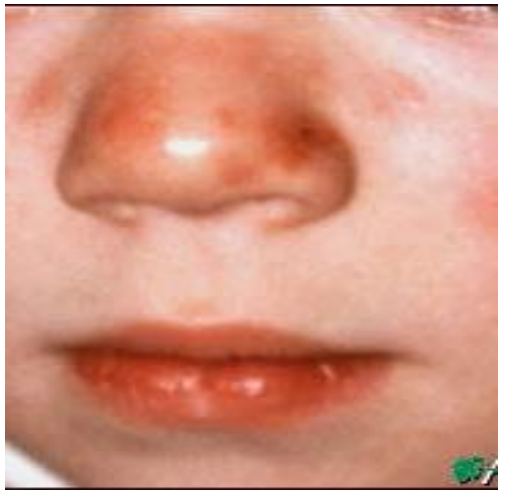

pSLE Drug Development

-Lessons Learned-

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AstraZeneca Clinical Development

Immunology

Current Timelines in Pediatric Drug Development

X years

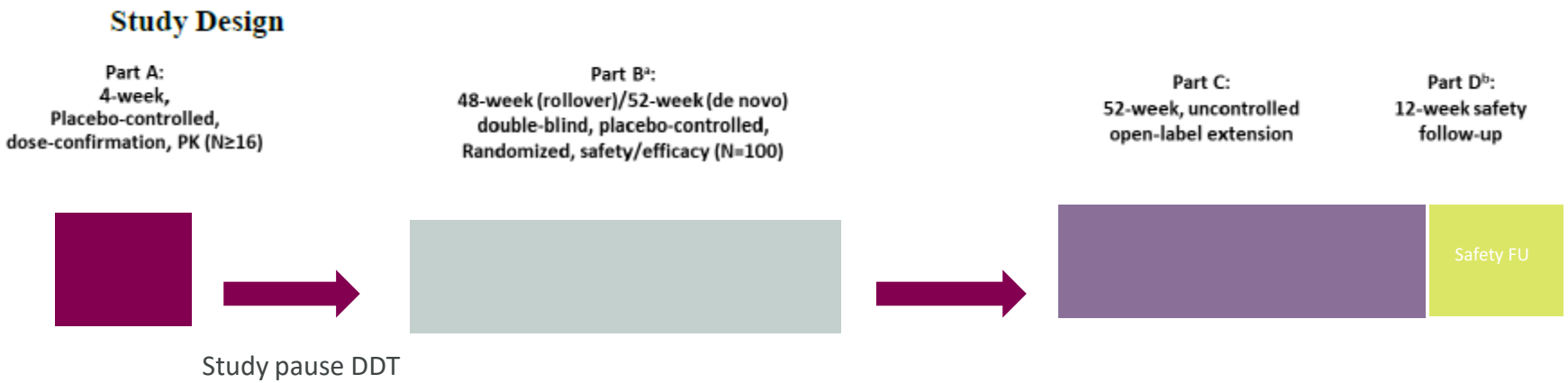
Adult FDA Approval

6-10 years
pediatric approval
and/or labeling

Belimumab	2011	2019 (93 participants)
Anifrolumab	2021	ongoing (100 participants)

Blossom p SLE Study Design (NCT05835310)

- Phase III randomized controlled trial in participants aged 5 to <18 years with moderate to severe active SLE to evaluate PK, PD, efficacy, and safety of IV anifrolumab
- Multi-cohort design (weight-based dosing)
- Planned enrollment: app. 100 participants
- Eligibility: fulfillment of 2019 EULAR/ACR SLE classification criteria
- Disease activity requirements: SLEDAI-2K ≥6, ≥1 BILAG A or ≥2 BILAG B scores, and PGA ≥1.0 on a 0-3 VAS



Challenges

- Alignment with different agencies
- Small population
- RCT designs
- Stringent eligibility criteria to maximize the ability to demonstrate treatment benefit
- Recruitment challenges -high disease activity or well controlled patients (off label use)
- Feasibility for parents

Different Requirements from Different Health Agencies

Waiver: < 5 years of age and deferral post-adult Phase 3

2013-2014

- OL,PK/safety study and extrapolation for efficacy-conditional to positive adult Ph3 and exposure-response relationship for efficacy
- A RWT required including LN, NPSLE (PIP withdrawn after PDCO rejection)

2018-2019

- RCT would be needed to fulfill PMR
- Proposed RWT and PIP02 approved

2020-2021

- An RCT efficacy study was required as PMR
- Anifrolumab IV approved in adult moderate to severe patients with SLE (excluding active LN and NPSLE)

2022-2023

- Positive feedback received on the RCT design and supportive Bayesian analyses
- PiP modification changing from RWT to RCT submitted in 2022; EU-CTR requirements fulfilled, endorsement received in 2023 following two review rounds (43 questions).

RCT vs. RWT: Pros and Cons

RCT

PROS:

- Regulatory gold standard
- Unbiased and measures efficacy
- Open to Bayesian borrowing from adult trials

CONS:

- Hesitancy on the part of physicians and/or parents to enroll pediatric patients to PBO longer term
- Large sample sizes required
- Long trial duration
- Logistic challenges

RWT

PROS:

- Regulatory acceptance growing -ICH E11A supports flexible designs
- Patients with uncontrolled disease not exposed to placebo – may align to Physician and Parent preference (?)
- Offers blinded control in withdrawal stage

CONS:

- Selection bias (enrichment bias)
- Long trial duration
- Ethical concerns- intentional flare induction

Conflicting Regulatory Requirements

- Strict regulatory requirements (Tanner staging, placebo rationales)
- Multiple protocol amendments driven by HA feedbacks
- Risk of duplicated studies due to misalignment
- PL controlled designs are not accepted by some countries

Lesson learned: Global regulatory strategy must be unified from outset

Childhood-onset SLE vs Adult-onset SLE-

Characteristic	Childhood-onset SLE	Adult-onset SLE
Incidence	0.3–0.9/100,000/year	1–25/100,000/year
Prevalence	1.1–9.7 per 100,000*	50–150 per 100,000
Proportion of all SLE	15–20%	80–85%
Peak onset	12–16 years	20–40 years
Female:Male	4-5 :1 (age-dependent)	~9:1
Clinical phenotype	phenotypic spectrum similar with adults Renal (40-80%)- early DC CNS (22-40%)* except seizure, chorea similar frequency	Renal (30-60%) CNS (42.5-74.7 %)*

*Per ACR 1999 case definitions

References: Hiraki LT et al. Arthritis Rheum. 2012*; Appenzeller S et al. The Lancet Child &Adolescent Health. 2022; Legge A &Hanly J . Nat Rheum 2024; Groot N et al. 2019 Arthritis Rheum; CARRA; EULAR recommendations.

Adult-like Design Doesn't Fit Pediatric Reality

- 10-20 times less common than adult SLE
- The eligible population is further reduced by stringent eligibility criteria
- Higher disease activity at onset carries both urgency and ethical obligations
  - 70% of pediatric rheumatologists (n=353;40 countries) preferred

    OL,PK/PD studies over RCTs (ethical concerns, concerns from families)
- Frequent flares requiring rescue treatment, resulting in SF or early discontinuation from the trial

Livingston et al. Seminars in Arthritis &Rheum 2012; Brunner et al. Ann Rheum Dis 2019

Summary:

- Pediatric and adult SLE share the same underlying pathophysiology and a similar clinical phenotype
- cSLE presents with a higher disease activity at Dx
- cSLE patients experience more frequent flares and accumulate damage faster
- Disease classification, disease activity assessments, treatment guidelines are the same

Lesson learned: pSLE drug development must be tailored to the realities of rare population, ethical constraints and parent expectations while still delivering robust evidence for BR

Brunner et al. 2008, Hiraki et al. 2008, Li et al. CSTAR 2021, Aggarwal 2024, Jidmahawong et al. 2026, Aydin et al. 2025, Mirguet et al. 2025, Mende et al. 2018.