Extrapolation of Adult Efficacy Data to Pediatric Systemic Lupus Erythematosus:

Evaluating Similarity in Exposure-Response

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Conflicts of Interests and Disclosures

This work was conducted under an IPA agreement with The Office of Pediatric Therapeutics, US Food and Drug Administration. The opinions expressed in this presentation are those of the author and should not be interpreted as the position of the U.S. Food and Drug Administration.

I **do** intend to discuss an unapproved/investigative use of a commercial product/device in my presentation/.

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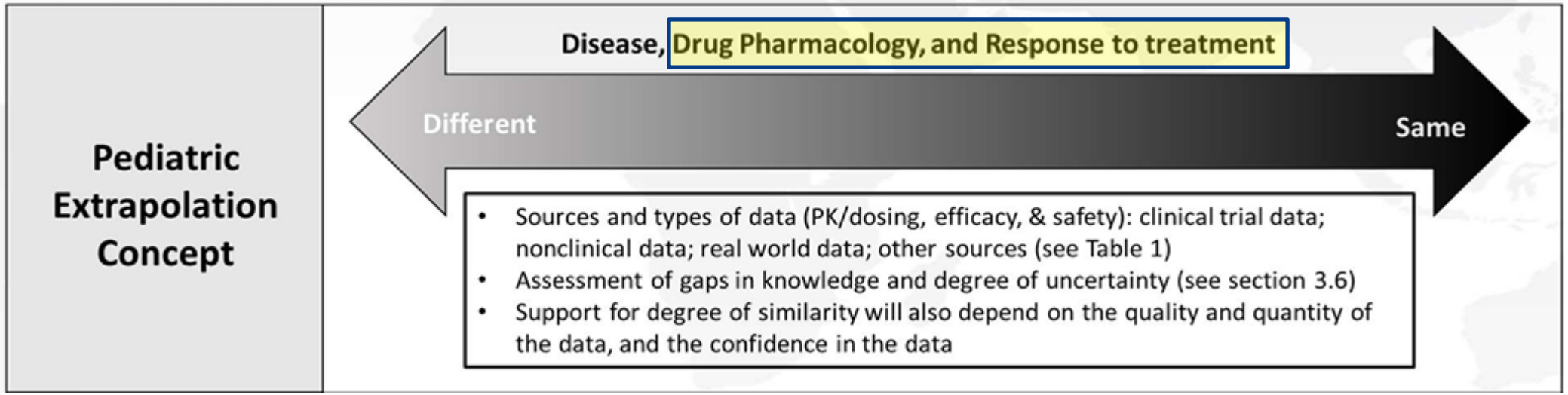
Exposure-Response Analyses



- **Clinical and Regulatory Gap**
  - The exposure-response relationship for drug products in adult and pediatric SLE and LN was unknown

Regulatory Science Study

Pediatric Pharmacology

Extrapolation of Adult Efficacy Data to Pediatric Systemic Lupus Erythematosus: Evaluating Similarities in Exposure–Response

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Methods

Overview

- **Objective**: Conduct an exposure-response analysis using data from the literature of common DMARDs in SLE and LN and determine whether use of adult efficacy data could be considered to support efficacy in children.
- **Approach**:
  1. PubMed search to identify studies evaluating DMARDs in adults and children with SLE

     -described drug exposure/effect, shared outcome measure
  2. Digitally extracted data from tables and figures

     -WebPlotDigitizer digitizing software (V4.4, Pacifica, California)
  3. Compared exposure-response either descriptively, or through PD modeling depending on the available data

Overview-6 Drugs, 16 Studies

Drug	Data Source	Approach
Belimumab	Clinical Trials	Compared % responders over time graphically
Mycophenolate	Observational	Developed PD Model to compare AUC vs Effect curves
Hydroxychloroquine	Observational	Graphically compared random concentrations and outcomes, cross-sectional
Cyclophosphamide	Clinical Trials	Descriptively compared clinical outcomes
Azathioprine	Clinical Trials	Descriptively compared clinical outcomes
Rituximab	Clinical Trials/ Observational	Descriptively compared dosage and biomarkers of response
Bonus! Prednisone	Observational	Exposure-response model in publication

Results

Drug Name

- Mechanism of Action:
- FDA approved uses:
- Ontogeny:

Selected Studies:

1. Dimelow. Clin Pharmacol Drug Dev. 2020 Nov 27;10(6):622–633.

Belimumab

- Monoclonal antibody inhibiting BLyS and is FDA approved for the treatment of SLE in children ≥5 years and adults with SLE and for LN
- Ontogeny: BLyS levels in children (PLUTO trial) similar to those in adult belimumab trials[1]

Discussed in Prior Presentation

1. Dimelow. Clin Pharmacol Drug Dev. 2020 Nov 27;10(6):622–633.

Mycophenolate

- The active metabolite of mycophenolate (mycophenolic acid) is an inhibitor of inosine monophosphate dehydrogenase (IMPDH)
  - resulting in inhibition of guanosine nucleotide synthesis, and T-lymphocyte and B-lymphocyte proliferation
- Used extensively off label in adults and children, with and without LN

Ontogeny: IMPDH activity does not differ between healthy children (2-19 years) and adults[1]

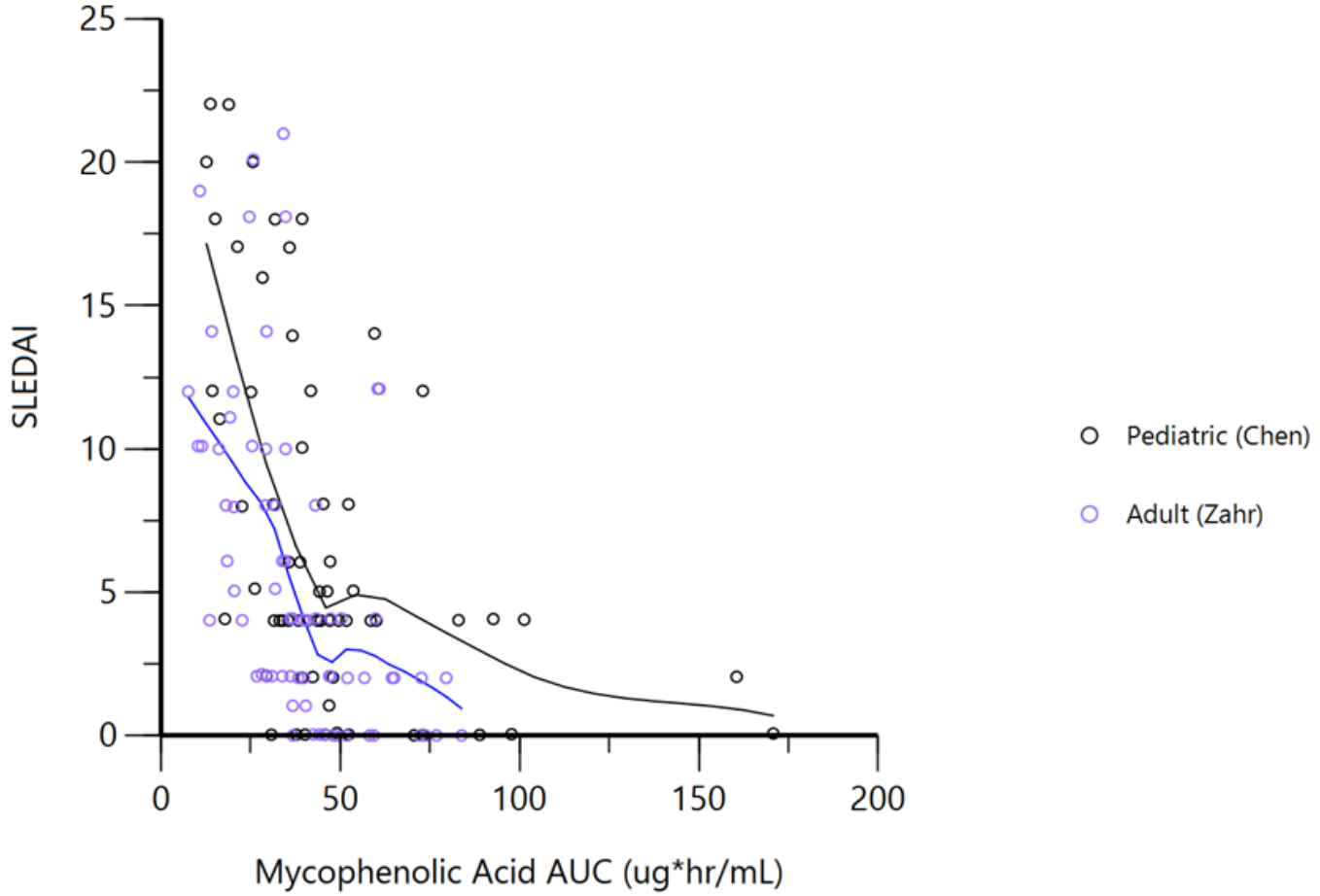
Selected Studies:

- Exposure: response in SLE
  - 1 prospective adult study (n=71) and 1 retrospective pediatric study (n=67, age 4-18 years) comparing AUC (exposure) and outcome (SLEDAI)
- Clinical Outcomes in LN
  - 1 randomized clinical trial of mycophenolate in lupus nephritis that enrolled 10 adolescents compared to 175 adults.

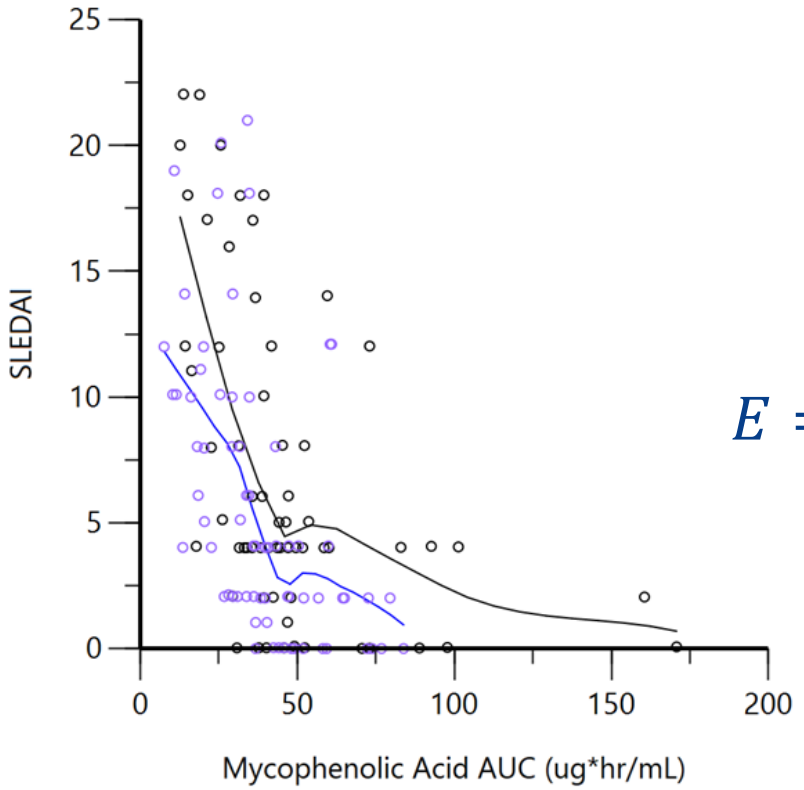
1. Rother et al. Eur J Clin Pharmacol. 2012 Jun;68(6):913-22.

Mycophenolate: Observational Data in SLE

Figure. Mycophenolate Exposure and Lupus Disease Activity



Mycophenolate: PD Modeling in SLE



$$E = E0 - \frac{Imax * AUC}{AUC50 + AUC}$$

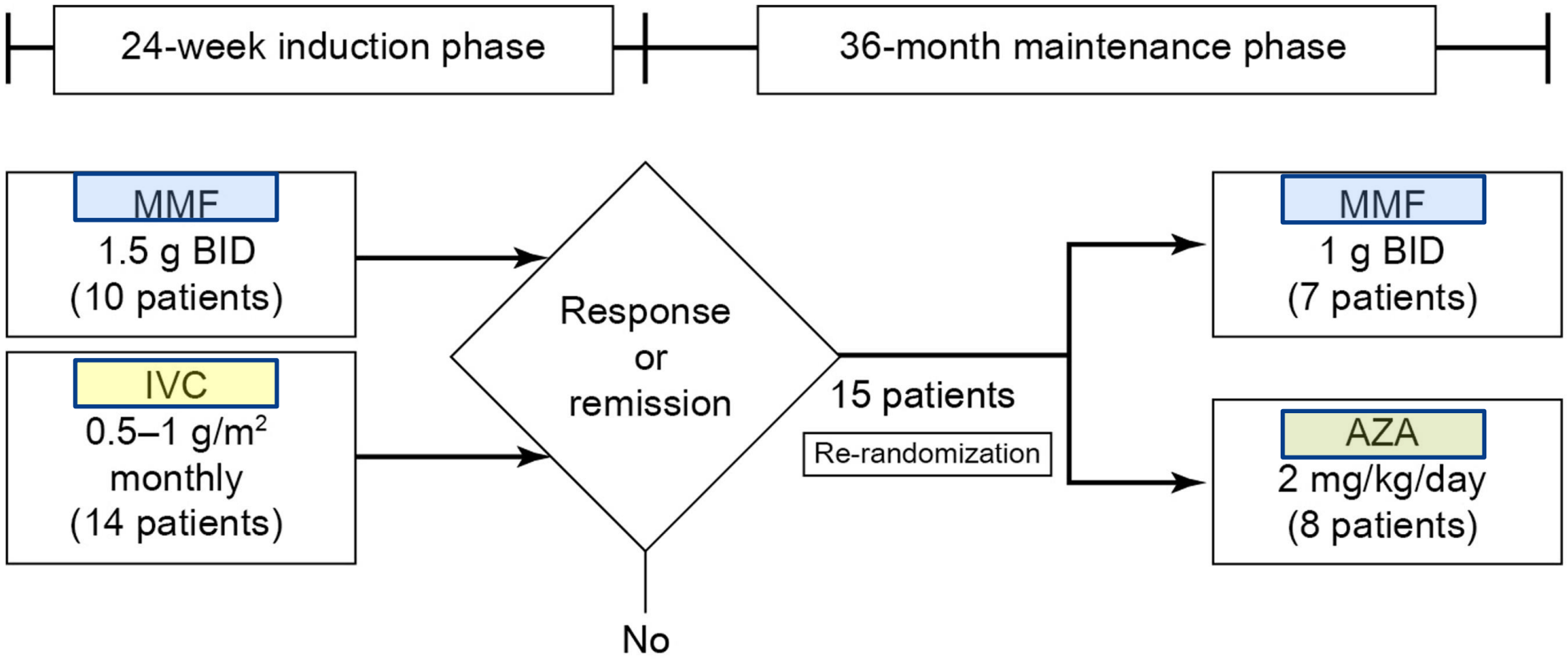
Mycophenolate: PD Modeling in SLE

- Estimated AUC50 was 1.23 ug*hr/mL for adults and 1.88 ug*hr/mL for children
- Children as a population was a statistically significant covariate on AUC50 ($p<0.05$)
  - Only explained 2.5% of the between-patient variability in the AUC_{50}

Summary: No clinically meaningful difference between mycophenolate potency between adults and children with SLE

Lupus Nephritis RCT

- RCT with adolescents (n=24) enrolled concomitantly with adults (n=346)



Same enrollment criteria; same visit schedule; same outcome measures

Sundel et al. R. Lupus. 2012 Nov;21(13):1433-43

Mycophenolate: Clinical Outcomes in LN Induction

- Number of responders was numerically higher for adolescents
  - Adolescents: (7/10, **70%**) responders
  - Adults: (97/175, **55.4%**) responders

Mycophenolate: Clinical Outcomes in LN Maintenance

- Treatment Failures highly similar across ages
  - Adolescents: (1/8, **12.5%**) responders
  - Adults: (18/108, **16.7%**) responders

Summary: In a RCT including both adults and adolescents, no numerical difference across ages for mycophenolate induction or maintenance in lupus nephritis, though limited by small sample sizes

Directionality argues strongly for adolescents having a similar response to adults

Cyclophosphamide: Clinical Outcomes in LN

- Pro-drug that is metabolized to alkylating metabolites, resulting in a cytotoxic effect to lymphocytes
- Used extensively off label in adults and children, with and without LN

Ontogeny: Lymphocyte count/function ~ adult values by late childhood to adolescence

Selected Studies:

- Clinical Outcomes in LN
  - 1 randomized clinical trial of mycophenolate in lupus nephritis that enrolled 14 adolescents compared to 171 adults
  - Same enrollment criteria; same visit schedule; same outcome measures
- Cyclophosphamide was administered at a dosage of 0.5 to 1.0 g/m2 IV monthly.

Cyclophosphamide- Induction for LN

- The renal response to intravenous cyclophosphamide was highly similar
  - Adolescents: 8/14 (**57.1%)**
  - Adults: 90/171 (**52.6%**).

Azathioprine: Clinical Outcomes in LN

- Derivative of 6-mercaptopurine that undergoes metabolism to multiple metabolites, some of which are incorporated into DNA, stop lymphocyte proliferation, and reduce purine synthesis.
- Used off label in adults and children with SLE

Selected Studies:

- Clinical Outcomes in LN
  - 1 randomized clinical trial of mycophenolate vs cyclophosphamide in lupus nephritis that compared maintenance of remission in 8 adolescents compared to 103 adults.
  - Same enrollment criteria; same visit schedule; same outcome measures

Azathioprine

- Percentage maintaining a renal response to azathioprine was numerically lower for adolescents compared with adults,
- Adolescents: 5/8 (**62.5%**) experienced treatment failure
- Adults: 30/103 (**29.1%**) experienced treatment failure

- Interestingly, the same preferential effect with MMF > AZA for maintenance of remission was seen in both adults and adolescents

Hydroxychloroquine (HCQ)

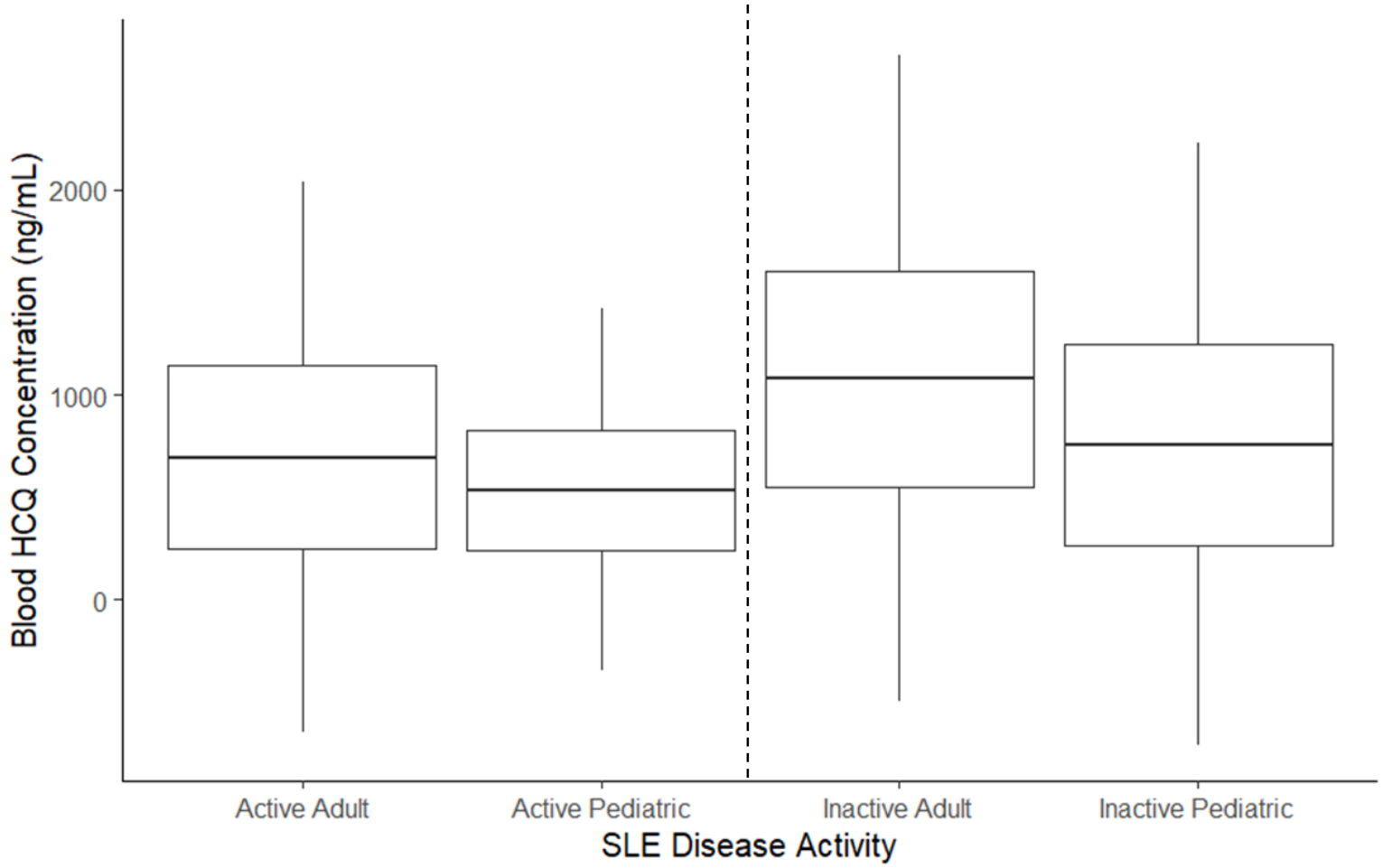
- Antimalarial with multiple proposed mechanisms of action in SLE, including inhibiting Toll-like receptor signaling and autoantigen presentation, and reducing B-cell and T-cell activation.
- FDA approved for the treatment of SLE in adults and is used extensively off label in children with SLE. **Same weight based dosing is used**
- Ontogeny: TLR-7 function approximates adults by 2-5 years of age[1]

Selected Studies:

- 1 retrospective pediatric study (n=55) and 1 prospective adult study (n=143) comparing whole blood HCQ concentrations to the same disease activity outcome (SLEDAI)
  - Cross-sectional

1. Kollmann et al. Innate Immunity. 2012 Nov 16;37(5):771-83

Hydroxychloroquine Exposure-Response



Rituximab

- Chimeric monoclonal antibody that binds to CD20 on and mature B-lymphocytes, resulting in B-cell lysis
- Used off-label in both adult and pediatric SLE, with and without lupus nephritis.
- **Ontogeny:** CD20 counts higher in infancy, gradually decline to adult levels by late childhood to adolescence

Selected Studies:

- 2 adult clinical trials (1 SLE and 1 LN) and 4 observational pediatric studies (SLE and LN combined)
  - heterogeneity across the pediatric studies, including: (1) rituximab dosing;(2) outcome measures; (3) baseline characteristics, and (4) number of doses

Rituximab Exposure-Response

	Lupus Nephritis Included	Time Biomarker Assessed (months)	Rituximab Dosing	DNA Antibody (Ratio Endpoint: Baseline)	Complement C3 (mg/dL) (Mean or Median Change from Baseline)	Complement C4 (mg/dL) (Mean or Median Change from Baseline)
Adult[34] (Merrill et al)	No	12	1000 mg on days 1, 15, 168, and 182	0.24	–	–
Adult[35] (Rovin et al)	Yes	12	1000 mg on days 1, 15, 168, and 182	0.31	+37.5	+9.9
Pediatric[36] (Watson et al)	Yes	2.5 (IQR 1.6 to 4.3)	750 mg/m^2 ×2 doses, approximately 14 days apart; 73% received IV cyclophosphamide with 1st course; 30% of cohort received >1 course of rituximab	0.32	+6	+6
Pediatric[37] (Nwobi et al)	Yes	2, 4, 6	Weekly for 2 to 4 doses. Initial dosage 188 mg/m^2, subsequent doses 375 mg/m^2	0.18	+24.6	+3.4
Pediatric[38] (Podolskaya et al)	Yes	12	Most 2 infusions of 750 mg/m^2, 2 weeks apart	0.39	+57.1	+10.3
Pediatric[39] (Tambralli et al)	Yes	12	Typically 750 mg/m^2 ×2 doses (maximum 1 g), approximately 14 days apart	0.1	+44.6	+14

Summary: Decrease in DNA antibody and increases in C3 and C4 were similar across adult and pediatric studies that included patients with lupus nephritis; decrease in DNA antibody also similar in those without lupus nephritis

Bonus- Prednisolone

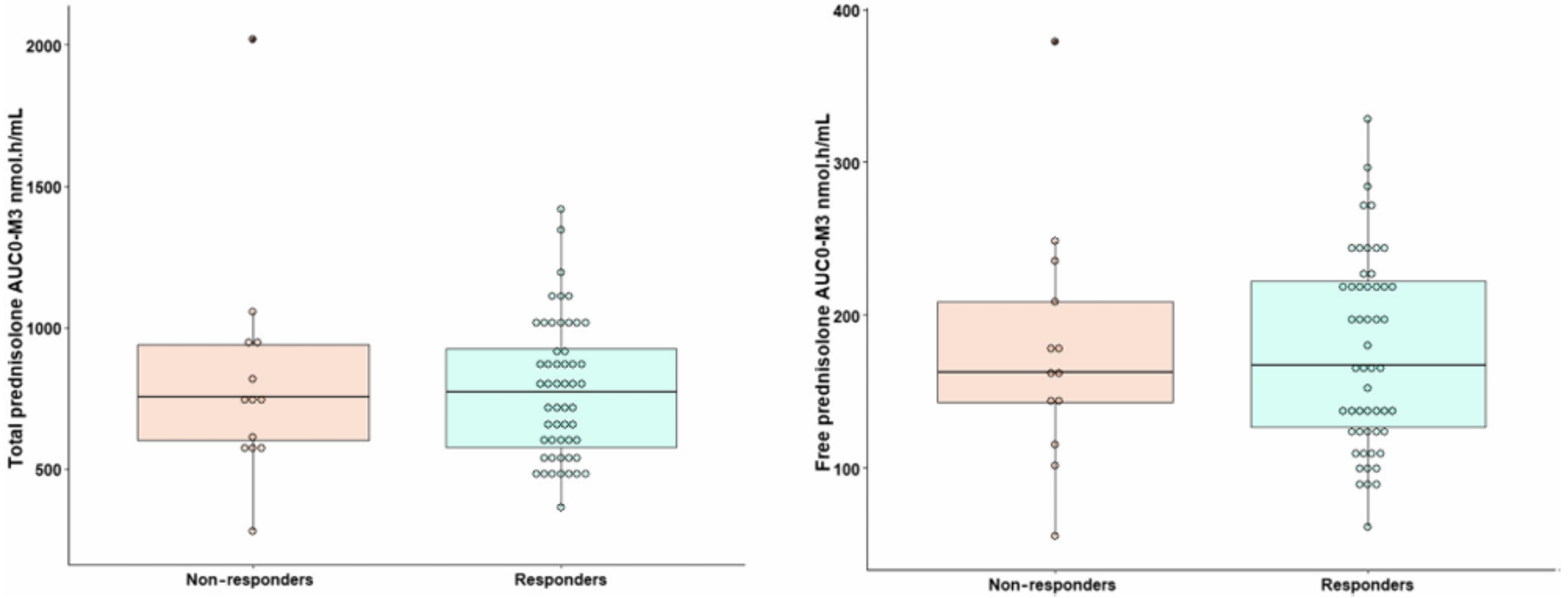
- Multiple mechanisms of action including dose-dependent genomic (including inhibition of NF-kβ) and non-genomic effects, resulting in broad immunosuppression
- FDA approved for the treatment of SLE (age?)

Selected Studies:

- Prospective observational study across 28 centers in France
  - Enrolled **34 children** (≥6 years) and **32 adults** receiving prednisolone ≥0.5 mg/kg
  - Could initiate MMF or CYC; prednisone dose could be tapered
  - Derived cumulative AUC and evaluated SLEDAI at month 3

Bouazza N, Semeraro M, Lui G, et al. *Br J Clin Pharmacol*. 2025; 91(10): 2854-2864.

Prednisolone Exposure-Response



Responders=
no flare (SELENA-SLEDAI)

FIGURE 2 Cumulative total (left) and free (right) prednisolone $AUC_{0\text{-}M3}$ between the responders and non-responders.

	Level	Non-responders ($n = 13$)	Responders ($n = 53$)	*P*-value
Age, year		23 [15, 35]	23 [14, 29]	0.96

Prednisolone- Take Home Points

- No difference in prednisolone exposure-response between adults and children with SLE, most of whom also had nephritis
- Higher prednisolone exposure was not associated with either efficacy or safety
  - *Possibly underpowered or limited by short duration (3 months)?*

Summary

- Response to **belimumab** is highly similar between adults and children with SLE
- Response to **mycophenolate** is similar between adult and children with lupus nephritis and likely SLE without lupus nephritis.
- Preponderance of data across all other drugs (**prednisolone**, **HCQ, rituximab, cyclophosphamide**) with the possible exception of azathioprine suggests that adults and children with SLE may respond similarly to treatment across several drug classes, including for the treatment of lupus nephritis.

Conclusions

- Adults and children with SLE and lupus nephritis may respond similarly to treatment across several different drug classes - possible exception; monogenic lupus (most studies age >5)
- Ontogeny of the immune system suggests treatment response is unlikely to differ based on age (late childhood through adolescence)
- Adult SLE data should be leveraged to guide the pediatric drug development program and identify areas with residual uncertainty regarding the effectiveness or safety of these drugs in children.

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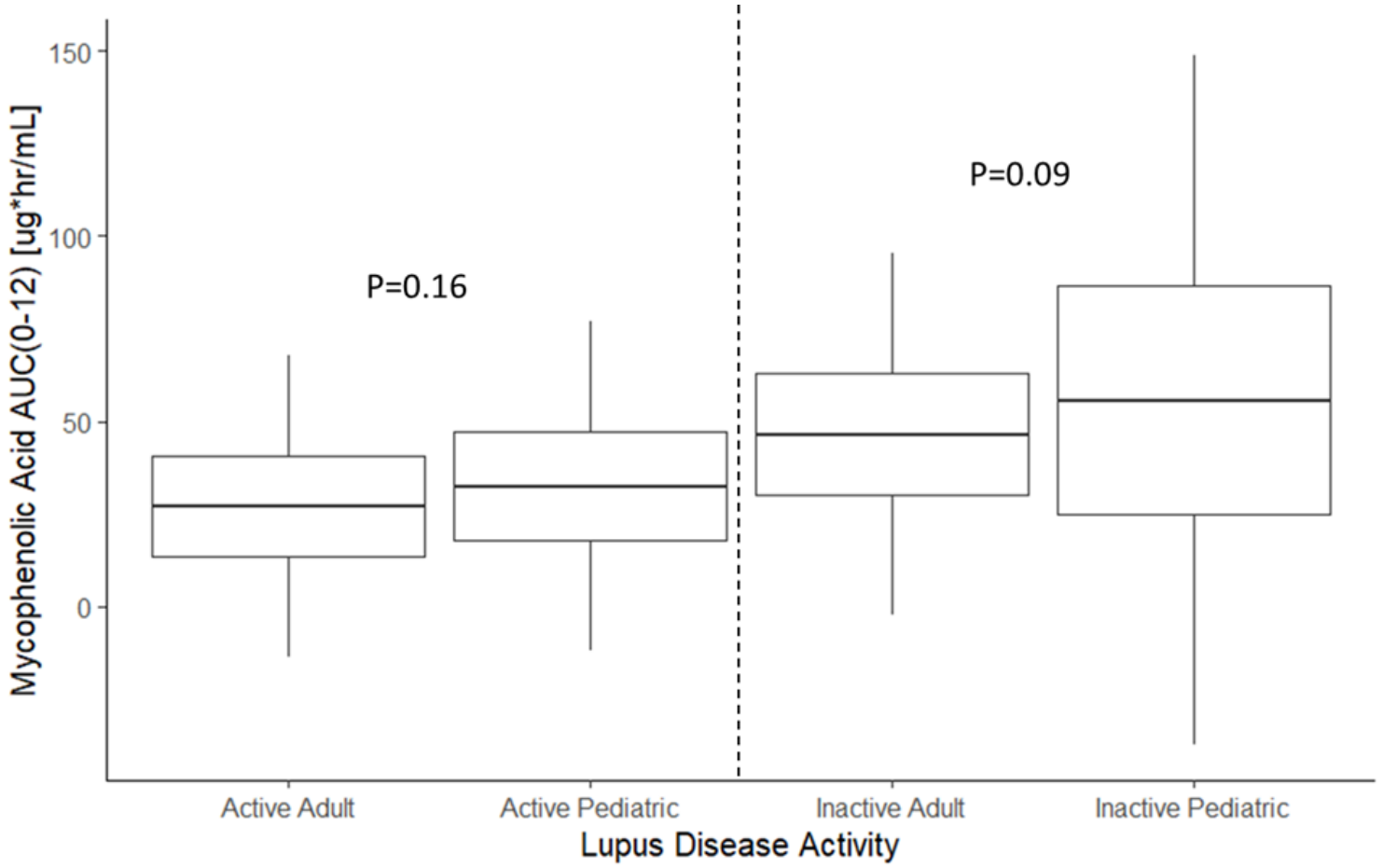
  - Duke/UNC
    - Laura Schanberg, Christoph Hornik, Danny Gonzalez

Thank you!


Duke Clinical Research Institute
FROM THOUGHT LEADERSHIP
TO CLINICAL PRACTICE

Backup Slides

Mycophenolate: Exposure-Response in SLE



Belimumab

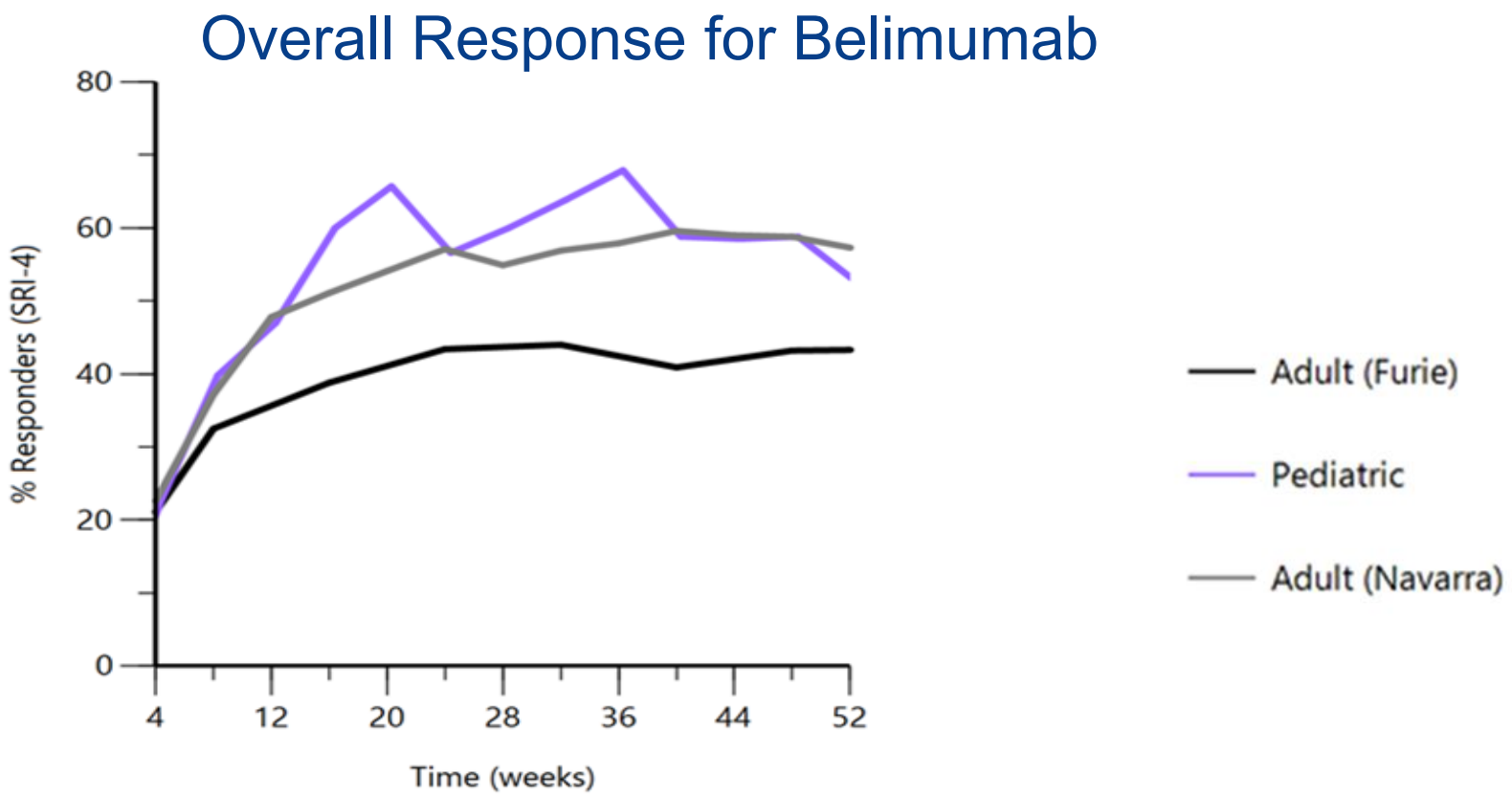
- Monoclonal antibody inhibiting BLyS and is FDA approved for the treatment of SLE in children ≥5 years and adults with SLE and for LN
- Ontogeny: BLyS levels in children (PLUTO trial) similar to those in adult belimumab trials[1]

Included Studies:

- There were two randomized, clinical trials of belimumab in adults and 1 in children (n=93). **Conduct of the trials were virtually identical**
  - Dose of belimumab= 10 mg/kg IV
- Primary outcome was the % responders using a composite lupus disease activity measure (SRI-4)

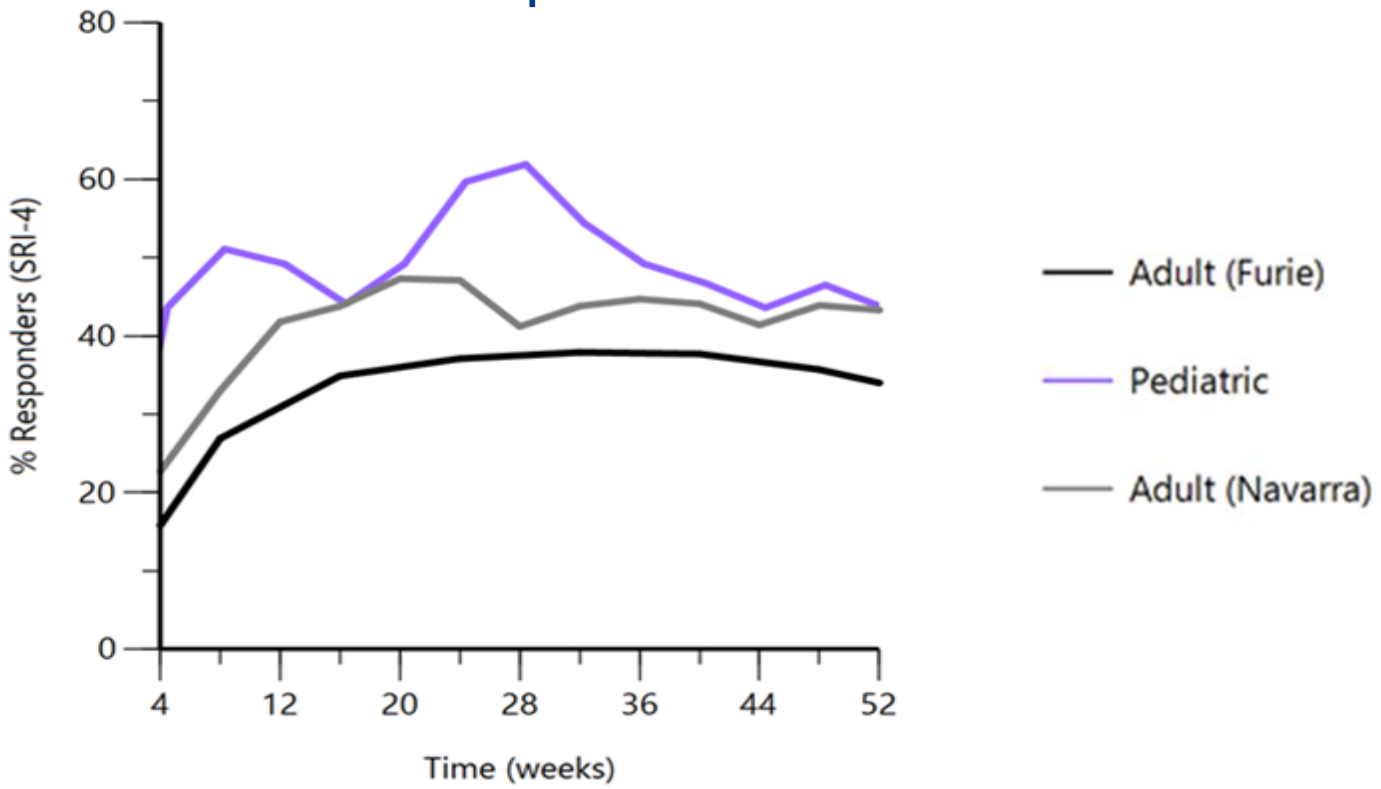
1. Dimelow. Clin Pharmacol Drug Dev. 2020 Nov 27;10(6):622–633.

Belimumab Results



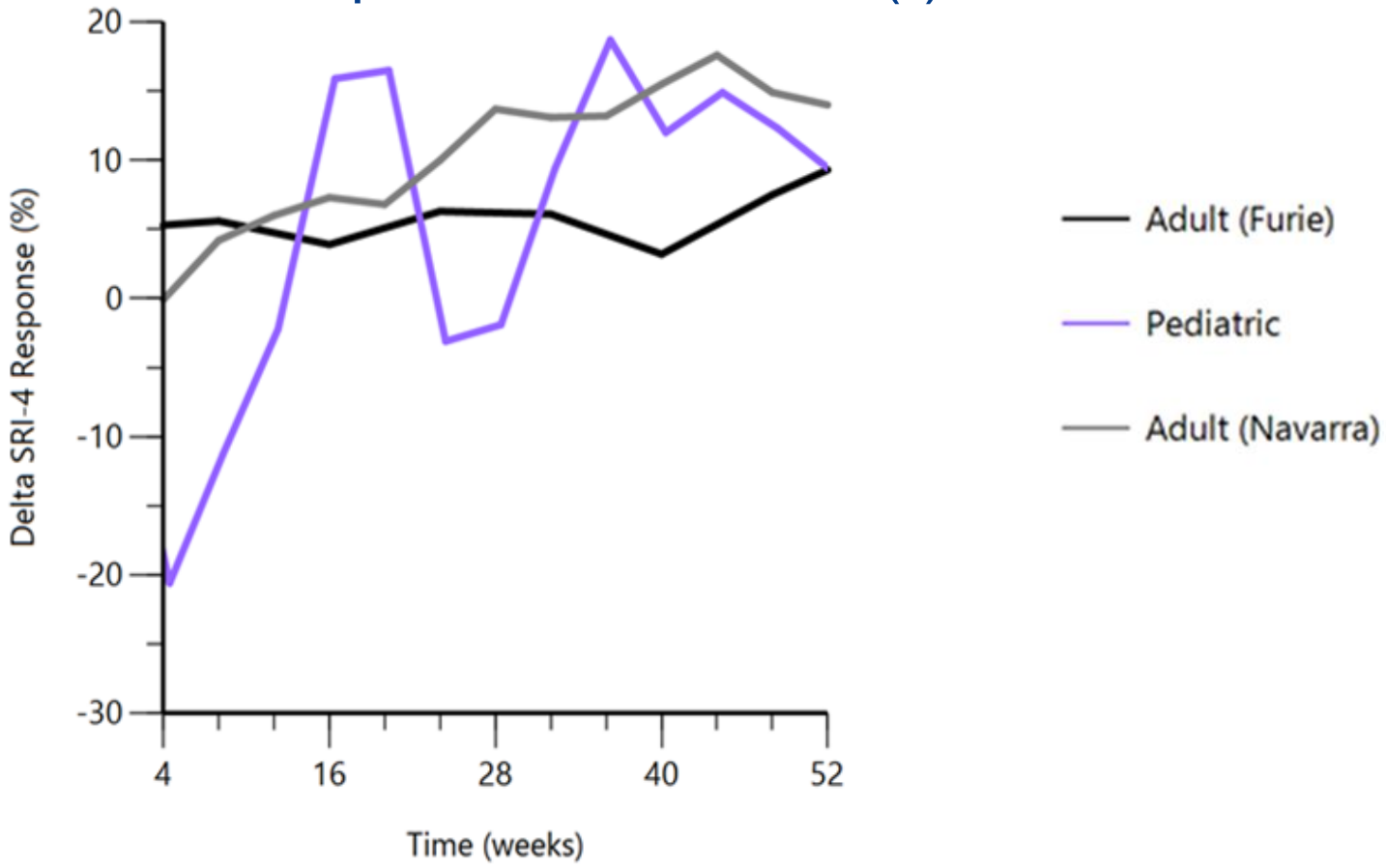
Belimumab Results

Overall Response for PLACEBO



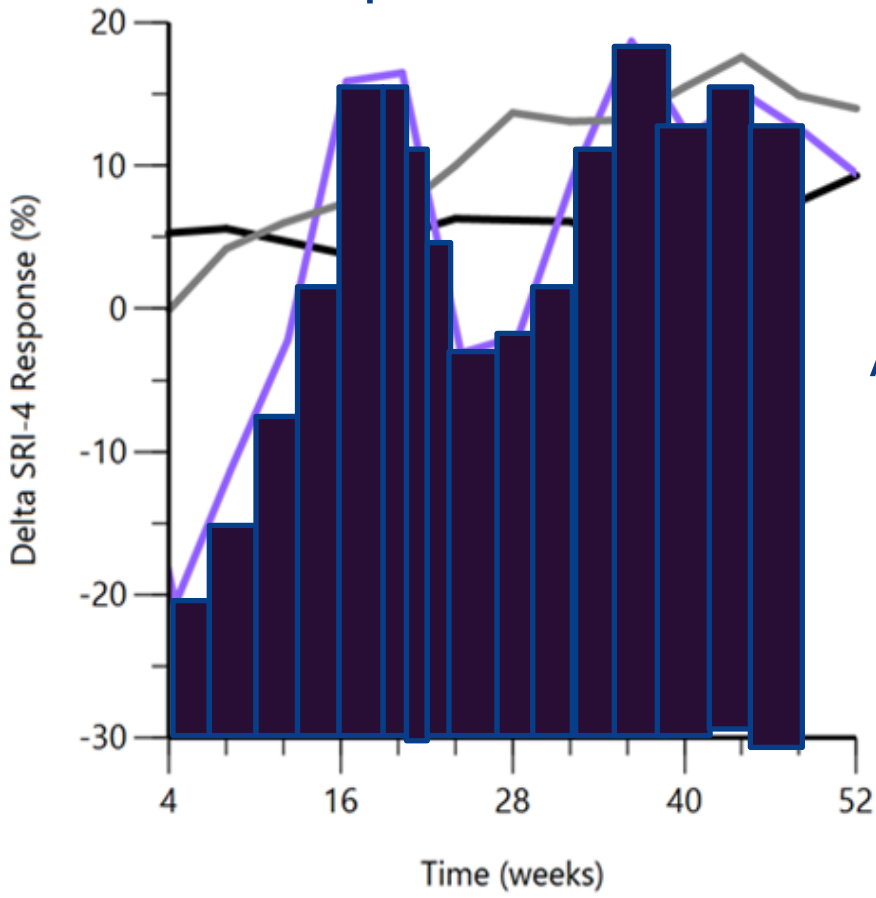
Belimumab Results

Net response: Belimumab (-) Placebo



Belimumab: Non-compartmental Analysis

Net response: Belimumab (-) Placebo



AREA UNDER THE EFFECT CURVE (AUEC)

Belimumab- Non-Compartmental Analysis

Table: Area Under the Time-Effect Curve for Change in SRI-4 (%), Belimumab 10 mg/kg IV

	Maximum Change in SRI-4	Minimum Change in SRI-4	AUEC Above Baseline[a]	AUEC Below Baseline[a]	Net AUEC[b]	Time above Baseline[a] (%)
Adult[20] (Furie)	9.3	3.2	274.4	0	274.4	100%
Adult[21] (Navarra)	17.6	-0.1	517.0	0.2	516.8	92.1%
Pediatric[19] (Brunner)	18.7	-20.6	404.6	146.4	258.2	65.4%

Belimumab- Change in Disease Biomarkers

Table: Change in biomarkers of disease activity

	DNA Antibody	Complement C4	CD20+
Adult[20] (Furie)[a]	-49.5	+51.9	-54.8
Adult[21] (Navarra)	–37.6	+30.4	--
Pediatric[19] (Brunner)	-44.9	+50	-65.8

Belimumab Conclusion

- clinical trial evidence supports the similarity of exposure-response to belimumab 10 mg/kg in adults and children ≥5 years with SLE

  (pediatric exposures at 10 mg/kg were overall similar to adults)