Scientific Necessity and Pediatric Extrapolation using Adult Data

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Rhonda Fenwick, *Time is Now I*
Through her art, Rhonda has explored psoriasis, a chronic skin disorder she has lived with since the age of six.

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- Robert “Skip” Nelson, MD PhD, is a full-time employee and stock holder of Johnson & Johnson.

Topics

- Ethical Principle of Scientific Necessity
- Extrapolation
  - Two (Implicit) Extrapolation Assumptions
  - Dealing with Uncertainty (using Bayesian methods)
- Extrapolation and Prior Pediatric Trial Results
- Designing Adult Clinical Trials to Support Pediatric Extrapolation

Ethical Principle of Scientific Necessity
(An unnecessary clinical trial is always unethical.)

- The use of extrapolation, when appropriate, is a moral obligation.
  - Derives from the justice of equitable selection (i.e., adults before children) and minimizing risks [21 CFR 56.111(a)(1) and (b); 45 CFR 46.111(a)(1) and (b)]
- "A more targeted generation of evidence [using extrapolation] should help to ensure that children only participate in clinical trials with specific objectives that further the scientific understanding of a medicinal product for use in children and, address the requirements for regulatory decision-making." (emphasis added)
  - EMA Reflection Paper on Use of Extrapolation (7 October 2018)

Extrapolation†

- Extrapolation is an inductive inference that extends known experience and/or data (“source”) into an area not known or previously experienced (“target”) to arrive at a (credible, but inherently uncertain or probabilistic) knowledge of the unknown area.

†In mathematics, extrapolation is the process of estimating, beyond the original observation range, the value of a variable on the basis of its relationship with another variable. It is similar to interpolation, which produces estimates between known observations. The use of modeling in population pharmacokinetics is an example of this type of mathematical extrapolation.

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Two (Implicit) Extrapolation Assumptions

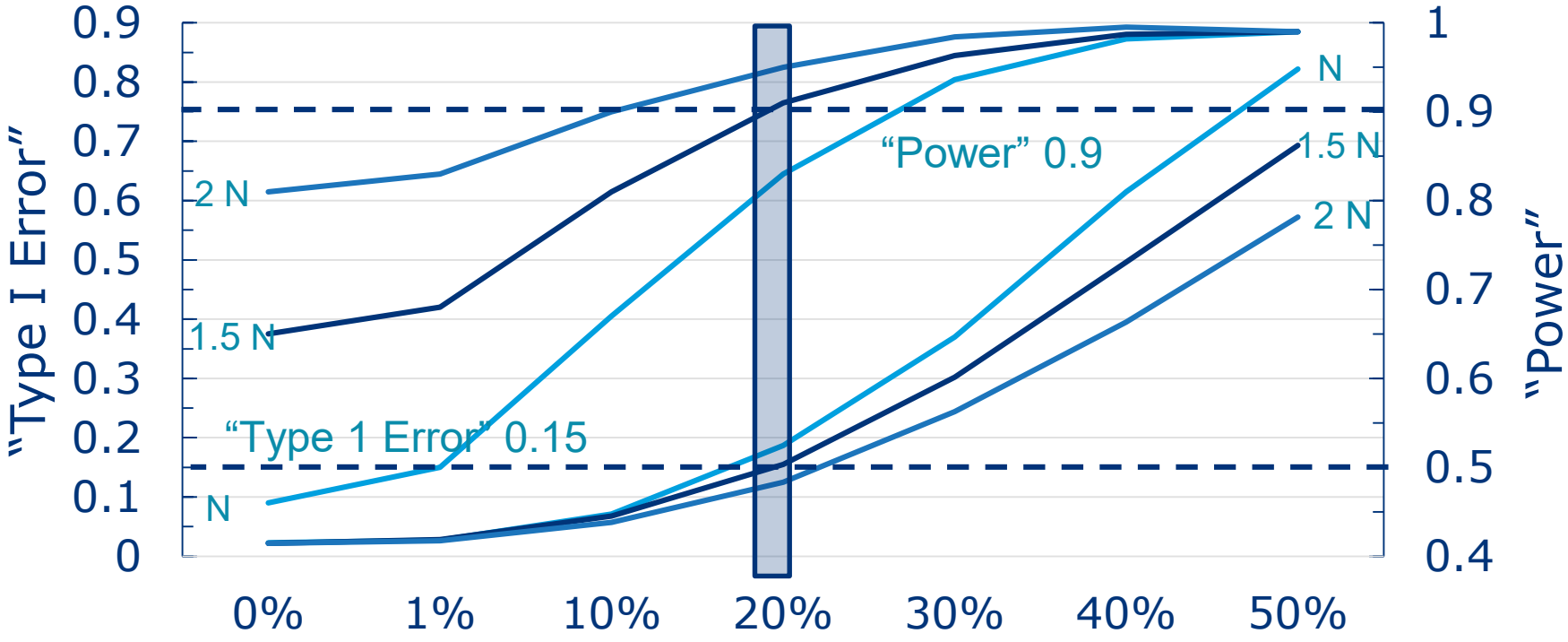
- The regulatory decision to require pediatric studies (e.g., PREA) assumes that the adult indication (FDA) or condition (EMA) exists in the pediatric population (i.e., is "sufficiently similar").
- The ethical requirement for evidence supporting a sufficient prospect of direct clinical benefit to justify the risks of exposing children to an investigational product (cf. 21 CFR 50.52) is generally satisfied by the efficacy and safety data generated in adults with the same indication/condition.
- Both of these judgements implicitly assume extrapolation from an adult to a pediatric population, suggesting that any pediatric studies associated with an adult indication should start with the assumption that some degree of extrapolation is appropriate.

Dealing with Uncertainty

- Inevitably there will be uncertainties associated with the source adult data, data supporting extrapolation to the target pediatric population, and the comparative data between source and target population.
- From a clinical perspective, Bayesian methodologies are able to incorporate these uncertainties in a direct and transparent manner.
- For example, the use of commensurate priors can adjust the level of borrowing source data (i.e., extrapolation) based on the similarity (or concordance) of the adult (source) and pediatric (target) data.
- In addition, the tolerable level of uncertainty (i.e., type 1 error) associated with the assessment that the intervention is effective can be modeled in relationship to the level of borrowing prior data.
  - Note: use of extrapolation increases type 1 error regardless of statistical approach.

Choice of Level of Weighting Prior Data

Impact on Simulated Type 1 Error and Power



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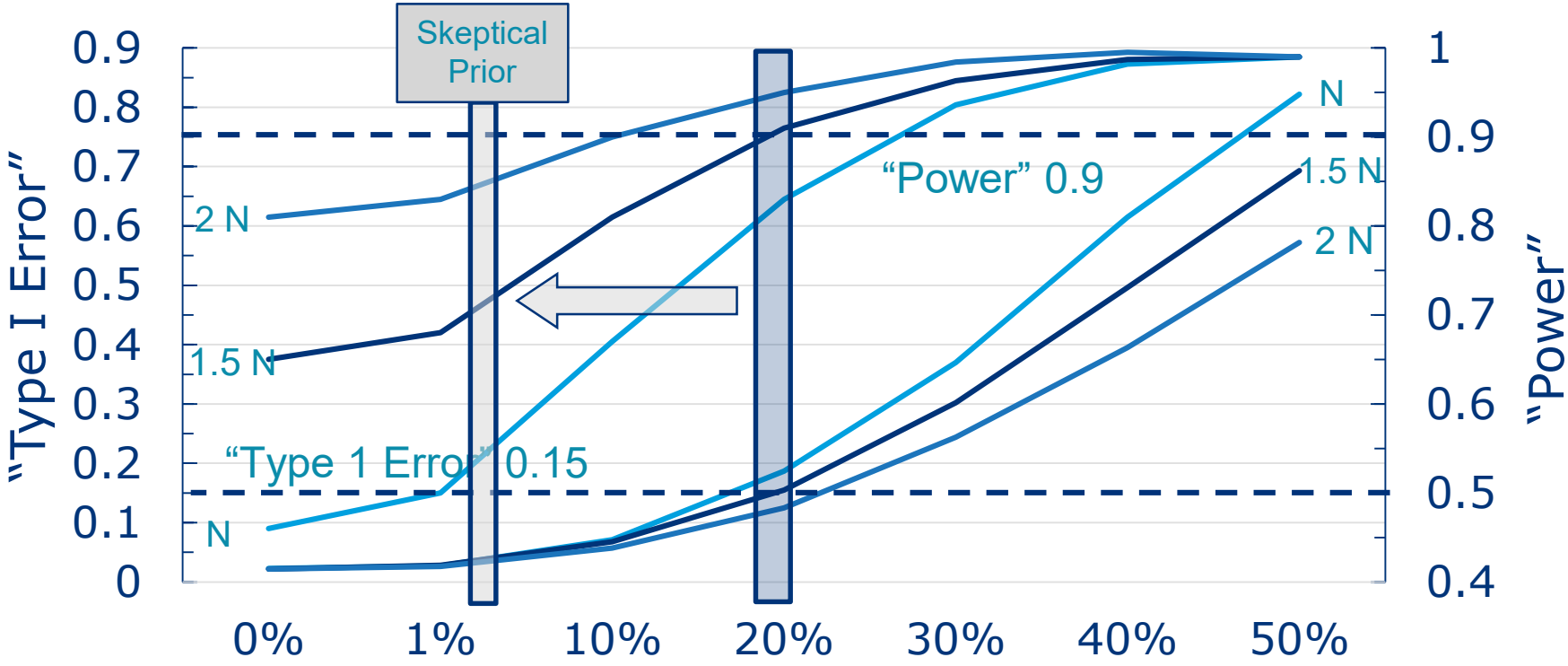

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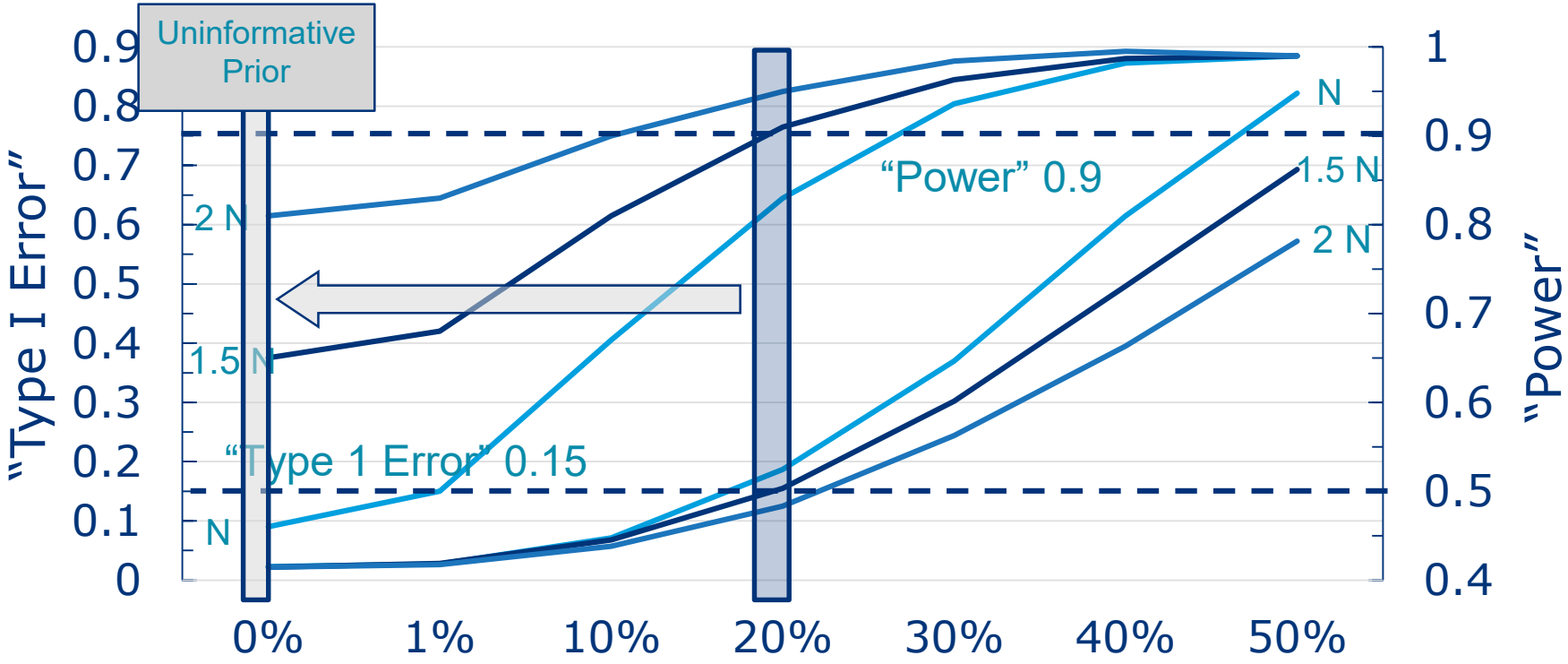

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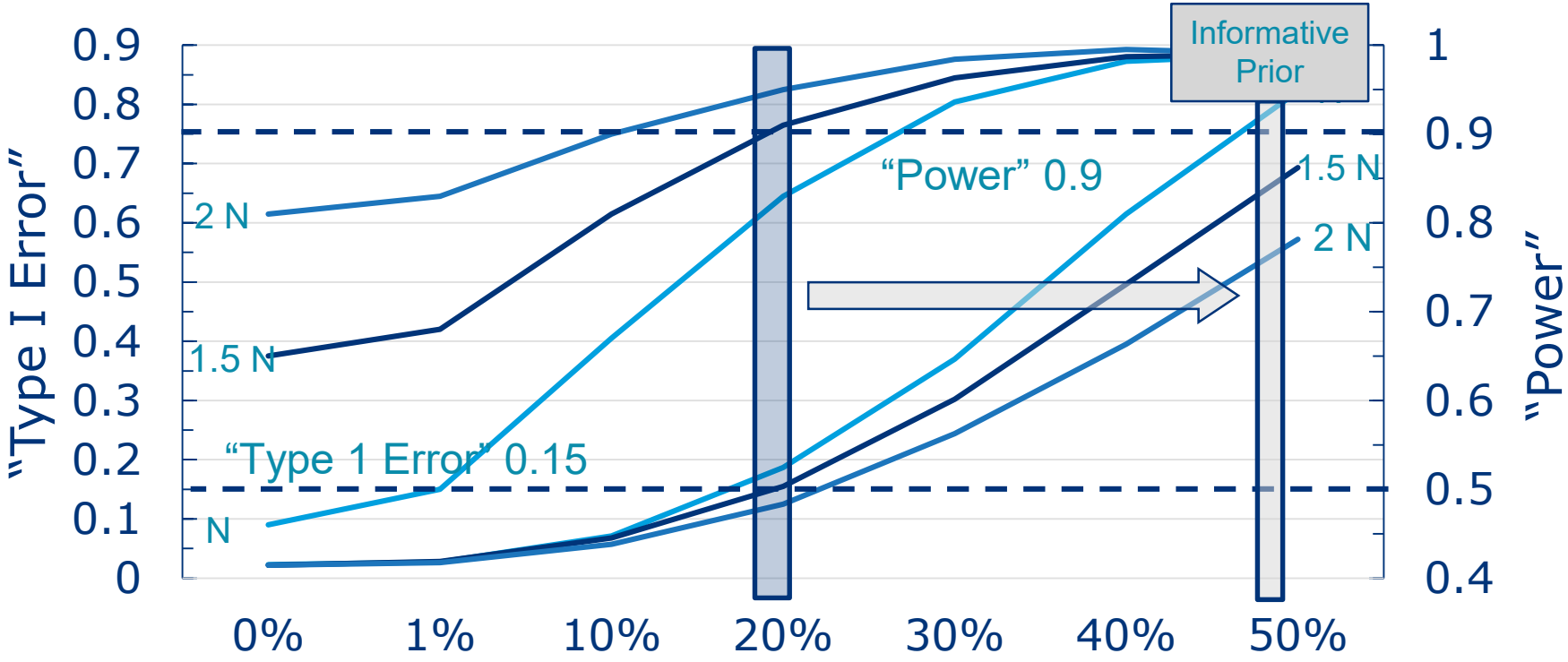

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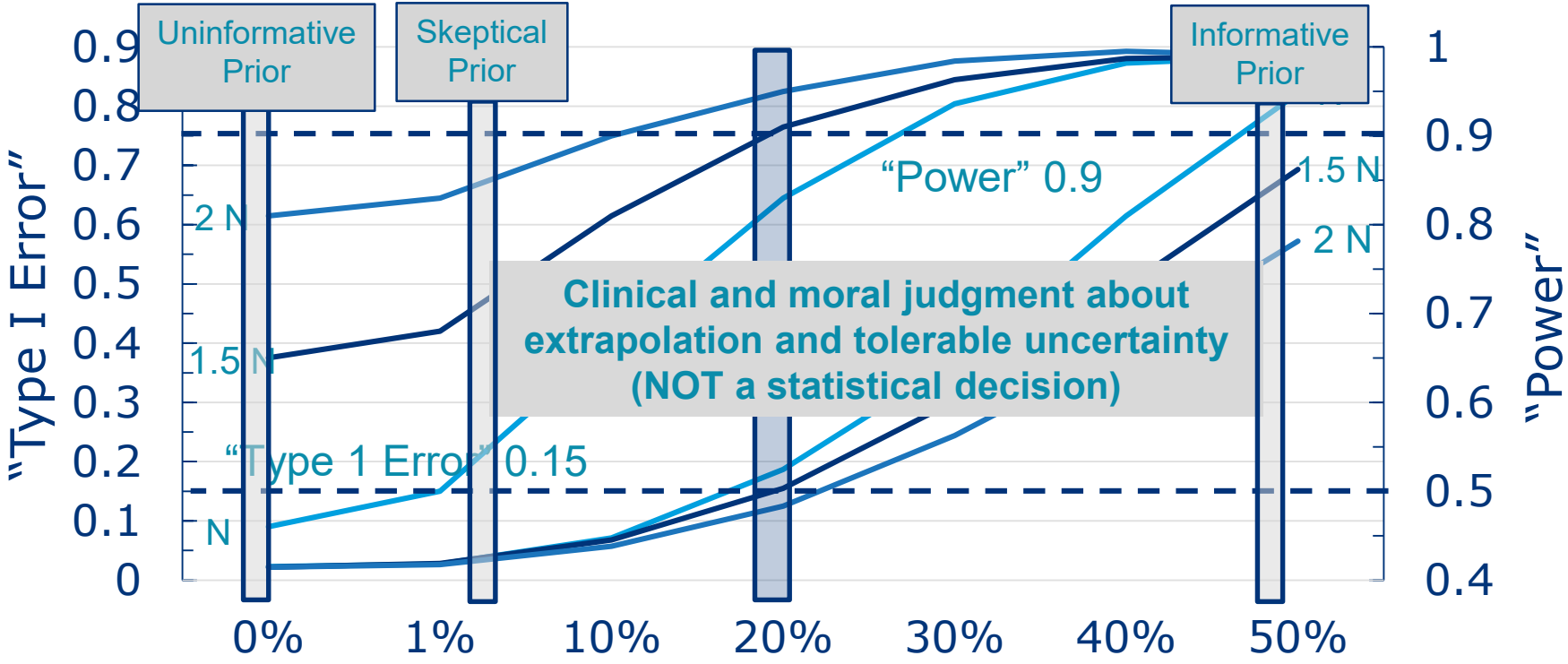

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Anti-TNF biologics‡ for Rheumatoid Arthritis/pJIA

Biologic	RA Approval	RA Study Design	pJIA Approval	pJIA Study Design
Etanercept	11/1998	PBO-controlled parallel group RCT	05/1999	RWD
Infliximab†	11/1999	PBO-controlled parallel group RCT	No pJIA indication [sBLA 04/2007]	PBO-controlled parallel group RCT
Adalimumab	12/2002	PBO-controlled parallel group RCT	02/2008 09/2014	RWD (>4) Open-label (2-4)
Certolizumab	04/2008	PBO-controlled parallel group RCT	CSR 05/2016 PMR not met	Open-label
Golimumab SC†	04/2009	PBO-controlled parallel group RCT	pJIA indication in EU, *not* US [sBLA 06/2017]	RWD
Golimumab IV†	07/2013	PBO-controlled parallel group RCT	Pending	Open-label

‡Data from Drugs@FDA, DailyMed and FDA PMR Database; †Janssen Products

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Implications for Extrapolation from RA to pJIA

- Demonstration of efficacy in multiple programs for both RA and pJIA establish similarity of disease and response to treatment.
  - Randomized withdrawal designs should no longer be necessary.

    (a question I raised in a talk at the 2008 ACR/ARHP Scientific Meeting while at FDA)
  - A subsequent negative study does not undermine this conclusion.

    A drug known to be effective may not be effective under the conditions of a clinical trial, which is why ICH E-10 Choice of Control Group advocates for the addition of a placebo control arm, if ethically appropriate, to assure assay sensitivity.
- For first-in-class products, we may want some evidence of pediatric efficacy (but this does not preclude extrapolation).
  - Example: FDA approval of Benlysta® (belimumab) IV for the treatment of children with systemic lupus erythematosus (SLE) (04/26/2019).

Example: BENLYSTA® (belimumab)

- On April 26, 2019, FDA approved Benlysta® (belimumab) IV for treatment of children with systemic lupus erythematosus (SLE). This is the first time FDA approved a treatment for pediatric SLE patients.
- Benlysta® IV was studied in 93 pediatric SLE patients, comparing patients receiving Benlysta IV plus standard therapy (N = 53) to placebo plus standard therapy (N = 40).
- "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 belimumab 10 mg/kg has a positive treatment effect in pediatric subjects." FDA Multidisciplinary Review (dated October 12, 2018)

Note that the FDA-requested Bayesian analysis was not pre-specified in the protocol.

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Designing Adult Clinical Trials in RA to Support Pediatric Extrapolation in pJIA (1/2)

- The similarity of disease and response to treatment between RA and pJIA has been sufficiently established to support the use of extrapolation.
- Given the ethical requirement to minimize risks to children, adult clinical trials should be designed to support one of two extrapolation paradigms:
  1) For "first in class" drugs, the use of adult (full or adequately sampled sub-population) efficacy data to reduce required pediatric sample size using a Bayesian framework (or, alternatively, a frequentist framework with an elevated type 1 error).
  2) Use of adult exposure-response data to establish the appropriate pediatric dosing, perhaps using a commensurate prior approach (as proposed by CH Hsu and colleagues, J Clin Pharm 2019)
- With respect to option 1, borrowing adult data from a placebo controlled parallel group trial into a pediatric RWD trial may be difficult. However, a pediatric placebo controlled trial may be ethically problematic.

Designing Adult Clinical Trials in RA to Support Pediatric Extrapolation in pJIA (2/2)

- For both options, the pediatric and adult endpoints should be similar, or there should be exploratory endpoints (e.g., biomarkers) in the adult trial that can be used as a bridge to use adult data in the pediatric analysis.
- With respect to option 2, extrapolation of adult efficacy based on achieving a sufficient (i.e., clinically meaningful) response in children at a given exposure does not require establishing a pediatric exposure-response curve, nor does it necessarily imply achieving the same response in children as in adults.
- That said, extrapolating efficacy based on the comparability of the pediatric to the adult response requires a sound pharmacological rationale to support dose selection in adults. This rationale may not require demonstration of an adult exposure-response curve.

Thank you

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