An Industry Perspective on Alternative Approaches & Trial Design Considerations

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Disclosure

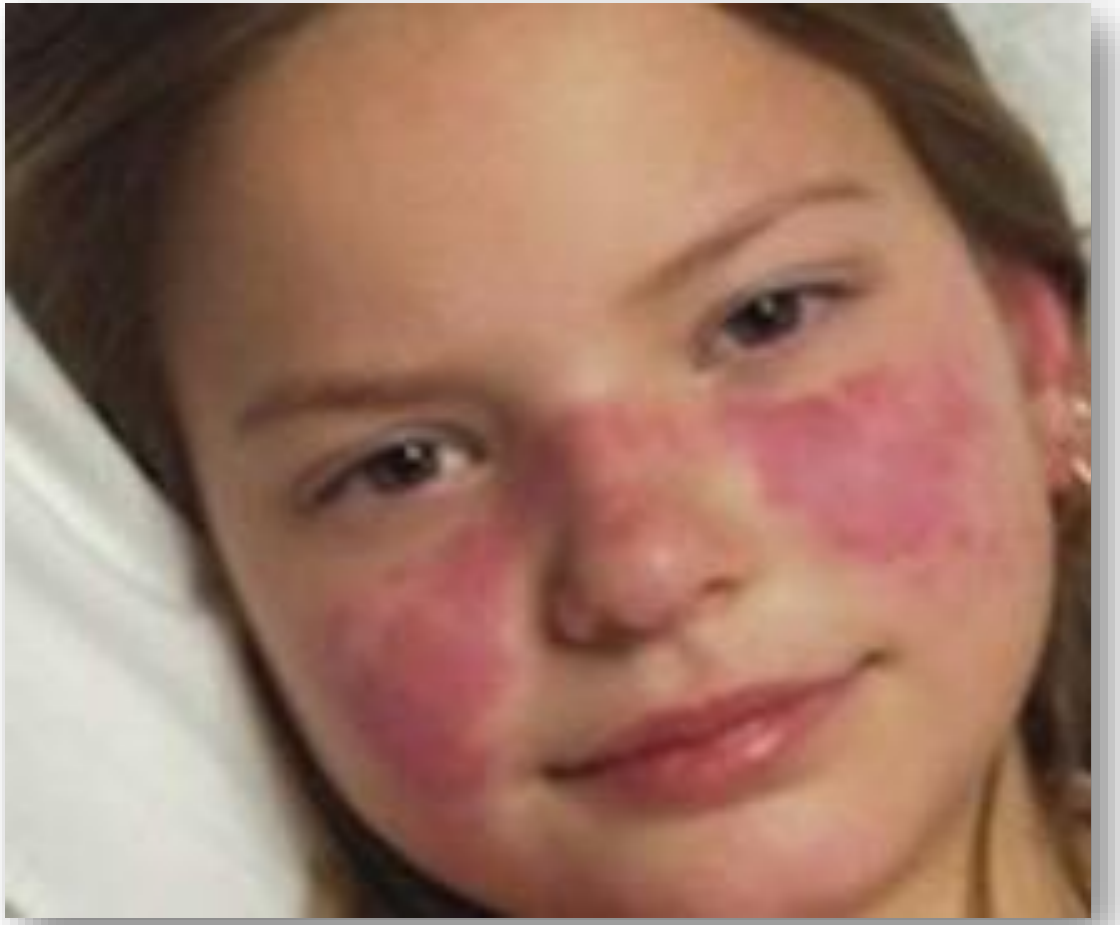
Martine Dehlinger-Kremer is employed and a shareholder of UCB Biosciences.

The following presentation reflects the personal views of the speaker and does not necessarily reflect the views of UCB Biosciences.

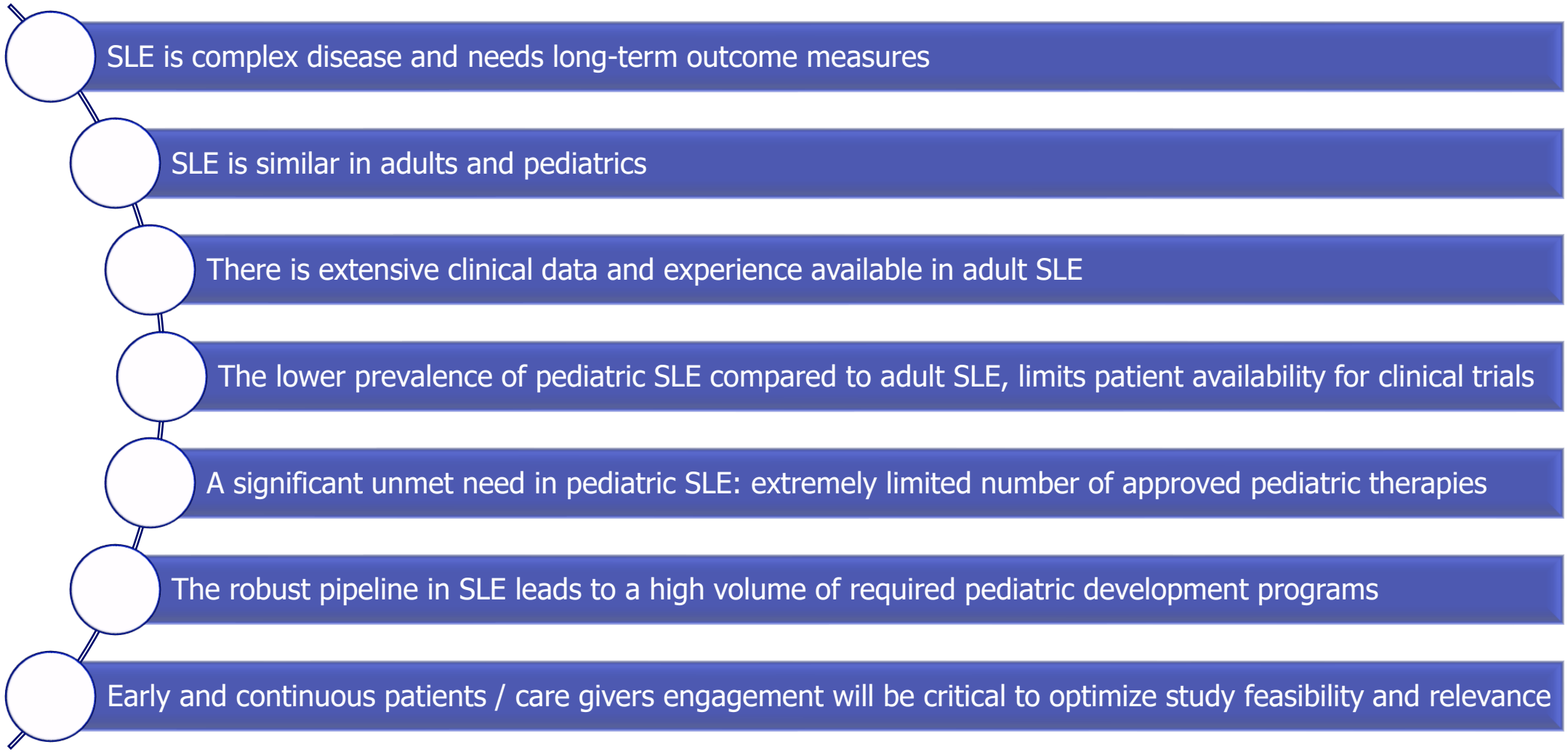
Agenda

Trial Design Considerations – Alternative approaches

- Background and Current Landscape
- Study Design Options in Pediatric SLE
- Integration of Pediatric and Adult Trial Strategies
- Conclusion



Background and Current Landscape for SLE



PIPs for SLE submitted for PDCO agreement between 2007 and Dec. 2024

Evaluation of 27 individual IMP submissions for PIPs in SLE

22 PIPs with a positive PDCO opinion

10 PIPs discontinued following discontinuation of the corresponding adult development programs

TABLE 1 List of PIP submitted for PDCO agreement for SLE until 2024.

PIP number	PIP IMP	Mechanism of action	Pediatric development and PIP status	Adult development status in SLE/LN[1]
EMEA-000118-PIP03-15	Abatacept	T cell activation inhibitors	PIP agreed (discontinued)	Discontinued
Not assigned	Not available	Anti-CD20 monoclonal antibodies	Withdrawn	Discontinued
EMEA-000311-PIP06-18	Ustekinumab (Stelara)	Interleukin 12 inhibitors; Interleukin 23 inhibitors	PIP agreed	Phase III (59)
EMEA-000380-PIP06-19	Secukinumab (Cosentyx)	IL17A protein inhibitors	PIP agreed (discontinued)	Discontinued
EMEA-000520-PIP02-13 EMEA-000520-PIP01-08	Belimumab	B cell activating factor inhibitors	PIP agreed	Adult EU indication granted
EMEA-000802-PIP02-11	Tabalumab	B cell activating factor inhibitors	PIP agreed (discontinued)	Discontinued
EMEA-001207-PIP02-19	Obinutuzumab	Anti-CD20 monoclonal antibody	PIP agreed	Phase III (60)
EMEA-001220-PIP05-19	Baricitinib	Janus kinase (JAK) inhibitor	PIP agreed (discontinued)	Discontinued
EMEA-001295-PIP01-12	Epratuzumab	Anti-CD22 monoclonal antibody	PIP agreed (discontinued)	Discontinued
EMEA-001435-PIP02-16	Anifrolumab (Saphnelo)	Interferon alpha beta receptor antagonists	PIP agreed	Adult EU indication granted
Not assigned	Not available	Interferon alpha inhibitors	Withdrawn	Discontinued
Not assigned	Not available	Anti-TWEAK [tumour necrosis factor (TNF)-related weak inducer of apoptosis] monoclonal antibody	Withdrawn	Discontinued
EMEA-001741-PIP09-23	Upadacitinib (Rinvoq)	Janus kinase (JAK) inhibitor	PIP agreed	Phase III
EMEA-001972-PIP01-16	Blisibimod	B cell activating factor inhibitors	Withdrawn	Discontinued
EMEA-002004-PIP01-16	Atacicept	B cell activating factor inhibitors	PIP agreed	Phase III
EMEA-002264-PIP01-17	Voclosporin (Lupkinys)	Calcineurin inhibitor	PIP agreed	Adult EU indication granted (LN)
EMEA-002284-PIP02-19	Evobrutinib	Bruton tyrosine kinase (BTK) inhibitor	Under evaluation (clock-stop)	N/A
EMEA-002338-PIP03-21	Ianalumab	B-cell activation factor receptor antagonists	PIP agreed	Phase III
EMEA-002350-PIP03-20	Deucravacitinib	Inhibitor of tyrosine kinase 2 (Tyk2)	PIP agreed	Phase II/III
EMEA-002374-PIP01-18	Avizakimab	Anti-interleukin 21 antibody	PIP agreed	Phase I/II
EMEA-002555-PIP02-21	Litifilimab	Anti-blood dendritic cell antigen 2 (BDCA2) antibody	PIP agreed	Phase III
EMEA-002702-PIP01-19	Dapirolizumab pegol	Antibody fragment against the CD40 ligand (CD40L)	PIP agreed	Phase III
EMEA-002815-PIP01-20	Rozibafusp alfa	B cell activating factor inhibitors	PIP agreed	Phase II
EMEA-002824-PIP01-20	Telitacicept	B cell activating factor inhibitors	PIP agreed	Phase II
EMEA-003108-PIP01-21	Cenerimod	Sphingosine-1-phosphate receptor 1 (S1P1) modulator	PIP agreed	Phase III
EMEA-003156-PIP01-21	Efavaleukin alfa	Regulatory T-lymphocyte stimulants	PIP agreed (discontinued)	Discontinued
EMEA-003342-PIP02-22	Enpatoran	Toll-like receptor 7/8 antagonists	PIP agreed	Phase II

An application for PIP can be withdrawn before the PDCO agrees on a final Opinion. Pre-opinion withdrawal of a PIP could occur, for instance, once adult (negative) results become available during the timespan required to agree a PIP (a 120 day procedure, with a clock-stop). After an Opinion has been agreed the PIP cannot be withdrawn any longer but discontinuation following appropriate communication with the EMA can be notified. The PIP number is a unique number assigned by EMA for each procedure. Using such number, it is possible to find the corresponding EMA Decision, which lists of the studies of the PIP, on the EMA website. Public assessment reports related to the product and its Product Information, if the product is already authorised, are also available. [1]Data collected from AdisInsights (14).

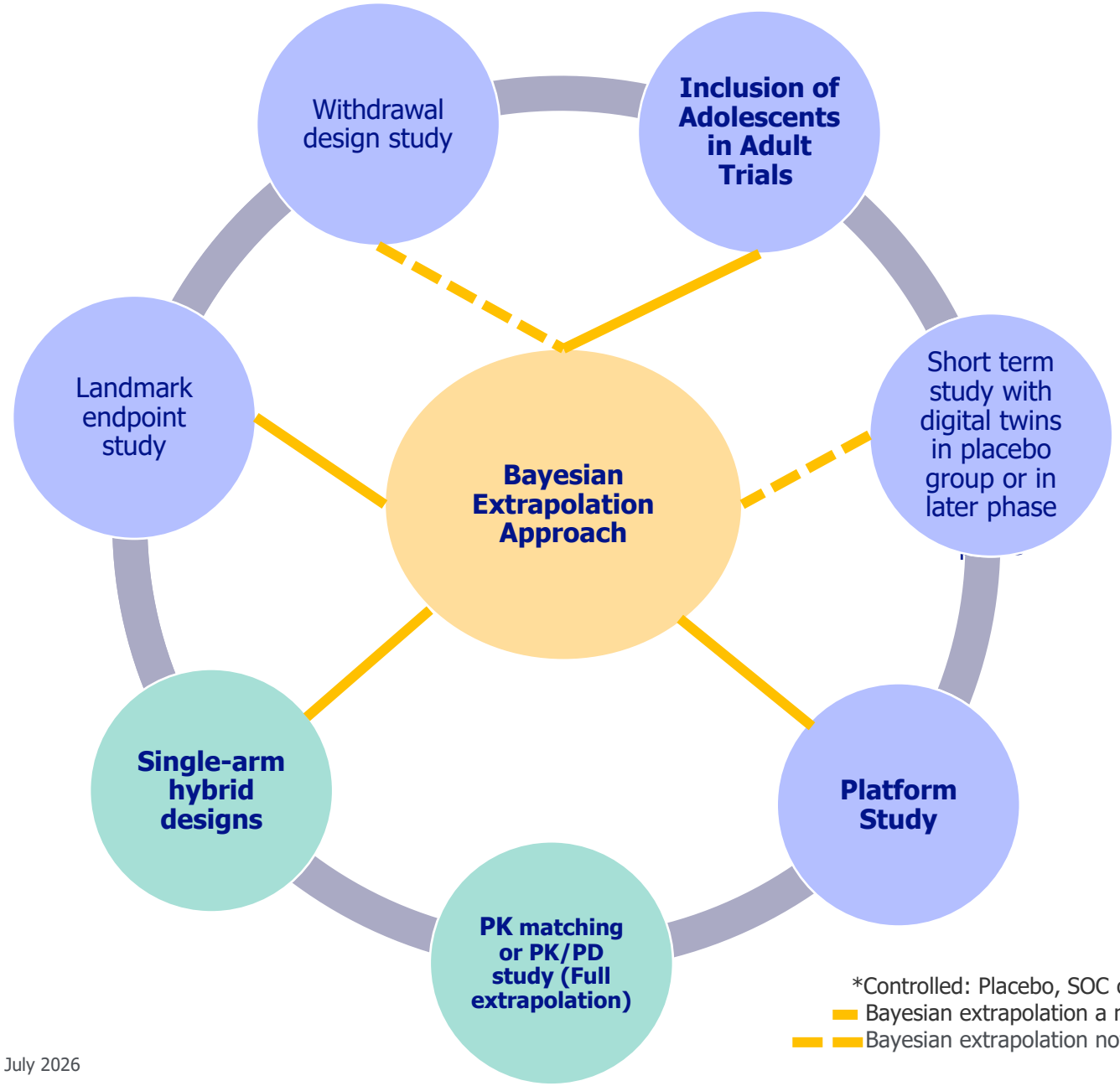
New medicines for childhood-onset systemic lupus erythematosus: an EU perspective on paediatric drug development, Roberto De Lisa at al. Frontiers In Medicine, 10 July 2025

FDA Pediatric SLE Workshop - 31 July 2026

Study Design Options in Pediatric SLE

Randomized controlled* designs

Single-arm designs



*Controlled: Placebo, SOC or Active Control

Bayesian extrapolation a natural component of design

Bayesian extrapolation not intrinsic to the design itself

Full Extrapolation of Efficacy from Adults supported by an Open Label PK Matching or PK/PD Study

Age-staggered enrollment

- Primary Endpoint: PK (Plasma conc)
- Secondary Endpoints: PK, (PD), safety, immunogenicity, clinical evaluations

Full Extrapolation of Efficacy from Adults supported by an Open Label PK Matching or PK/PD Study

Opportunities

-**High patient and caregiver acceptability** due to absence of placebo/control treatment

-**Minimizes pediatric sample size** through efficacy extrapolation from adults

-**Operationally feasible** in a rare disease setting

-Enables **accelerated pediatric development** and **earlier access**

-Leverages extensive adult efficacy and safety experience

Considerations

-Requires strong justification that **disease biology and treatment response are sufficiently similar** between adults and pediatric patients

-**PK comparability** (and PD comparability, if included) must be demonstrated

-Residual uncertainty remains regarding the magnitude of pediatric efficacy

-Potential differences in disease phenotype and baseline characteristics (e.g., higher prevalence of LN and greater disease activity in pSLE) may affect extrapolation

Single Arm Hybrid Designs

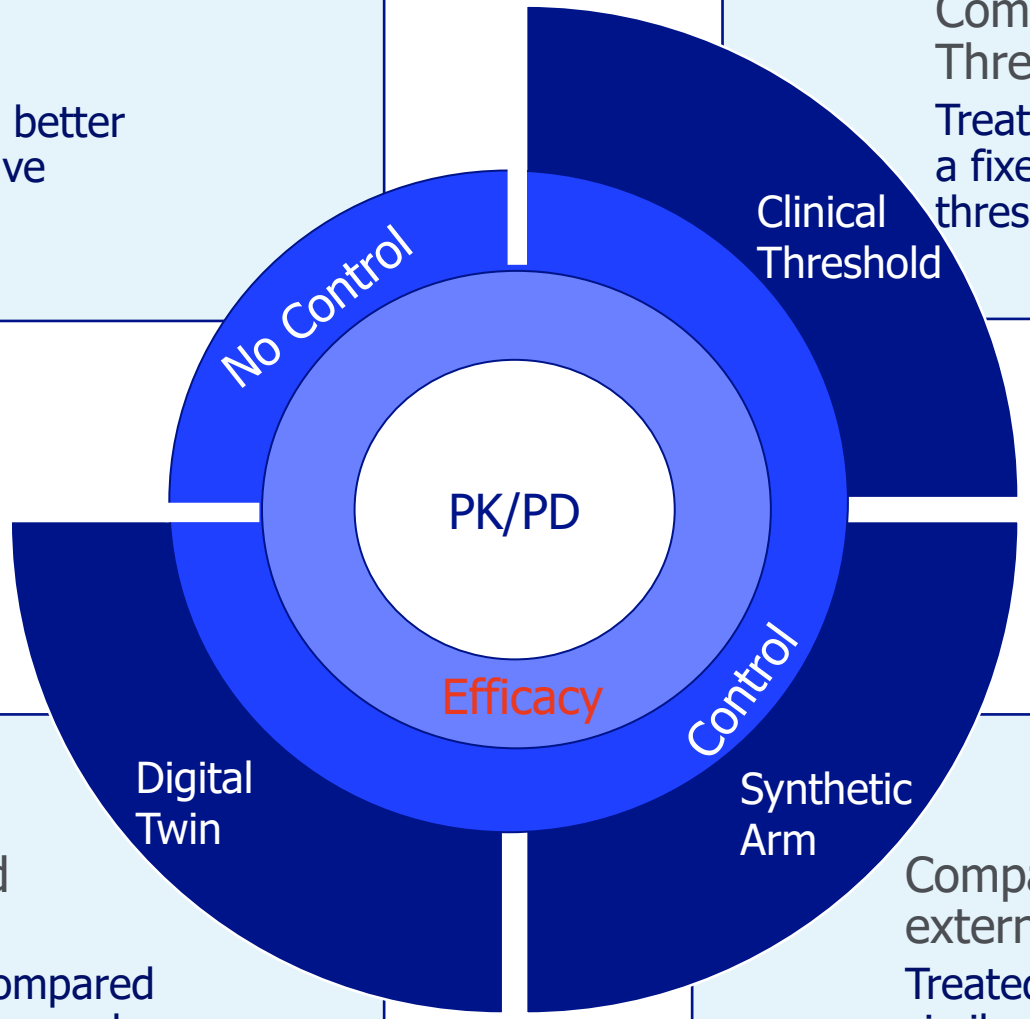
How is efficacy inferred?

Exposure-Response relationship

Higher Exposure causes better outcome → Drug effective

Compare against a Threshold

Treated patients do better than a fixed clinically relevant threshold



Compare to predicted untreated outcomes

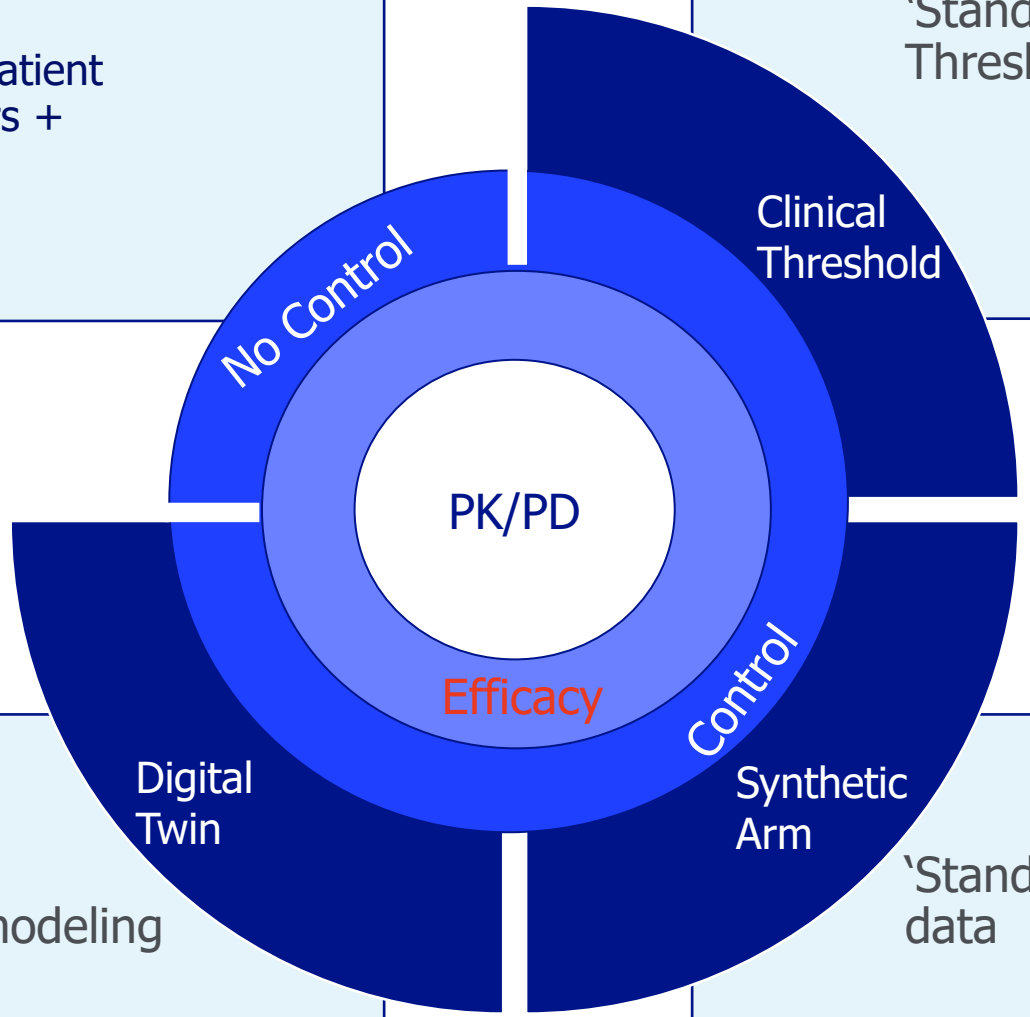
This patient improves compared to what would have happened without treatment

Compare against observed external patients

Treated patients do better than similar real-world patients

Single Arm Hybrid Designs

What data are needed?



'Standard'
i.e. Treated Individual Patient Data (IPD) + biomarkers + outcomes

'Standard' + agreed Threshold

'Standard' + Rich longitudinal data + modeling

'Standard' + external patient data

Single Arm Hybrid Designs

Strengths and Limitations

Fully mechanistic, Works with very small samples size, Strong for dose justification + extrapolation

No direct comparator,

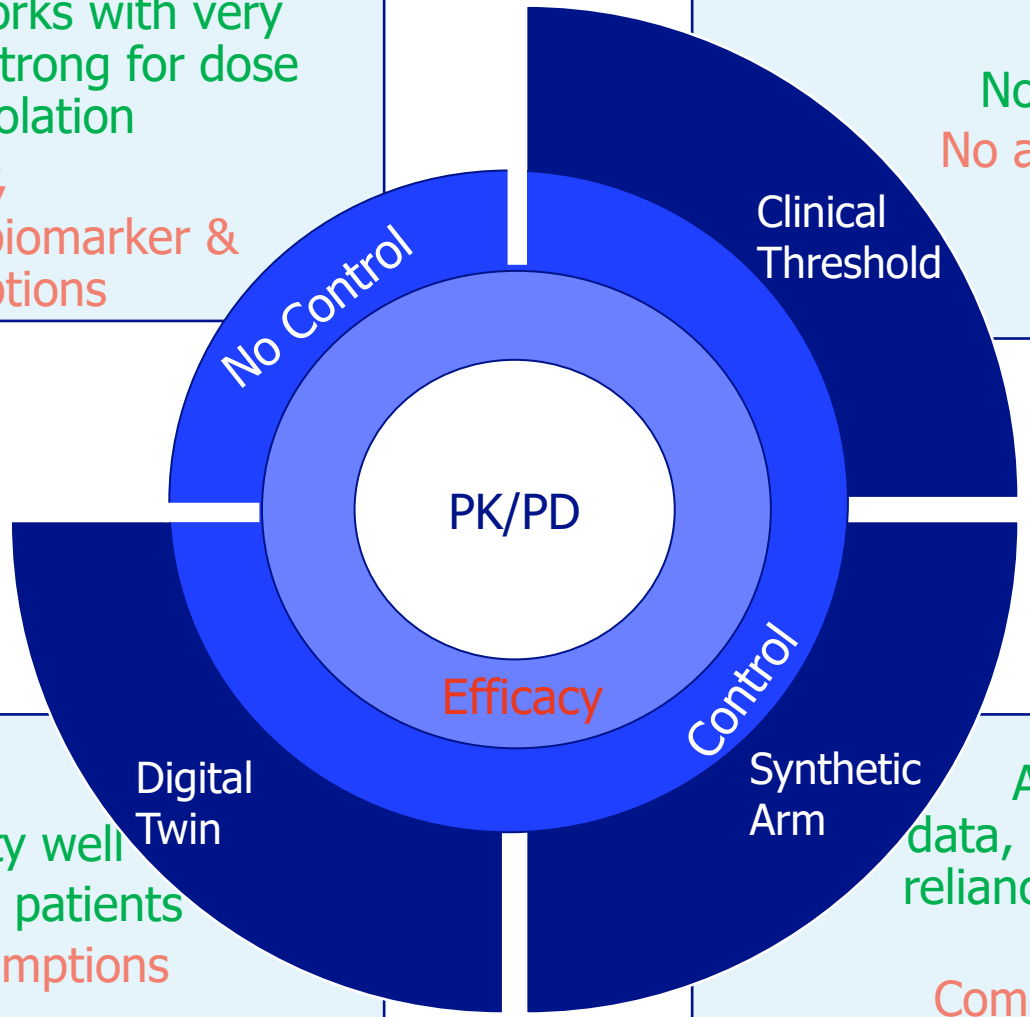
Relies on validity of biomarker & extrapolation assumptions

Most intuitive

No need for external data

No accounting of variability,

Solely based on expert judgement



Fully individualized

Handles heterogeneity well

No need for matched patients

Heavy modeling assumptions

Difficult to validate

Anchored to real patient data, More intuitive, Reduces reliance on biomarker validity alone

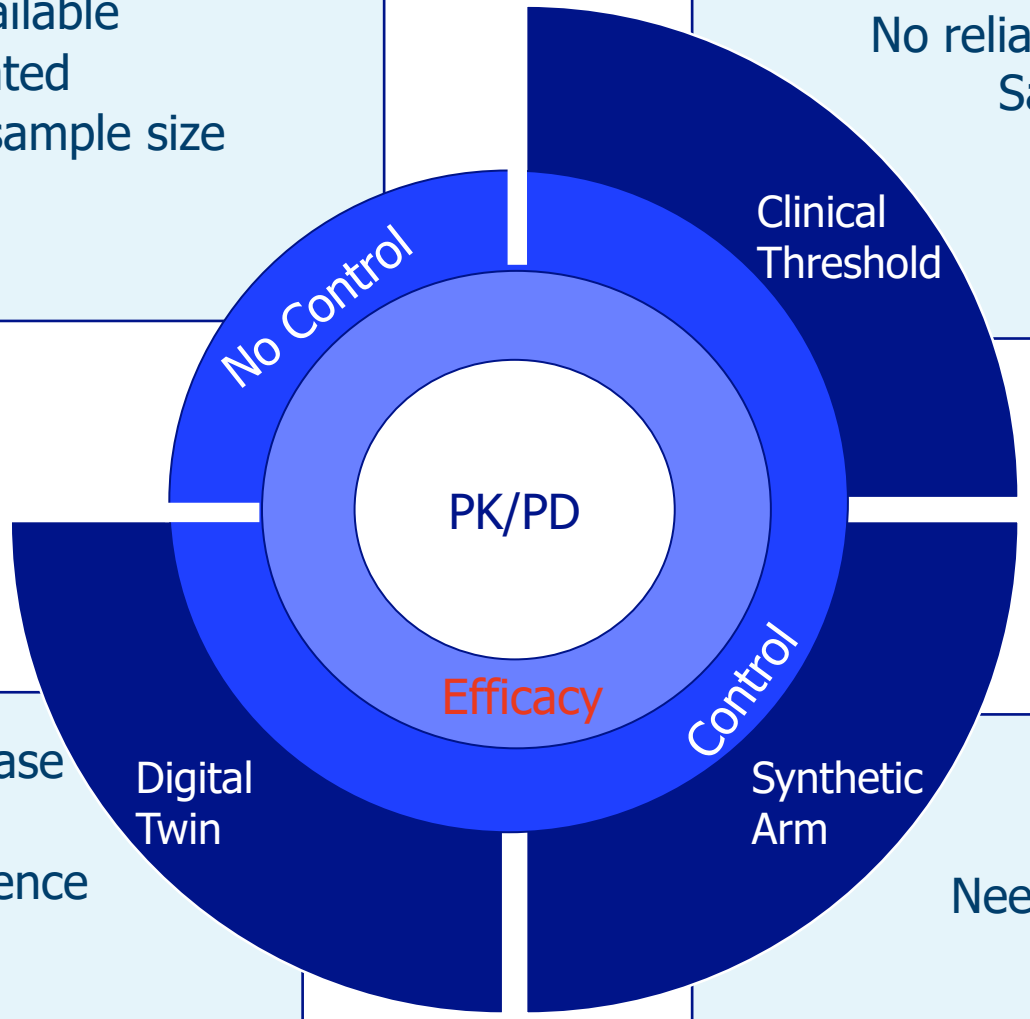
Comparability issues, Needs ideally IPD & strong adjustment

Single Arm Hybrid Designs

When to Use Each Design?

Strong adult data available
Biomarker well validated
Very small pediatric sample size

No reliable external data exists
Sample size is very small
There is consensus on meaningful effect size



Very heterogeneous disease
Rich natural history data
Want individualized inference

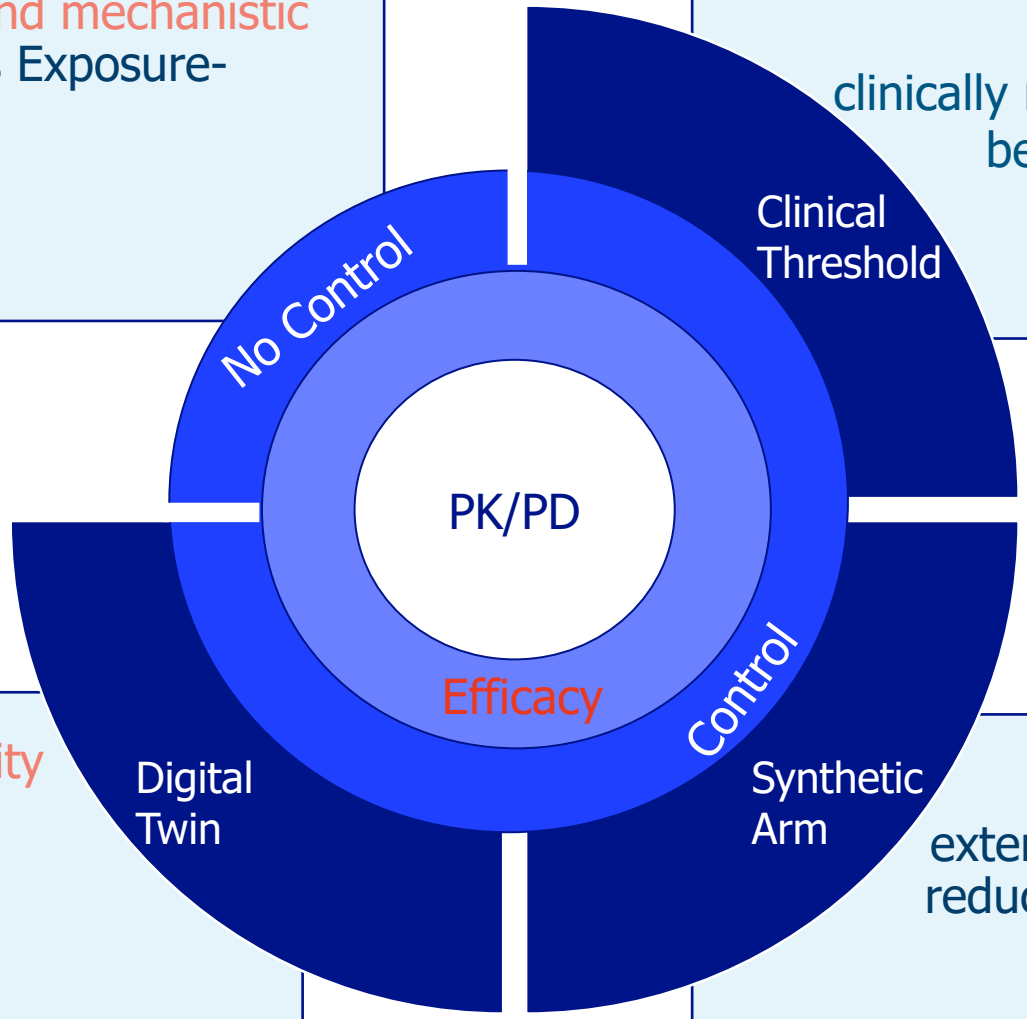
Good registry data available
Need stronger comparative evidence

Single Arm Hybrid Designs

Strong PD markers and mechanistic understanding allows Exposure-Response inference

Small sample sizes; clinically meaningful benefit may be more informative than direct comparisons

Why relevant for pSLE?



High disease heterogeneity favors individualized counterfacts

Rare disease; external data can replace or reduce the need for controls

Bayesian (Dynamic) Extrapolation Designs

Design overview
Use information from another source (e.g., adults), while allowing the pediatric data to determine the extent of borrowing

Concept
Instead of saying: Pediatric Effect = Adult Effect

we say: Pediatric Effect ~ **around** Adult Effect (with uncertainty)

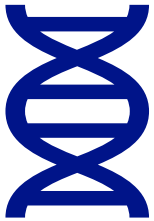
and the model learns **how close they really are**

Dynamic element

Response

By borrowing strength from adult data, the sample size is reduced, and so this design enables a streamlined study that can support regulatory efficacy claims based on a clinical endpoint.

Rationale for Bayesian (Dynamic) Extrapolation Design in pSLE



Most targeted therapies are initially developed and evaluated in adults

Extensive adult efficacy data available

Substantial biological similarity between adult and pediatric disease

Clinical endpoints broadly aligned

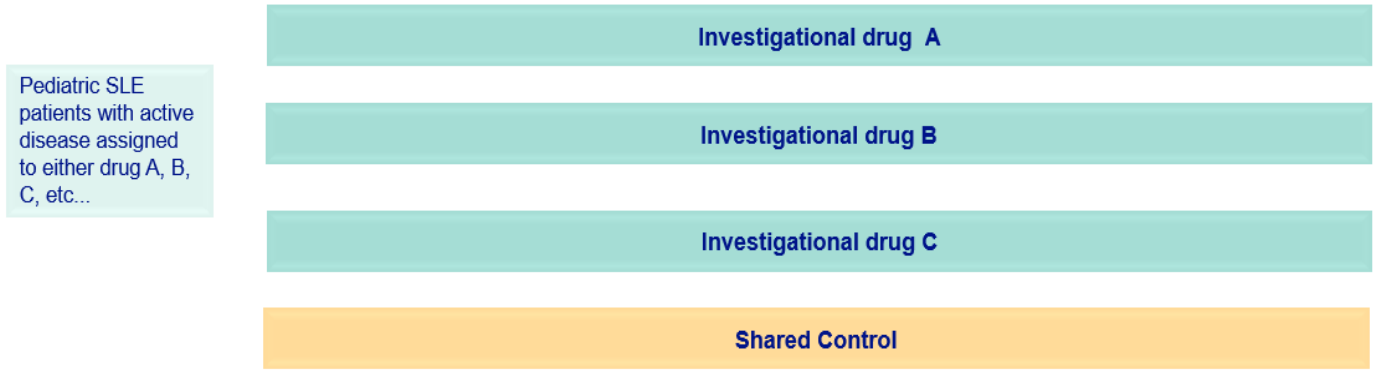
Limited number pediatric patients making large trials difficult to conduct

Adult information is relevant to children but uncertainty remains

Bayesian borrowing allows pediatric data to determine the amount of adult information incorporated

Reduce the amount of pediatric efficacy data required while maintaining confidence in treatment benefit.

Platform Study for Pediatric SLE



Relevance to SLE
In the context of limited patient populations and a growing therapeutic landscape, a shared master protocol can optimize evidence generation by enabling the concurrent evaluation of multiple therapies in SLE.

Opportunities

- Single shared control arm across all treatment groups, reducing overall sample size requirements
- Multiple therapeutic approaches in parallel
- Improved recruitment potential driven by access to multiple therapeutic options
- High acceptance by parents/caregivers, patients and Ethics Committees
- Reduces family burden and decision fatigue when considering research options
- Reduced administrative burden versus individual trials, enabling greater operational efficiency
- Potential to accelerate access to safe and effective medicines for children

Challenges

- Asset selection and prioritization
- Reliance on collaboration among competing sponsors
- Stakeholder alignment across multiple parties
- Complex governance and decision-making
- Operational complexity in protocol development, amendments, and trial execution requiring enhanced quality oversight

Inclusion of Adolescents in Adult Trials

Prerequisites to be fulfilled for SLE and the Test Drug

Disease

- exists on a continuum between adults and adolescents

- no significant differences in pharmacodynamic responses, disease prognosis, or manifestations

Drug Pharmacokinetics

- characterized in adult patients

- expected to be similar between adolescents and adults

(can be confirmed using modelling and simulation approaches)

Efficacy and Safety data from adult patients

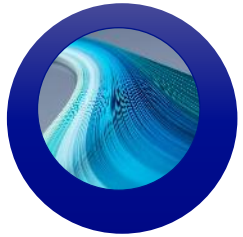
potential benefits for adolescents outweigh the risks associated with their inclusion in the phase 3 clinical trials

→ "Prospect of direct benefit to pediatric patients"

ICH E11A Supporting inclusion of adolescents in adult trials

Engage with regulators early in the drug development process, as regulatory feedback can influence the pediatric study plans required by EMA and FDA

Inclusion of Adolescents in Adult SLE Trials - Advantages



Accelerated Development & Access

Reduces / eliminates need for a dedicated adolescent trial and when required, pediatric studies can be smaller.

Faster approval for adolescents.

Accelerates access to innovative therapies for pediatric SLE patients.

Reduces off-label use.

Operational Efficiency

One protocol, one trial, shared infrastructure, sometimes shared sites (or sub-sites), and monitoring.

Statistical Power & Robustness

Larger combined sample size improves precision of efficacy and safety estimates.

Adolescents can contribute to subgroup analyses without requiring a separate powered study.

Consistency in Data

Same protocol, endpoints, and assessments reduce variability.

Regulatory Alignment

ICH E11A recommends inclusion of ado. in adult trials or parallel trials unless there is a reason why it is not possible.*

* ICH E11A Pediatric Extrapolation (Final, 2024; implemented 2025)

Inclusion of Adolescents in Adult Trials - Key Considerations

Endpoints Suitability

- Same prim. & sec. enpoints for adults and adolescents.
- Tertiairy endpoints as optional for adolescents to increase attractiveness for the trial.
- Capture adolescent-specific outcomes, e.g., growth & development
- SLE QoL tools validated for adults only
- Fatigue QoL important for adolescents.

Safety

- Adolescents may have different AE profiles (growth, puberty-related factors, kidney involvement): perform a separate safety group analysis.

Psychosocial and Compliance Challenges

- Adolescents may have different adherence patterns and psychosocial needs compared to adults, which could impact data quality.

Under-Representation Risk

- Limited adolescent enrollment may not generate robust age-specific evidence.
- Bayesian borrowing and pre-specified minimum adolescent sample sizes can reduce this risk.

Site Logistics Requirements

- Pediatric-qualified investigators
- Potential need for mixed site networks
- Transition from pediatrician to adult rheumatologist when reaching age of adulthood

Combined Trial Integrated into the Pediatric Plan

- Regulatory feedback (PDCO/FDA) might impact adult Phase 3 design

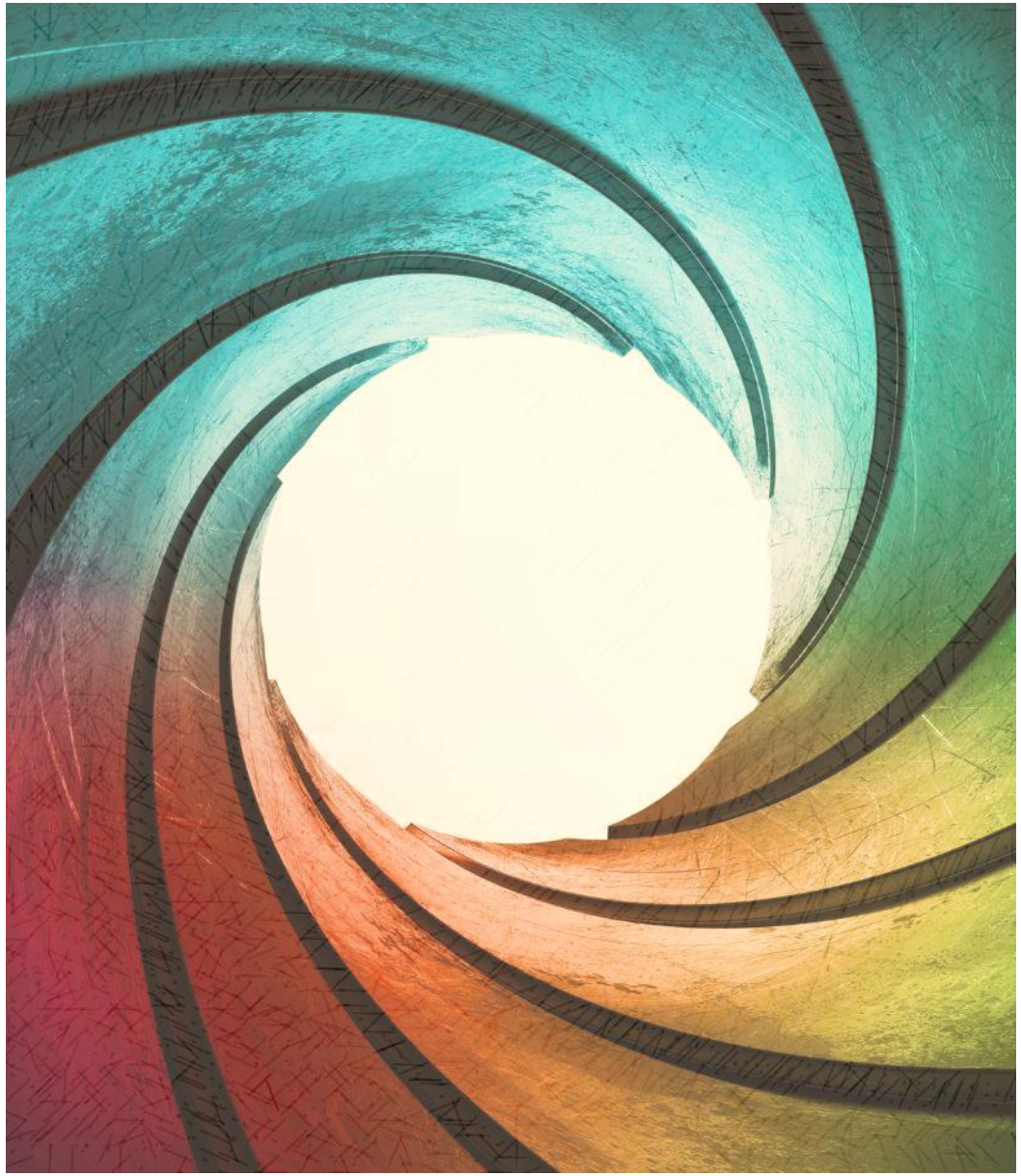
Innovative Study Designs for pSLE and Patient Access

Fullfill HTAs and Payers Requirements

- Comparative evidence
- Patient-relevant outcomes
- Methodological rigor
- Real-world relevance

Critical Success Factor

- Early HTA alignment on comparator, endpoints, and evidence plan



Conclusion

Disease Similarity and Extrapolation
Similarity between adult and pediatric SLE enables using adult data to guide pediatric clinical trials effectively

Challenges in Pediatric SLE Trials
Rarity of pediatric SLE and the competitive landscape limits trial recruitment and feasibility, requiring innovative study designs.

Patients, Parents/Caregivers Engagement Importance
Early engagement with patients and families/caregivers important to improve trial relevance, recruitment, and retention in pediatric SLE studies.

Regulatory Harmonization
Alignment between regulatory agencies to streamline pediatric development in SLE and accelerate therapy access.

Scientific innovation, patient engagement, and regulatory collaboration to accelerate pediatric SLE therapy development.

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Thank You

Inspired by **patients.**
Driven by **science.**