Response similarity between adult and pediatric SLE: Lessons learned from belimumab

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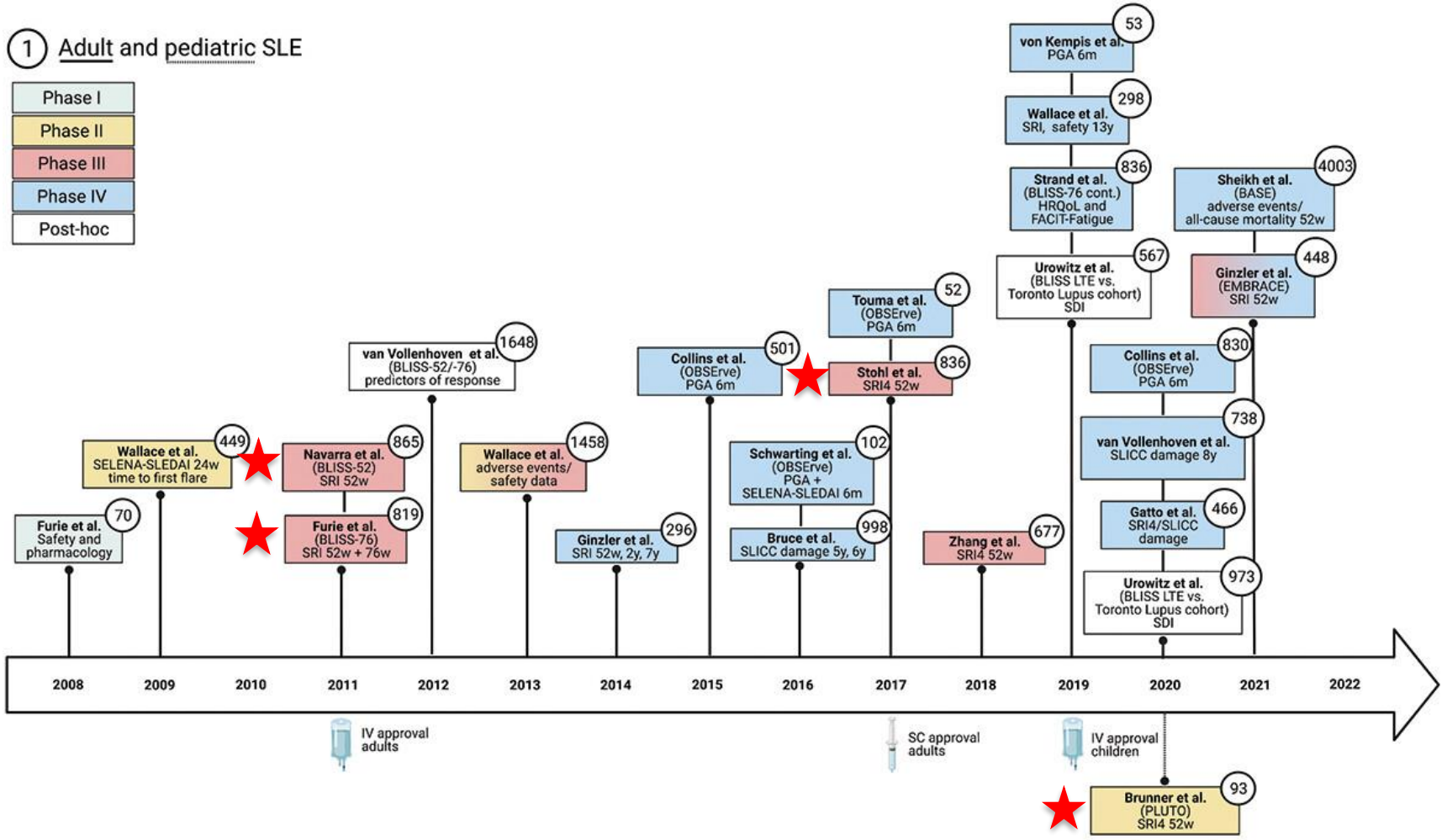
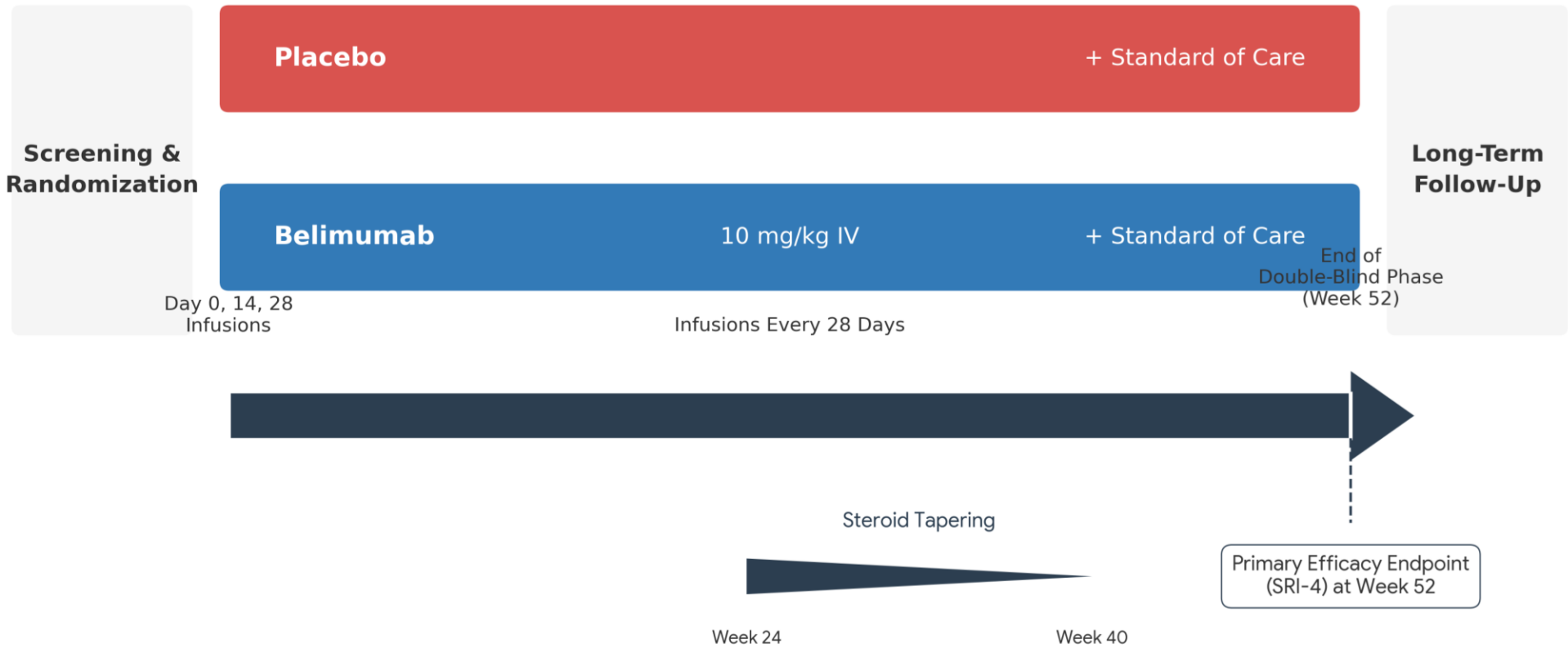
Belimumab Clinical Trials in SLE



Plüß, M., Piantoni, S., Tampe, B., Kim, A. H. J., & Korsten, P. (2022). Belimumab for systemic lupus erythematosus – Focus on lupus nephritis. *Human Vaccines & Immunotherapeutics*, *18*(5). https://doi.org/10.1080/21645515.2022.2072143

Trial Design for Belimumab SLE



Similar Patient Characteristics between Adults and Pediatrics

	PLUTO	BLISS-76	BLISS-52	BLISS-SC
N	93	819	865	836
Diagnosis	**American College of Rheumatology criteria for systemic lupus erythematosus**			
Active Disease	**SELENA SLEDAI score ≥ 6**			**SELENA SLEDAI score ≥ 8**
SELENA SLEDAI Score	10.3 (3.5)	9.7 (3.8)	9.8 (3.8)	10.4 (3.1)
Seropositivity	**ANA titer > 1:80 and/or anti-dsDNA antibody level > 30 IU/mL**			
Anti-dsDNA antibody positive Antinuclear antibody positive	65 (70%) 87 (95%)	524 (64%) 764 (92%)	664 (75%) 812 (94%)	597 (71%) 746 (89%)
Background Therapy	**prednisone (or equivalent) alone or combined with antimalarial drugs, NSAIDs, and/or immunosuppressive therapies**			
Steroids: >0 to < 7.5 mg/day >7.5 mg/day	88 (95%) 40 (43%) 48 (52%)	623 (76%) 257 (30%) 376 (46%)	830 (96%) 230 (27%) 600 (69%)	722 (86%) 219 (26%) 503 (60%)
Prednisone (mg/day)	10.4 (7.2)	9 (8)	13 (10)	10.9 (8.5)
Antimalarial	74 (81%)	519 (63%)	581 (67%)	580 (69%)
Immunosuppressants	60 (65%)	455 (56%)	365 (42%)	381 (46%)
NSAIDs	23 (25%)	334 (41%)	170 (20%)	196 (23%)
Severe Manifestation	**severe active lupus nephritis, active central nervous system**			
Prior Treatment	**IV cyclophosphamide, any B-lymphocyte-targeted drug**			

Similar Organ Involvement between Adults and Pediatrics

	PLUTO	BLISS-76*	BLISS-52*	BLISS-SC
N	93	819	865	836
Mucocutaneous	85 (91%)	670 (82%)	709 (82%)	735 (88%)
Immunologic	69 (74%)	607 (74%)	732 (85%)	633 (76%)
Musculoskeletal	68 (73%)	594 (73%)	508 (59%)	656 (79%)
Cardiovascular and Respiratory	6 (7%)	71 (9%)	34 (4%)	47 (6%)
Hematologic	5 (5%)	95 (12%)	64 (7%)	63 (8%)
Vascular	3 (3%)	47 (6%)	64 (7%)	64 (8%)
CNS	3 (3%)	28 (3%)	17 (2%)	9 (1%)
Renal	18 (19%)	93 (11%)	174 (20%)	99 (12%)

*Not summarized by the Applicant and not reported in public domain previously, recalculated by the presenter based on data submitted to the Agency in 2010

Similar Efficacy Response between Adults and Pediatrics

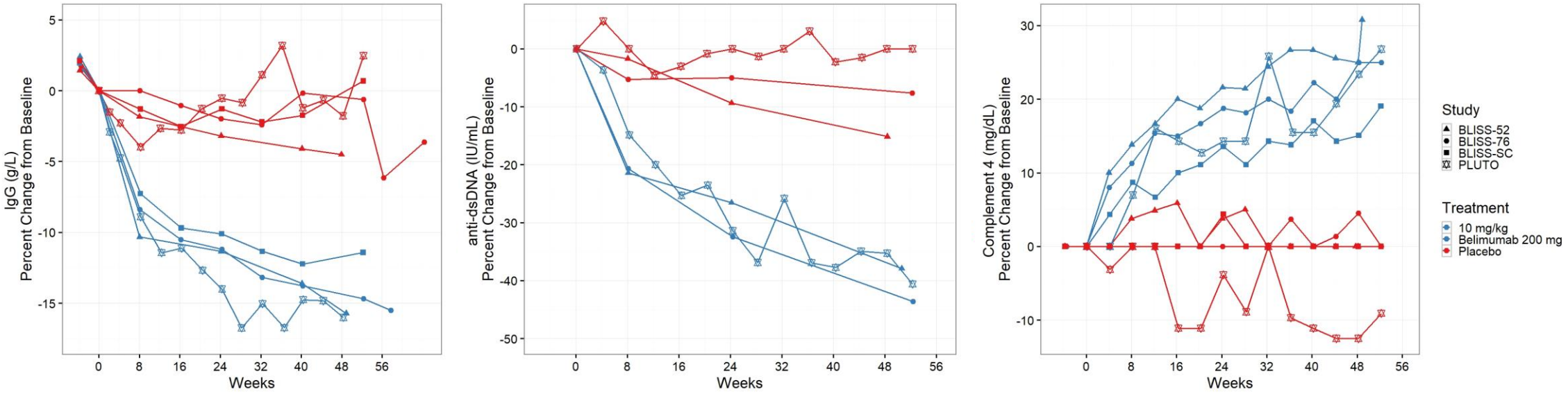
	PLUTO	BLISS-76	BLISS-52	BLISS-SC
N (Placebo/Belimumab)	40/53	275/273	287/290	279/554
AUCss,4wks (day.ug/mL, mean(CV%))	3012 (43.2%)	2811 (34.6%)		2,847 (31.7%)
SRI-4 Response	1.49 (0.64 to 3.46)	1.5 (1.1, 2.1)	1.83 (1.30, 2.59)	1.68 (1.25, 2.25)
Placebo (n (%))	17 (44%)	93 (34%)	125 (44%)	135 (48%)
Belimumab (n (%))	28 (53%)	118 (43%)	167 (58%)	340 (61%)
• **4-point reduction in SELENA-SLEDAI**	1.6 (0.7, 3.8)	1.63 (1.15, 2.32)	1.71 (1.21, 2.41)	1.69 (1.26, 2.27)
• **No Worsening in PGA**	1.7 (0.7, 4.4)	1.32 (0.92, 1.90)	1.74 (1.18, 2.55)	1.61 (1.15, 2.27)
• **No New 1A/2B BILAG Domain Scores**	2.0 (0.8, 5.0)	1.20 (0.84, 1.73)	1.62 (1.09, 2.42)	1.46 (1.04, 2.07)
≥25% CFB and < 7.5 mg/day#	0.92 (0.29, 2.88)*	1.3 (0.6, 2.6)	1.8 (1.0, 3.1)	1.65 (0.95, 2.84)
Time to first severe flare	0.4 (0.2, 0.8)	0.72 (0.50, 1.05)	0.57 (0.39, 0.85)	0.51 (0.35, 0.74)
Placebo (n (%))	17 (42.5%)	67 (24%)	66(23%)	51 (18.2%)
Belimumab (n (%))	12 (22.6%)	48 (18%)	40 (14%)	59 (10.6%)

#PLUTO:≥25% CFB

*PLUTO: Included all the 88 pediatrics on CS at baseline; BLISS: Included only adults with CS > 7.5 mg/day at baseline.

Similar Pharmacodynamics Response Between Adults and Pediatrics

Baseline Levels	PLUTO	BLISS-76	BLISS-52	BLISS-SC
IgG (g/L)	15 (5.5)	15.7 (6.2)	17.3 (5.9)	15.5 (5.6)
Anti-dsDNA (IU/mL)	1239.6 (2993.02)	144.20 (62.36)	145.00 (62.39)	593 (1420)
C4 (mg/dL)	13 (8.0)	17 (10)	16 (9.7)	16 (9)



*Plotted by the presenter based on data submitted to the Agency

Similarity between Adults and Pediatrics with SLE

- ✓ Disease characteristics
  - Disease activities
  - Seropositivity
- ✓ Concomitant Use of Background Treatment / Standard of Care
- ✓ Placebo Response
  - Clinical efficacy response except for steroids use and disease flares
  - Pharmacodynamic response
- ✓ Response to Treatment
  - Clinical efficacy response
  - Pharmacodynamic response

Statistical Issues for the Pediatric Study

<u>Challenge: Sample Size & Power</u>

- The pediatric study (PLUTO) was not powered to conduct formal statistical hypothesis testing.
- In fact, placebo-controlled phase 3 powered study in pediatric subjects was not feasible because of the rarity of the disease in children.
  - Only 93 subjects could be enrolled over 6 years in the pediatric study — insufficient power for standalone statistical inference
  - Recruiting an adequately powered pediatric trial would have taken significantly long time.
  - This made a Bayesian borrowing approach not just attractive, but necessary.

Trial Results Similarity

The 52-week treatment period of PLUTO was randomized and double-blind comparing

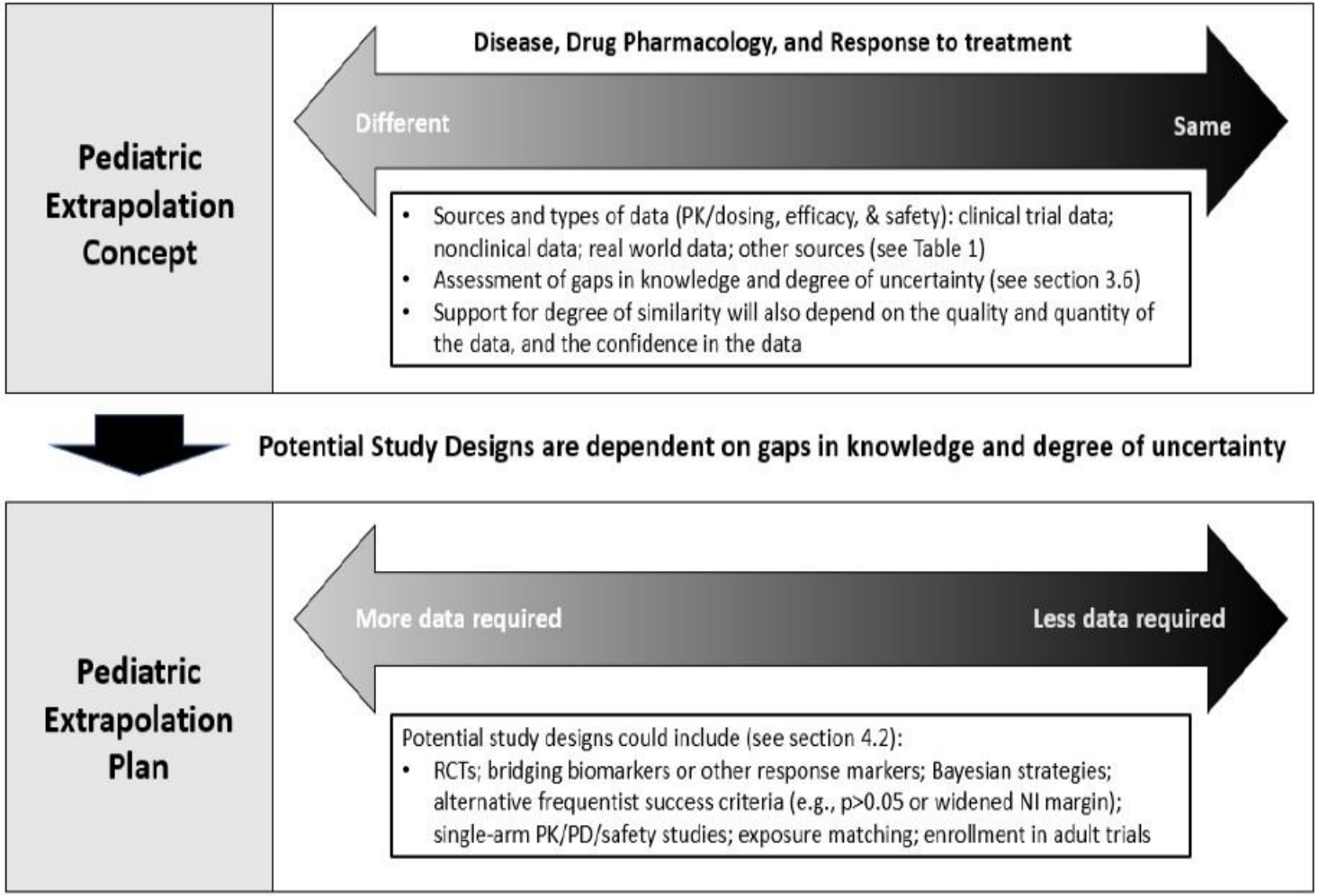
- Belimumab 10 mg/kg vs Placebo

Primary efficacy analysis of SRI response rate at week 52 in the adult and pediatric studies.

Study	N	Placebo → Beli. Response Rate	Odds Ratio (95% CI)	Conclusion
BLISS-76 (Adult 1)	N=548	34% → 43%	OR 1.5 (1.1, 2.2)	✓ **Significant**
BLISS-52 (Adult 2)	N=577	44% → 58%	OR 1.8 (1.3, 2.6)	✓ **Significant**
PLUTO (Pediatric)	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%). But the small sample size makes the confidence interval too wide to be conclusive on its own.*

Framework for Pediatric Extrapolation



Extrapolation Appropriate, if:

- Diseases are similar in adults and pediatric subjects
- Response to treatment are similar in PK/PD and Clinical parameters, although confidence interval is wider for the pediatric study due to the smaller number of subjects

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

How Bayesian Borrowing Works

Step 1
Summarize Adult Data

Combine results from 2 large adult trials (N≈1,125) (random-effects meta-analysis)

OR = 1.67

(95% CI: 1.3 , 2.1)

→

Step 2
Set the 'Weight' (w)

Choose how much to discount adult data:
w = 0 (trust only kids)
w = 1 (no discounting)

This controls the degree of borrowing and forms the basis of our prior knowledge.

→

Step 3
Combine with Pediatric Data

Blend adult evidence with the 93 pediatric patients to obtain an updated ('posterior') estimate of belimumab's effect in children

→

Step 4
Check the Result

Is the probability that the drug works > 97.5%?

(Equivalent to one sided $p < 0.025$ in a traditional test)

FDA Bayesian Draft Guidance (Jan 2026): When borrowing from adults for pediatric extrapolation, the prior should 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)	Total Pediatric Patients Added	% Info Borrowed from Adults	Estimated OR (belimumab effect)	95% Credible Interval excl. 1?	Conclusion
0 (kids only)	2	2%	1.5	**No** (0.6, 3.5)	✗ Too wide
0.10	44	32%	1.5	No	✗
0.20	120	56%	1.6	No	✗
0.30	210	69%	1.6	No	✗
0.40	308	77%	1.6	No	✗
0.50	412	82%	1.6	No	✗
0.55 ★ TIPPING POINT	**466**	**83%**	**1.6**	**Yes (1.04, 2.14)**	✓ **Conclusive**
0.60	522	85%	1.6	**Yes**	✓
1 (full reliance)	1034	92%	1.6	Yes	✓

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.

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.

Conclusion & Lessons Learned

- **Regulatory Achievement**
  - Belimumab IV became the first treatment approved for cSLE 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.

References

- Benlysta® (belimumab) for pSLE FDA Multi-Disciplinary Review https://www.fda.gov/media/127912/download

- E11A Pediatric Extrapolation Guidance for Industry
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11a-pediatric-extrapolation

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  doi: 10.1177/09612033251349930.

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BACKUP SLIDES

SRI-4: Similar between Adults and Pediatrics

	PLUTO	BLISS-76	BLISS-52	BLISS-SC
SRI-4 Response	1.49 (0.64 to 3.46)	1.5 (1.1, 2.1)	1.83 (1.30, 2.59)	1.68 (1.25, 2.25)
Placebo	17 (43.6%)	93 (34%)	125 (44%)	135 (48.4%)
Belimumab	28 (52.8%)	118 (43%)	167 (58%)	340 (61.4%)
4-point reduction in SELENA-SLEDAI	1.6 (0.7, 3.8)	1.63 (1.15, 2.32)	1.71 (1.21, 2.41)	1.69 (1.26, 2.27)
Placebo	17 (43.6%)	98 (36%)	132 (46%)	137 (49.1%)
Belimumab	29 (54.7%)	128 9(47%)	169 (58%)	345 (62.27%)
No Worsening in PGA	1.7 (0.7, 4.4)	1.32 (0.92, 1.90)	1.74 (1.18, 2.55)	1.61 (1.15, 2.27)
Placebo	26 (66.7%)	173 (63%)	199 (69%)	203 (72.76%)
Belimumab	40 (75.5%)	189 (69%)	231 (80%)	450 (81.23%)
No New 1A/2B BILAG Domain Scores	2.0 (0.8, 5.0)	1.20 (0.84, 1.73)	1.62 (1.09, 2.42)	1.46 (1.04, 2.07)
Placebo	24 (61.5%)	179 (65%)	210 (73%)	207 (74.19%)
Belimumab	39 (73.6%)	189 (69%)	236 (81%)	448 (80.87%)

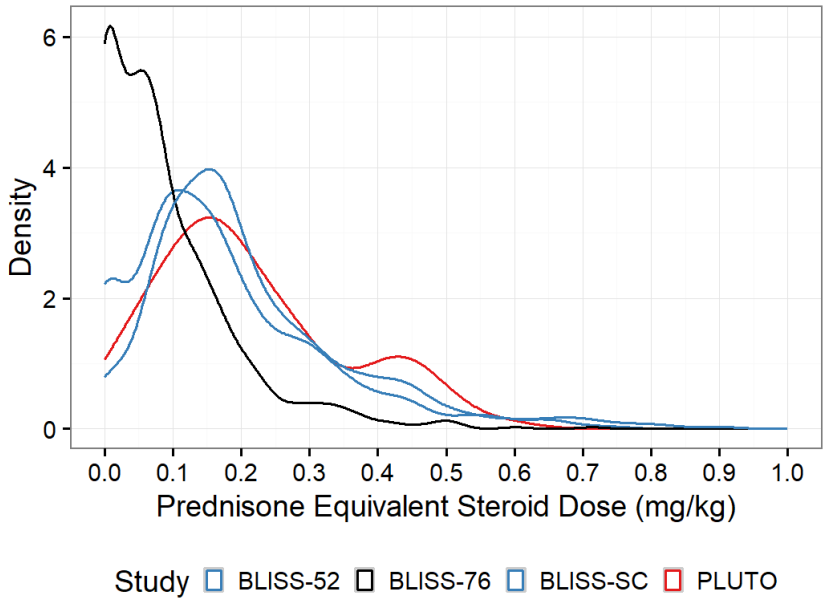
Disposition of Responses: Similar between Adults and Pediatrics

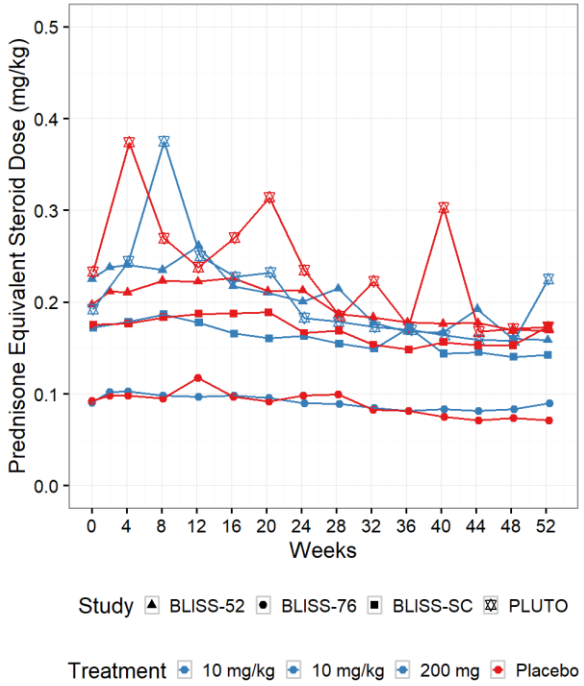
	PLUTO	BLISS-76	BLISS-52	BLISS-SC
Dropout – Not a Medication Failure				
Placebo	4 (10.3%)	43 (16%)	38 (13%)	42 (15%)
Belimumab	5 (9.4%)	45 (17%)	31 (11%)	55 (10%)
Medication Failure#				
Placebo	9 (23.1%)	47 (17%)	30 (11%)	27 (10%)
Belimumab	6 (11.3%)	17 (10%)	18 (6%)	42 (8%)
< 4 Point Reduction in SELENA SLEDAI				
Placebo	9 (23.1%)	87 (32%)	87 (30%)	73 (26%)
Belimumab	13 (24.5%)	73 (27%)	72 (25%)	112 (20%)
≥4 Point Reduction in SELENA SLEDAI				
Placebo	0	5 (2%)	7 (2%)	2 (1%)
Belimumab	1 (1.9%)	10 (4%)	2 (1%)	5 (1%)

Includes subjects who withdrew early and subjects who met all 3 response criteria at week 52 but took a protocol prohibited or restricted medication or dose

Steroids Tapering:
More CS dose increment before Week 24 in pediatrics

	PLUTO	BLISS-76	BLISS-52	BLISS-SC
Prednisone (mg/kg/day)	0.210 (0.138)	0.0888 (0.0969)	0.214 (0.157)	0.173 (0.145)
≥25% CFB and < 7.5 mg/day#	0.92 (0.29, 2.88)	1.3 (0.6, 2.6)	1.8 (1.0, 3.1)	1.65 (0.95, 2.84)
Placebo	8 (21.1%)	16 (13%)	23 (12%)	20 (11.90%)
Belimumab	10 (20.0%)	20 (17%)	38 (19%)	61 (18.21%)





Time to First Severe Flare:
more severe flares but also more pronounced efficacy in pediatrics

	PLUTO	BLISS-76	BLISS-52	BLISS-SC
N (Placebo/Belimumab)	40/53	275/273	287/290	279/554
Time to first severe flare	0.4 (0.2, 0.8)	0.72 (0.50, 1.05)	0.57 (0.39, 0.85)	0.51 (0.35, 0.74)
Placebo	17 (42.5%)	67 (24%)	66(23%)	51 (18.2%)
Belimumab	12 (22.6%)	48 (18%)	40 (14%)	59 (10.6%)