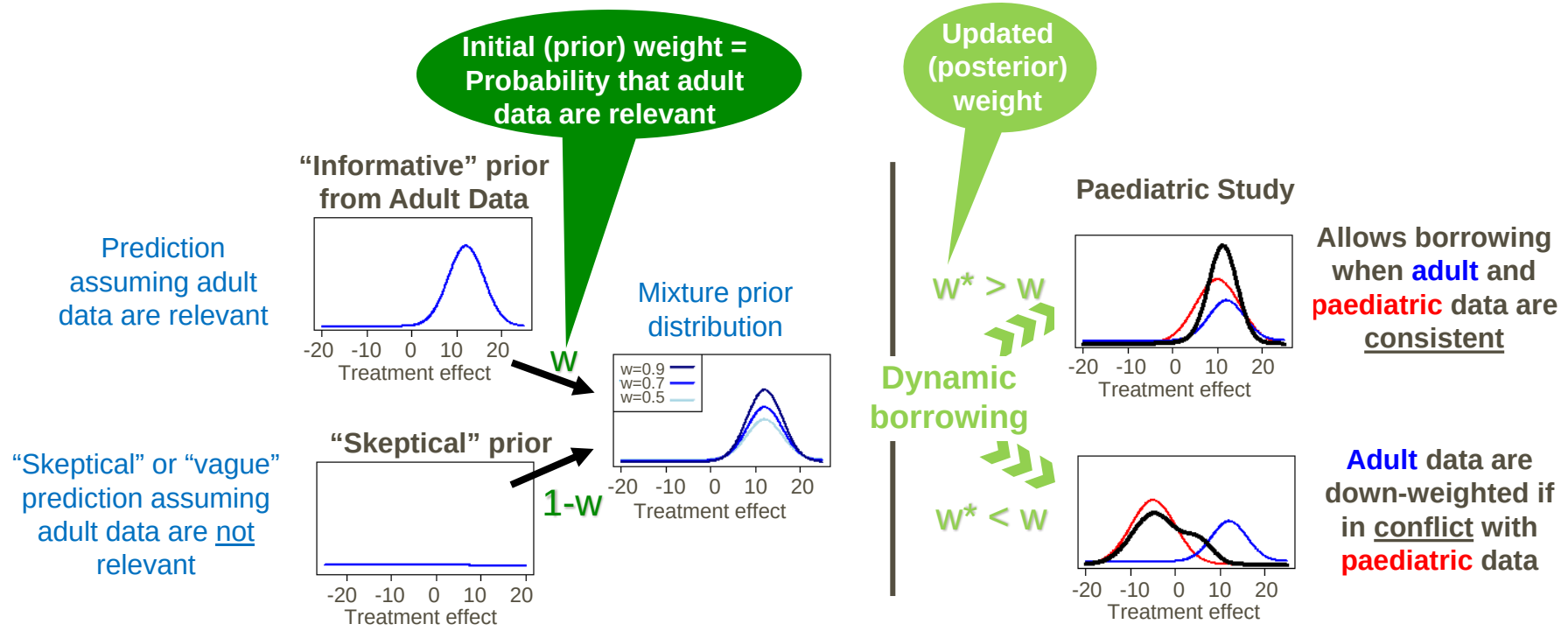
FDA review of Benlysta paediatric submission

- PLUTO study completed in 2018 and GSK submitted an application to FDA for a paediatric label expansion in October 2018, with approval received in April 2019.
- During the pre-NDA meeting, FDA made some analysis requests:
  - FDA noted that the previous adult studies "may provide some useful information that is relevant to the paediatric population"
  - Recommended that we conduct sensitivity analyses using Bayesian dynamic borrowing (Bayesian mixture prior) which utilizes efficacy information from the adult studies
  - Specifically requested a "tipping point" style analysis to **quantify how much prior belief (range of prior weights)** in the applicability of the Adult result it would take in order for the Paediatric study data to **look convincing**

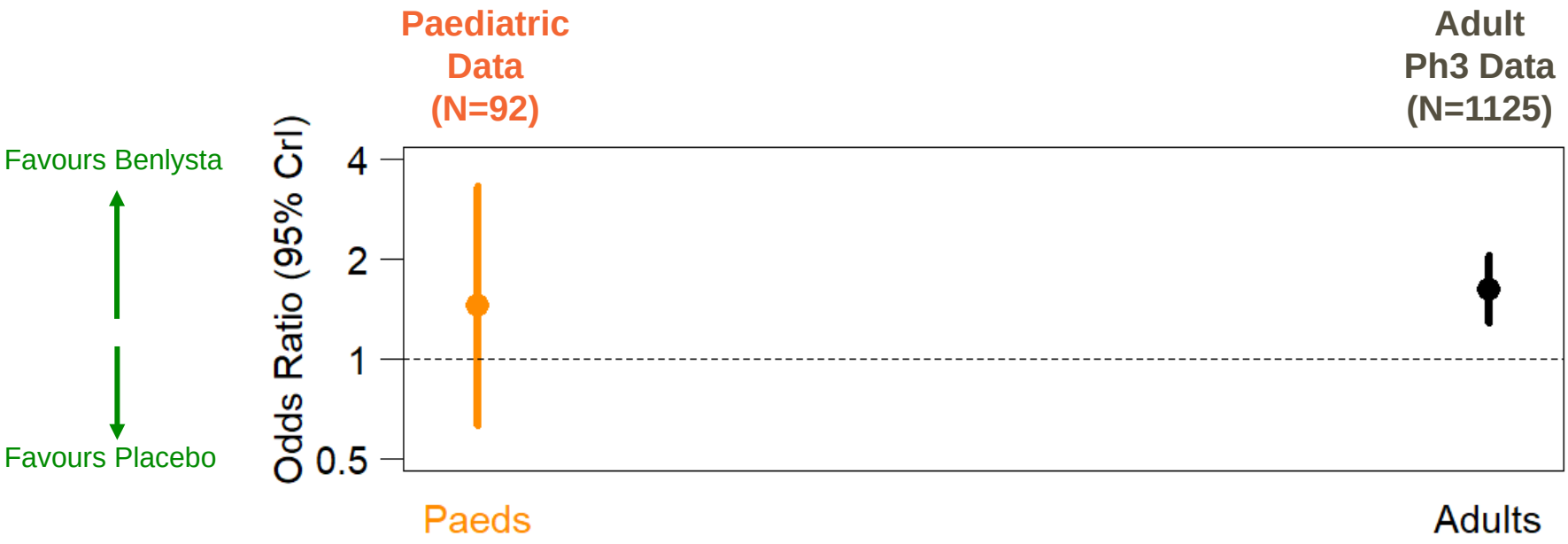
Bayesian Dynamic Borrowing



Bayesian Dynamic Mixture priors



Tipping point Bayesian dynamic mixture prior analysis of Benlysta paediatric study: SRI Responder endpoint



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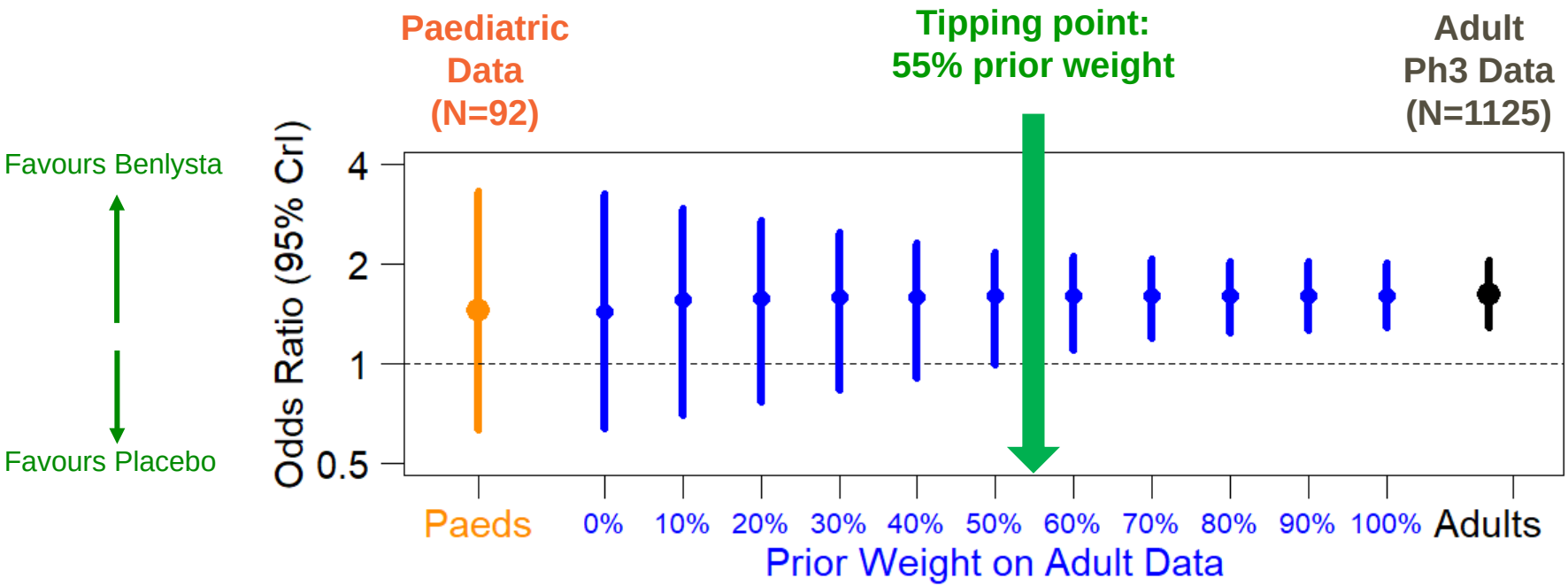
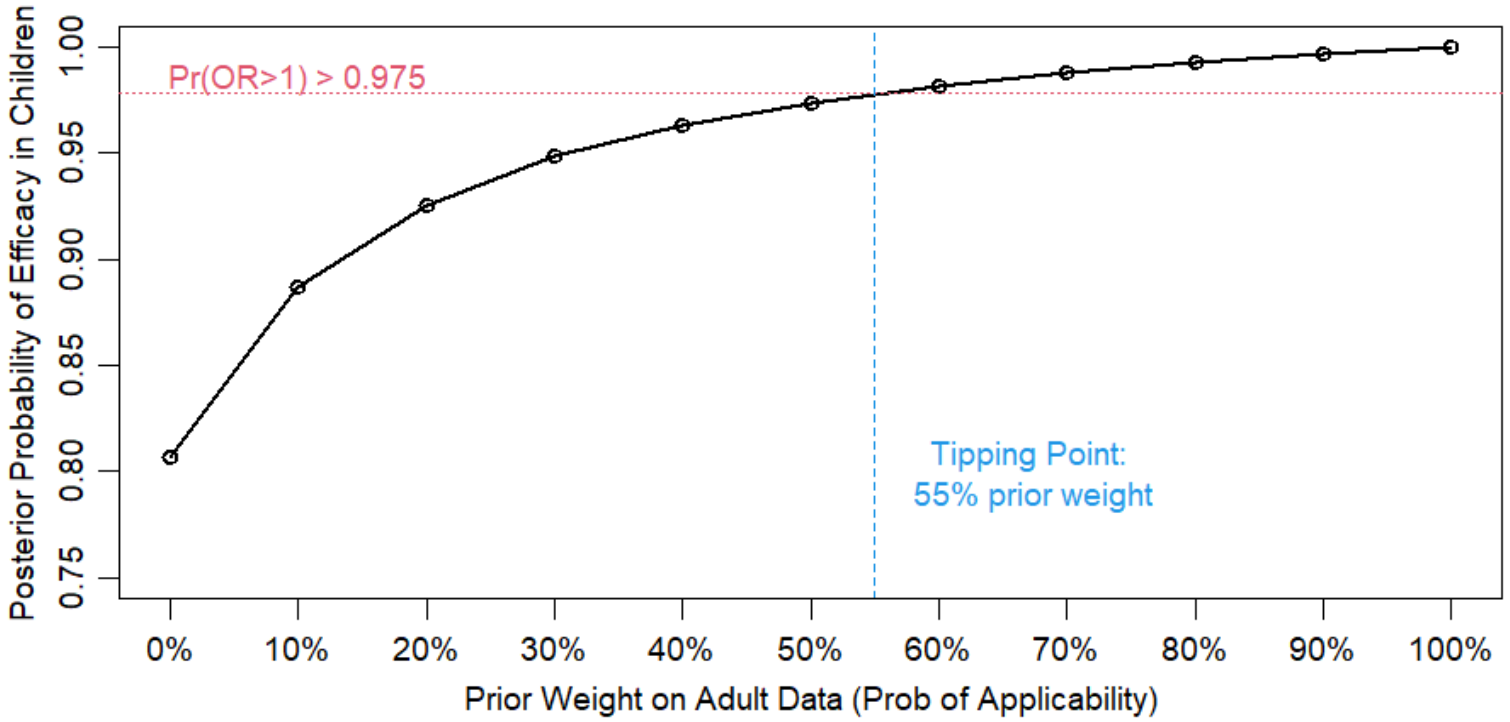


Tipping point Bayesian dynamic mixture prior analysis of Benlysta paediatric study



Analysis of Credibility

- Tipping point approach is a type of “analysis of credibility”
  - identify properties of the prior distribution needed to achieve a certain posterior statement for the data at hand
  - used to assess the plausibility of scientific claims and findings
- The weight corresponding to the tipping point = minimum prior belief in the relevance of the adult data needed to find the evidence from the paediatric study convincing
- Allows a range of decision-makers – who may hold different prior beliefs – to assess the credibility of the evidence in the paediatric population.

Held, L. (2019). The assessment of intrinsic credibility and a new argument for $p < 0.005$. *R. Soc. open sci.* **6:**181534
Matthews R. (2018). Beyond ‘significance’: principles and practice of the analysis of credibility. *R. Soc. open sci.* 5, 171047
Good, I.J. (1950). Pobability and the Weighing of Evidence. Griffin, London, UK

FDA conclusion

"Based on discussion and feedback obtained from the clinical team, it appears reasonable to assume at least 55% weight on the relevance of the adult information to the pediatric population and we can therefore conclude that there is at least 97.5% posterior probability that Benlysta has a positive treatment effect in pediatric subjects"

https://www.fda.gov/media/127912/download

Concluding remarks

- Recruitment of paediatric patients is challenging in many settings
  - Sample size of paediatric trials typically limits ability to convincingly show evidence of a treatment effect when paediatric data is considered in isolation
- Bayesian dynamic borrowing can be a useful approach to formally incorporate adult data into paediatric clinical trials
  - transparent assumptions about relevance of adult data
  - mathematical rule to learn how much of the adult information to borrow
  - direct measure of totality of evidence (adult + paediatric) on clinical scale
- The results of this innovative retrospective Bayeisan analysis supported the approval of a paediatric label expansion for Benlysta
- Bayesian dynamic borrowing can also be used as pre-specified primary analysis
  - Faster, more efficient way to generate evidence in challenging paediatric settings

Thank you