EMA
EUROPEAN MEDICINES AGENCY

Landscape of Pediatric SLE Drug Development: Regulatory Perspective

FDA-University of Maryland CERSI Public Workshop: Accelerating Product Development for Pediatric Systemic Lupus Erythematosus (SLE) July 30 & 31, 2026

Great Room, FDA White Oak Campus Silver Spring, MD

Dr Roberto De Lisa – Paediatric Medicines Office
EMA

Disclaimer

The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties

Presentation outline

From regulatory framework to evidence strategy for paediatric SLE development

1. **Regulatory pathway for paediatric development**
   PDCO opinion, PIP agreement and core development-plan components
2. **Adult–paediatric similarity and cSLE characteristics**
   Disease severity, organ involvement and implications for trial design
3. **EMA experience with SLE PIPs**
   Portfolio view across timelines, study designs and substances under development
4. **Development challenges and extrapolation gaps**
   Vulnerable populations, endpoints, placebo ethics and transferability of evidence
5. **Data sources, case example and key messages**
   DARWIN EU evidence, belimumab pathway and regulatory takeaways

EU regulatory pathway for a paediatric develop

PDCO Opinion

Normally agreed at end of Phase I in adults

Formulation development	Non-clinical developme	alyses apolation
• Age-appropriate pharmaceutical form	•	• PopPK, PK/PD and other exposure response analyses
	men, tion	
	tion and subset , sample size	
	dy duration and follow-up	

Our experience so far…

An eventful timeline…

2011
Belimumab (first biologic treatment) authorised for adults

2019
PDCO-CHMP break-out session

2023
Presentation at ESDPPP European Society for Developmental Perinatal and Paediatric Pharmacology

31 PIP applications assessed
24 PIPs adopted

2024
Darwin EU RWE study on treatment patterns in cSLE + Article

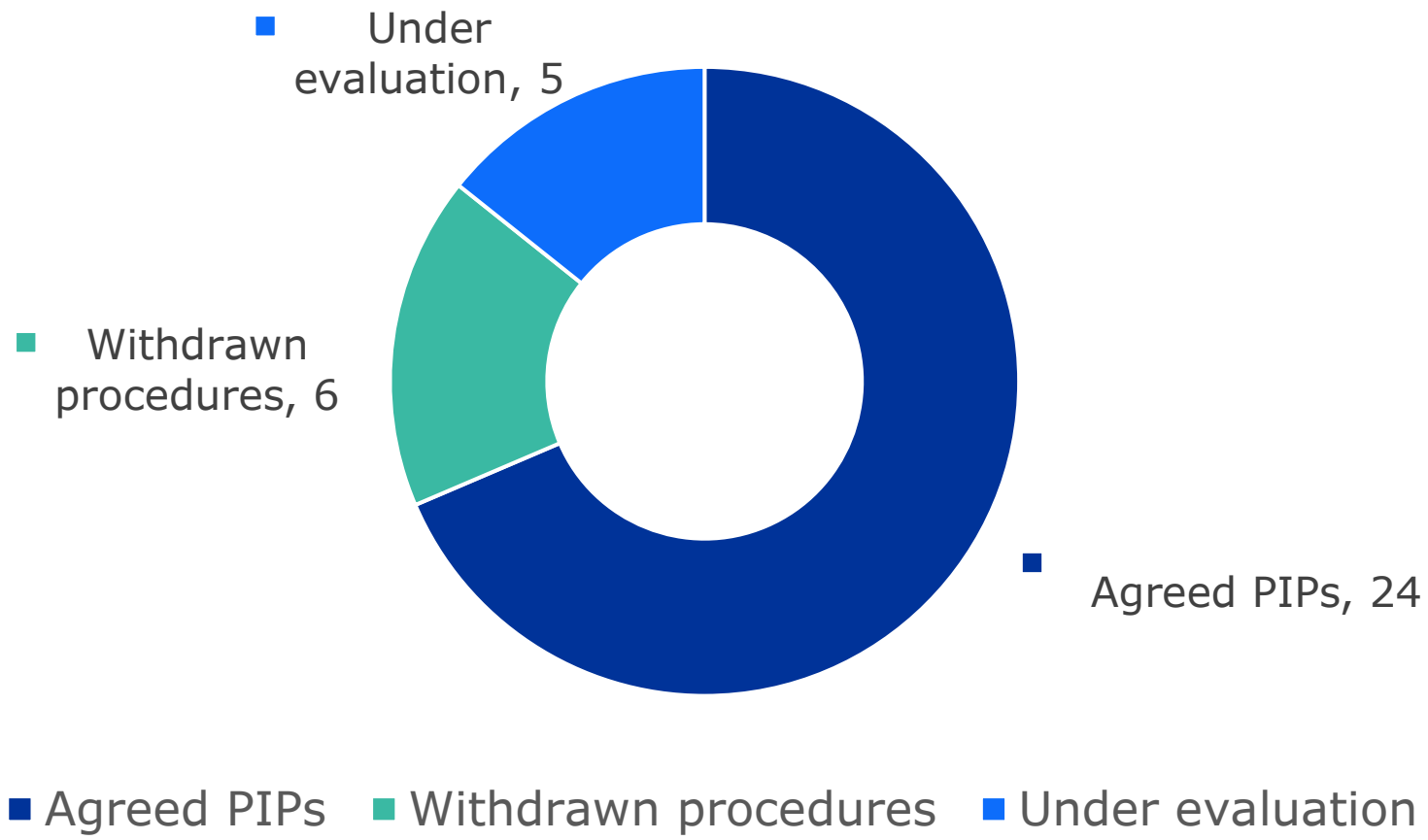
2023
Bilateral EULAR/PRES/PRINTO and EMA

2025
NEW Article being drafter for Frontiers in Medicine with Academia

2024
Paediatric cluster discussion

2024
Panel discussion at Pediatric Rheumatology Collaborative Study Group PRCSG Advisory Council meeting

Paediatric Development Plans for SLEs



So far (since 2007), the EMA has reviewed and agreed a number of PIPs for Systemic Lupus Erythematosus in the paediatric population.

Some of the agreed PIPs were then withdrawn due to discontinued development in adults.

One procedure is still in the clock-stop phase.

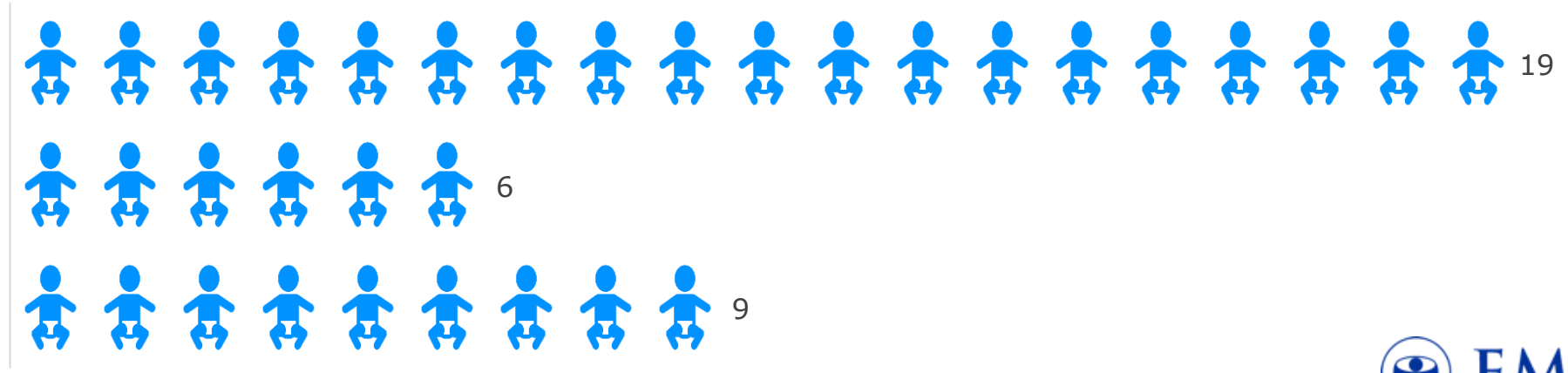
Study design (all studies)

- 16 of the agreed PIPs comprised one single planned clinical study to address both PK and safety/efficacy, 7 PIPs included two studies on which one was mainly a PK one and the second a safety/efficacy study, and 1 PIP four studies

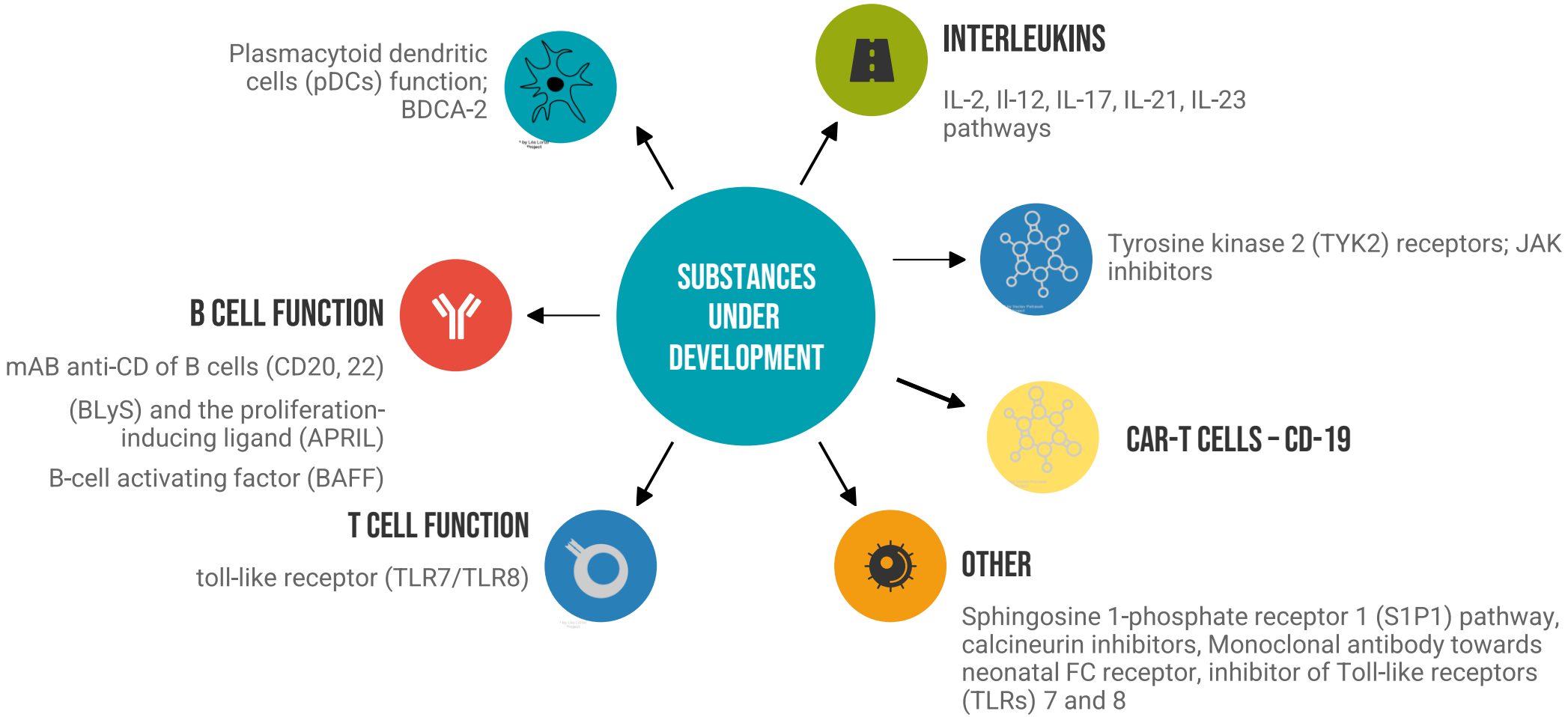
- Overall, at the beginning of development, due to lack of availability of adult data, a **RCT vs placebo as add on**, was requested

- In some cases, a RCT with a **withdrawal design (randomised withdrawal trial)** was considered feasible

- For PIPs targeting subset **Lupus Nephritis** a single arm trial was agreed

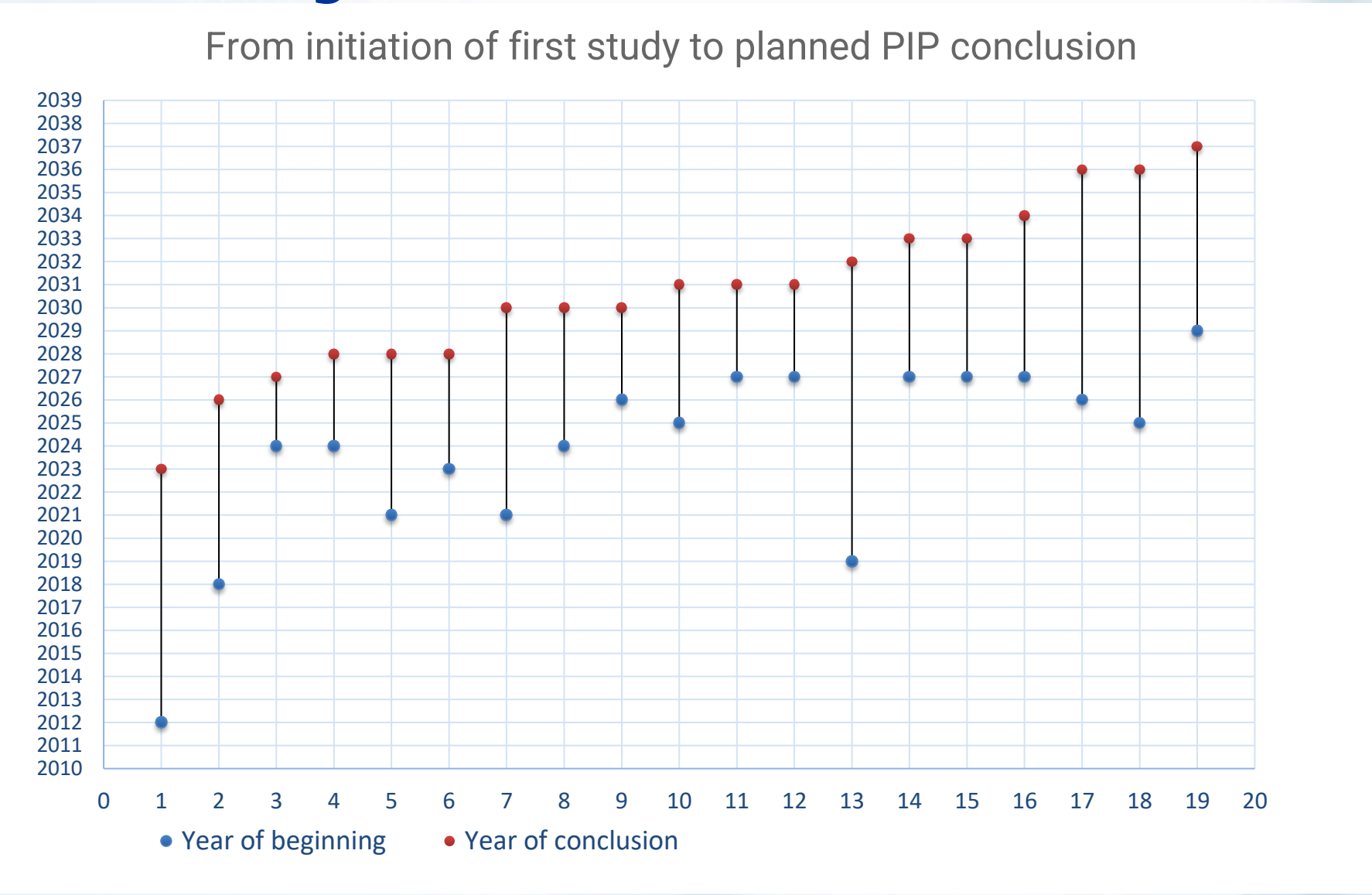


Mechanism of action



Icons by Cells by Lea Lortal, Vaclav Petrasek from Noun Project

Agreed timelines of PIPs



Challenges in a vulnerable population

- **Inclusion criteria**: patients with renal and/or CNS involvement are not routinely requested to be included. However, there is a risk they are neglected from research
- Allocation to **placebo** does not seem ethical in the presence of licensed therapies: add-on to standard of care should be the default design despite different adult development?
- **Design**: RWD
  - Ethically challenging due to risk of relapses
  - Carry-over effect from open-label active study period may reduce flaring in patients switched
  - Only indirect evidence of efficacy

ICH E11A 21 August 2024 Paediatric Extrapolation

- The **assessment of similarities and differences** of the disease between a reference and target population is a key factor in developing the pediatric extrapolation concept
- To increase confidence in understanding the similarity of disease between the populations, evaluation of disease similarity should also attempt to determine the **gaps in knowledge**
- The extrapolation plan should include the objective(s) and methodological approaches for the data that need to be generated to confirm assumptions made, address uncertainties and gaps in knowledge, and **support benefit/risk assessment** in the target population

What are the gaps in the extrapolation concept?

Are adult trials able to provide evidence to be leveraged to make conclusions on paediatric patients?

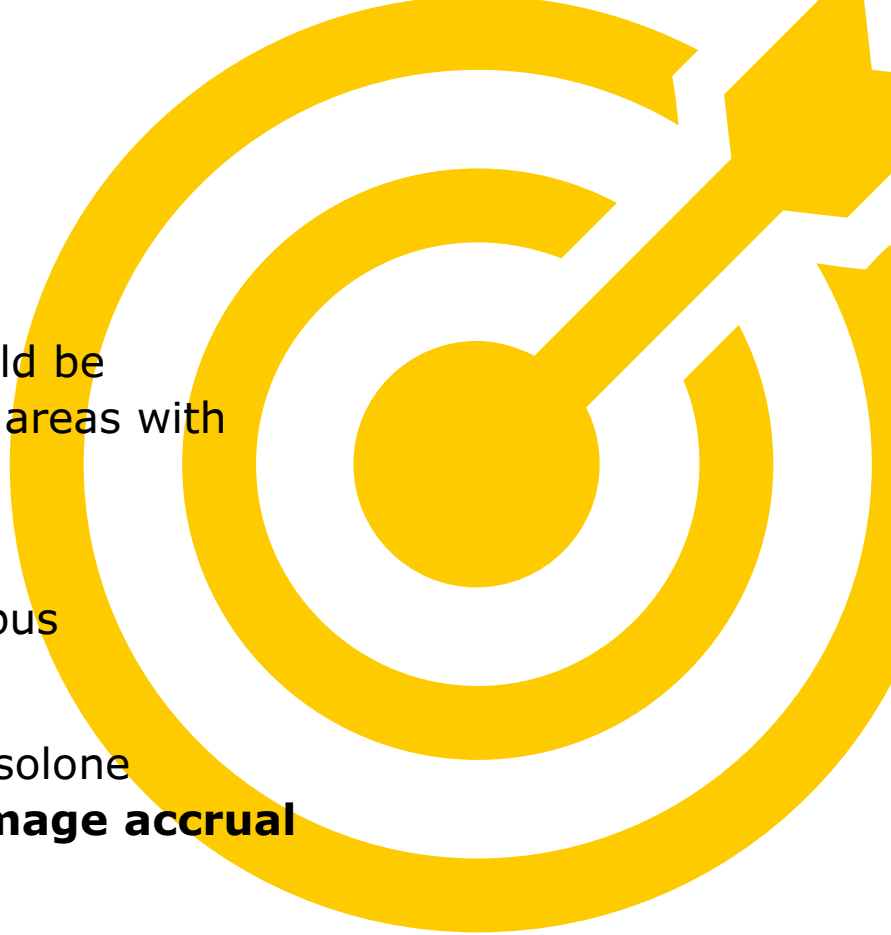
Extrapolation: similarity of disease

Image created with AI tools-

Grades of similarity adult vs childhood SLE (cSLE)

- cSLE is typically more aggressive at presentation, with higher disease activity scores, greater need for steroids/immunosuppressants, and more cumulative damage than aSLE
- Standardized mortality ratios do not seem higher with onset in younger age, cSLE (≈ 2.6-fold higher risk of death compared to the general population in adulthood)
- Organ involvement
  - **Renal (kidney) disease**: more frequent and severe in cSLE (e.g., 44–78% in cSLE vs 26–52% in adults), with higher risk of progression to end-stage kidney disease; renal damage accrual is more common in cSLE
  - **Neuropsychiatric (CNS) disease**: seizures, psychosis, headaches, cognitive issues occur more often in cSLE, and are associated with higher activity and damage; NP involvement predicts worse renal and patient survival in cSLE LN cohorts
  - Hemolytic anemia, thrombocytopenia, lymphopenia are more frequent in cSLE
  - cSLE shows **higher rates** of anti-dsDNA and antiphospholipid antibodies compared with adults, aligning with more nephritis and cytopenias; adults have more anti-SSA/SSB in several cohorts

Most recent publications…



- Evaluating **similarities in exposure-response**: adult SLE data should be leveraged to guide pediatric drug development programs and identify areas with residual uncertainty regarding the effectiveness or safety of a drug in children(Balevic SJ et al. J Clin Pharmacol. 2023)
- Remission and **long-term remission** of paediatric-onset systemic lupus erythematosus (Chen YC, et al. Front Pediatr. 2023 Oct)
- Disease activity levels (AMS/PGA) and proxy indicators (methylprednisolone exposure, baseline damage) were found to be **key predictors of damage accrual** (Hanif et al. May 2025)
- Updated interdisciplinary clinical practice guidelines for the management of juvenile-onset systemic lupus erythematosus (jSLE) in a patient-centred, **treat-to-target (T2T)** approach

Clinical characteristics of cSLE: how do they impact on paediatric drug development?

- While cSLE and aSLE are thought to share a similar pathophysiology, paediatric patients seem to differ in some characteristics of the disease
  - A higher male to female ratio
  - Different **organ involvement** (more frequent renal involvement with nephritis and CNS involvement): need different inclusion criteria?
  - Quicker **organ damage** accrual than adults: impact on study design?
  - Treated with **higher doses** of approved medications: multiple dose to be evaluated?
- This vcould means that response to treatment might have a different impact according to age of onset
- Paediatric specific therapeutic needs are not routinely covered by adult development

©image by stock.adobe.com

What solutions could be explored?

We are actively looking for data: SLE study with DARWIN EU

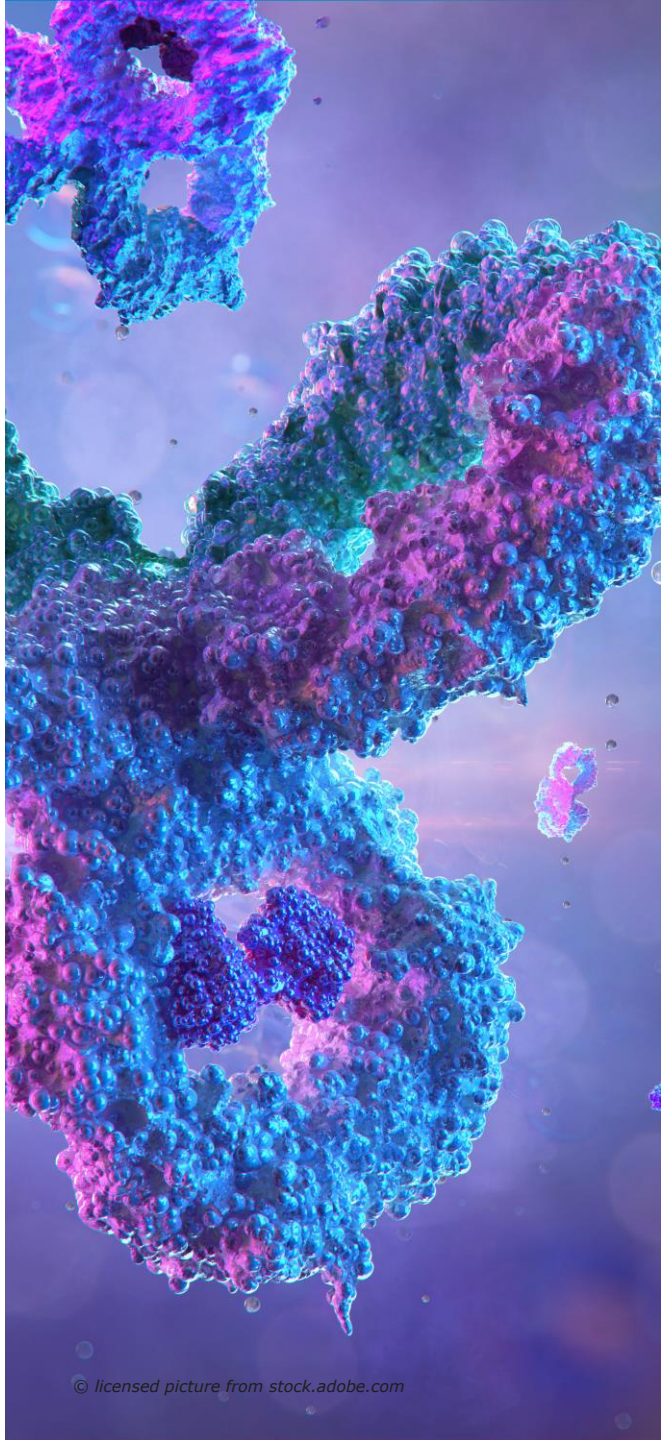
- **Objective:** to explore SLE treatment patterns in adults vs children as there is limited real-world data of SLE medication utilisation, especially in childhood-onset SLE (cSLE)
- **Methods:** longitudinal cohort study using five routine healthcare databases from four European countries (United Kingdom, France, Germany, and Spain)
- **Main results**: 5718 patients. In the paediatric cohort (n = 378), 66-83 % of SLE patients were female, with median age of 12 to 16 years at diagnosis. Hydroxychloroquine and glucocorticoids were common first-line treatments in both adults and children, with second-line treatments including mycophenolate mofetil and methotrexate
- **Main conclusion**: high glucocorticoid prescriptions in paediatric patients, steroid-sparing treatment alternatives needed

Du M, et.al. Treatment of systemic lupus erythematosus: Analysis of treatment patterns in adult and paediatric patients across four European countries

Eur J Intern Med. 2024 Aug 11:S0953-6205(24)00344-3. doi: 10.1016/j.ejim.2024.08.008

Belimumab: path to the EU paediatric indication

- Benlysta is indicated as add-on therapy **in patients aged 5 years and older** with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy
- Primary endpoint of the paediatric study was the SLE Responder Index (SRI4) response rate at Week 52. The preplanned analysis of this endpoint **did not reach the statistical significance** threshold
- From an EU perspective differences between the groups in the pediatric trial were considered largely comparable to the differences observed in the phase 3 studies in adults
- This was sufficient to provide the required level of evidence for licensure in patients 5 years and above and no further Bayesian analyses were considered necessary beyond **demonstration of effective exposure was reached**



Travis J, Rothmann M, Thomson A. Perspectives on informative Bayesian methods in pediatrics. J Biopharm Stat. 2023 Nov 2;33(6):830-843. doi: 10.1080/10543406.2023.2170405. Epub 2023 Jan 29. PMID: 36710384.

Conclusions and Key messages

- To date, **regulatory expectations** have remained broadly consistent for the purpose of PIP agreement
- Certain features of cSLE appear to leave **residual uncertainties** that limit reliance on single-arm trials alone. RCTs often need to be included in plans to support a full benefit-risk assessment when adult evidence is not yet available
- As regulatory experience expands, **adaptive trial designs, including basket or platform approaches**, may become feasible; global networks and stakeholder engagement can help ensure progress is captured and reviewed promptly
- A universal model for extrapolating efficacy is difficult to be pursued: MoA and adult or parallel paediatric development remain key determinants. Extrapolation should follow a **structured approach** that defines evidence gaps and identifies strategies to address them.
- Using adult efficacy data for paediatric populations is a possible option **when adult trials generate usable evidence** and residual uncertainty is adequately quantified for the medicinal product concerned

De Lisa R, de Andres-Trelles F, Bax R, Galluzzo S, Alward B, Thomson A, Karres D, Brunner HI, Ruperto N, Egger GF. New medicines for childhood-onset systemic lupus erythematosus: an EU perspective on paediatric drug development. Front Med (Lausanne). 2025 Jul 10;12:1583140. doi: 10.3389/fmed.2025.1583140. PMID: 40708640; PMCID: PMC12286927.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Thank you

Roberto.delisa@ema.europa.eu

Follow us