Response Similarity Between Adult and Pediatric SLE: Lessons Learned from Belimumab

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Background & Rationale

- **Disease Overview**
  - SLE is a heterogeneous autoimmune disease marked by abnormal B cell function and autoantibody production
  - Pediatric SLE (pSLE) is rarer (~4.3–9.7 per 100,000) and tends to be more severe than adult-onset SLE
- **Unmet Pediatric Need**
  - Prior to 2019, no treatments had been approved specifically for pediatric SLE patients
  - Belimumab (IV) was approved in adults in 2011; a post-marketing pediatric study (NCT01649765) was required under PREA
- **Challenge: Small Sample Size**
  - Only 93 subjects enrolled in the pediatric study — insufficient power for standalone statistical inference
  - A Bayesian borrowing approach was employed to supplement pediatric data with adult efficacy evidence

Study Design & Population Similarity

- **Adult Studies (C1056, C1057) vs. Pediatric Study (C1109)**
  - Same drug, dose (10 mg/kg IV), route, and primary endpoint: SRI response rate at Week 52 (SRI-4)
  - Same inclusion criteria (ACR diagnosis, ANA titer ≥1:80 and/or anti-dsDNA ≥30 IU/mL)
- **Key Demographic Similarities**
  - Female sex: ~93–95% across all three studies
  - Baseline PGA scores similar: mean ~1.4 across all studies
  - Mean SELENA-SLEDAI: 9.7, 9.8 (adults) vs. 10.3 (pediatric) — slightly higher in pediatric patients
- **Notable Differences**
  - Racial demographics differed: pediatric population fell between the two adult studies
  - Pediatric patients had higher BILAG organ domain involvement (71.0% vs. 63.5%/58.3%), consistent with more severe pSLE
- **Pharmacokinetics (PK) Similarity**
  - Steady-state PK parameters (C_{max}, C_{min}, C_{avg}, AUC) were comparable between pediatric age groups and adults

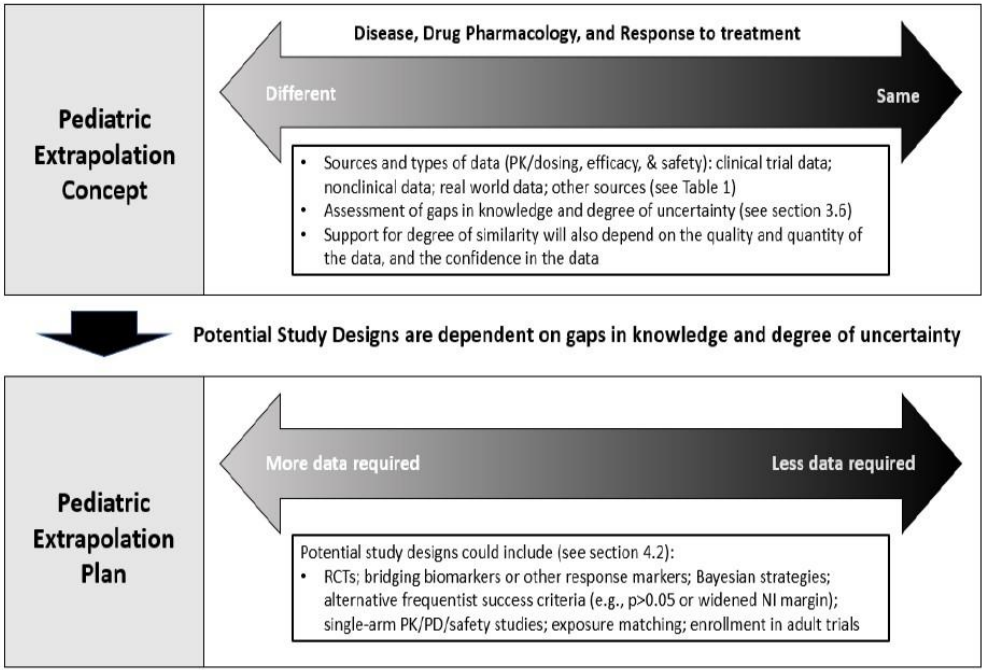
Trial Results

Adult Trial Results (The 'Prior Knowledge')

Study	N	Placebo → Beli. Response Rate	Odds Ratio (95% CI)	Conclusion
C1056 (Adult 1)	N=548	34% → 43%	OR 1.5 (1.1, 2.2)	✓ **Significant**
C1057 (Adult 2)	N=577	44% → 58%	OR 1.8 (1.3, 2.6)	✓ **Significant**
Pediatric C1109	N=93	44% → 53%	OR 1.5 (0.6, 3.5)	✗ **Inconclusive**

⚑ *Key observation: The pediatric response pattern (44% placebo / 53% belimumab) looks very similar to Adult Study C1057 (44% / 58%). The drug appears to work — but the small sample size makes the confidence interval too wide to be conclusive on its own.*

Framework for Pediatric Extrapolation

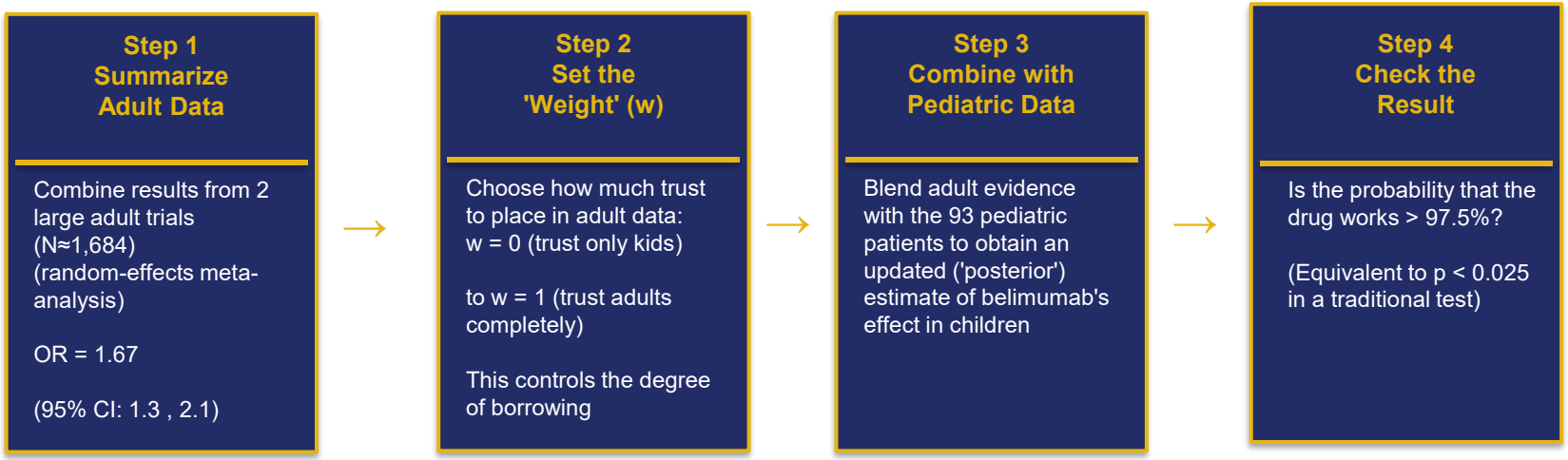


Extrapolation Appropriate, if:

- Disease the same in adult and pediatric patients.
- Response to treatment the same in adult and pediatric patients.
- High confidence in evidence.
- No significant knowledge gaps.

Source: FDA Guidance for Industry: E11A Pediatric Extrapolation, 2024.

How Bayesian Borrowing Works



What does 'weight' mean clinically? At w = 0.55, the statistical analysis treats the adult data as if it contributes the equivalent of ~233 additional pediatric patients per treatment arm — on top of the 93 actually enrolled. The analysis then asks: given all this evidence, how confident are we?

FDA Bayesian Draft Guidance (Jan 2026): When borrowing from adults for pediatric extrapolation, the prior must be discounted to avoid the adult data overwhelming the pediatric results. The robust mixture prior used here does exactly this — it automatically borrows less if the pediatric data look very different from adults.

Results: How Much Borrowing is Needed?

The team tested every level of borrowing (w = 0 to 1) to find the minimum needed for a confident conclusion.

Adult Data Weight (w)	Equiv. Pediatric Patients Added	% Info from Adults	Estimated OR (belimumab effect)	95% Credible Interval excl. 1?	Conclusion
0 (kids only)	1	2%	1.5	(0.6, 3.5)	✗ Too wide
0.10	22	32%	1.5	—	✗
0.20	60	56%	1.6	—	✗
0.30	105	69%	1.6	—	✗
0.40	154	77%	1.6	—	✗
0.50	206	82%	1.6	—	✗
0.55 ★ TIPPING POINT	**233**	**83%**	**1.67**	**> 1.0**	✓ **Confident**
0.60	261	85%	1.67	> 1.0	✓
1 (adults only)	517	92%	1.67	—	✓

If we assume at least w=0.55 prior weight, then we have at least a 97.5% posterior probability that belimumab is efficacious.

This analysis in conjunction with favorable results in analyses of secondary endpoints was sufficient to expand the indication down to 5 years and older.

OR = Odds Ratio. An OR > 1 means belimumab is more likely to produce a response than placebo. A '95% Credible Interval' that does not include 1.0 means we are confident the drug works. At w = 0.55, this confidence is achieved — equivalent to a traditional p-value < 0.025.

Conclusion & Lessons Learned

- **Regulatory Achievement**
  - Belimumab IV became the first treatment approved for pSLE in the United States (2019)
  - Demonstrates that first-in-class approval does not preclude extrapolation-based approaches
- **Value of Bayesian Pediatric Extrapolation**
  - Allows flexible, data-driven borrowing when disease and response similarity can be demonstrated
  - Reduces evidence burden from small/rare pediatric populations without compromising evidentiary standards
- **Critical Importance of Pre-Specification**
  - This analysis was post-hoc; pre-specification of borrowing weight at study design stage would strengthen credibility
  - Early regulatory engagement is essential to agree on prior information and model design upfront
- **Multidisciplinary Considerations**
  - Calibrating the degree of borrowing requires clinical, pharmacological, and statistical input
  - Sensitivity analyses should be pre-planned to assess the robustness of conclusions
- **Future Implications**
  - This approach serves as a template for pediatric diseases where large trials are not feasible
  - Further methodological work needed on measuring borrowing and defining sensitivity analysis frameworks