TEDDY SCIENTIFIC MEETING • BARI

Targeting RIPK1 in CRIA syndrome

Advancing an ultra-rare disease programme towards clinical development

A paediatric development perspective

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CoSyne Therapeutics: drug discovery from a new angle.

Bringing together human insight with machine intelligence, operating at scale that makes solving for one patient possible.

WHY THE MODEL WORKS

1. **Enhanced focus**
   Dedicated teams and capital for each opportunity
2. **Operational efficiency**
   Shared infrastructure, leaner development
3. **Risk mitigation**
   Diversified portfolio across assets and indications
4. **Flexible funding**
   Multiple funding pathways across subsidiaries and programmes

COSYNE THERAPEUTICS

AtlaSyne	ElioSyne	Incubating	Incubating
Sleep/wake disruption in demyelinating disease	CRIA / monogenic autoinflammatory disease	Seizure control in monogenic epilepsy	Overall survival in genetically stratified low- and high-grade gliomas
PHASE 2	RARE / REGISTRATION	RARE / REGISTRATIONAL	PHASE 1

CRIA syndrome disease burden

Early-onset recurrent autoinflammation with a high burden for children and families



Age of onset

Typically infancy to childhood



Max fever

Episodes commonly reach 39–40.5°C



Frequency of fever

Recurrent flares, often every 2–4 weeks



Lymphadenopathy

Prominent, recurrent enlarged lymph nodes



Splenomegaly

Observed in a subset of patients



Hepatomegaly

Observed in a subset of patients



Abdominal pain

Common during inflammatory flares



Oral ulcers

Recurrent apbthous ulcers in some patients

Illustrative summary of reported CRIA clinical features

Current known patients and likely under-diagnosis

37 genetically identified CRIA patients worldwide likely represent only a fraction of the true patient population

37

Known patients worldwide

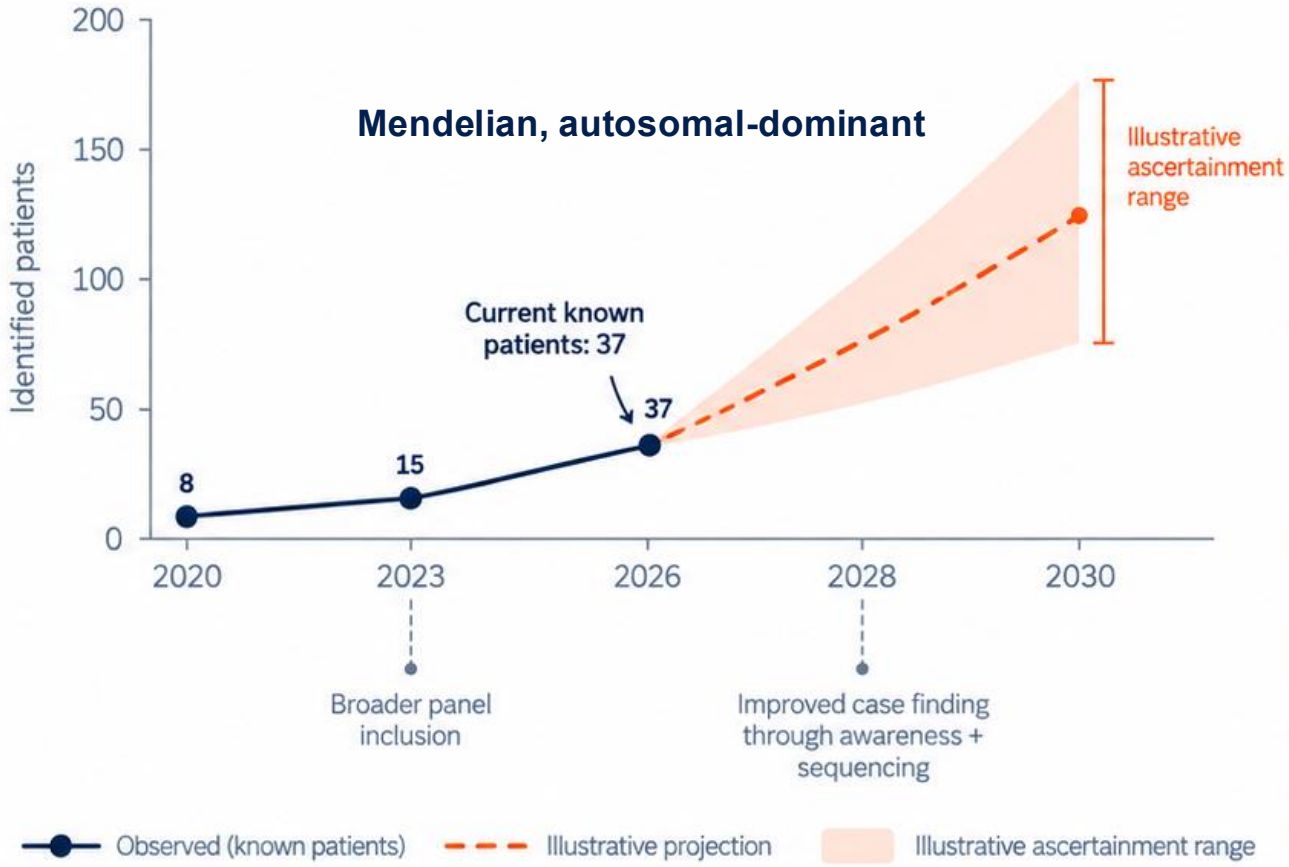
Genetically identified and mapped internationally

Why we believe CRIA is under-diagnosed

- RIPK1 was added to broader diagnostic panels only recently (2023)
- Phenotype overlaps with other recurrent fever and autoinflammatory disorders
- Patients may cycle through multiple specialties before genetic diagnosis
- Greater awareness and sequencing access should increase case finding

Hypothesis informed by experience across rare monogenic autoinflammatory diseases.

Illustrative case-finding trajectory



Illustrative hypothesis, not a prevalence estimate. Intended to show potential increase in diagnosis as testing and awareness expand.

The goal: disease modification without chronic steroid burden

Sustained, steroid-free control to protect growth, development and everyday life.

Corticosteroids: cumulative harm [1]

Can relieve flares, but repeated or long-term exposure carries risks:

Growth and bones
Slower growth; osteoporosis and fracture risk

Metabolic and daily-life effects
Weight gain; sleep and mood disturbance

Infection risk
Increased susceptibility

Adrenal suppression
Requires supervised tapering

IL-6 blockade: benefit with ongoing burden [2,3]

Can improve CRIA; response and tolerability vary.

Serious infection
Ongoing vigilance

Blood-test changes
Low neutrophils; raised liver enzymes and lipids

Treatment routine
Injections / infusions and monitoring

Desired disease modification

Investigational goals from upstream RIPK1 inhibition

Sustained inflammatory control
Fewer fever days and flares; control between episodes.

Steroid-free disease control
Lower cumulative exposure, with supervised withdrawal where possible.

Protect growth and function
Reduce future treatment-related harm; preserve bone health and development.

A more predictable childhood
More school, activity and family time; less disruption from treatment.

RACC-UK

The ambition: less inflammation and less treatment-related harm throughout childhood.

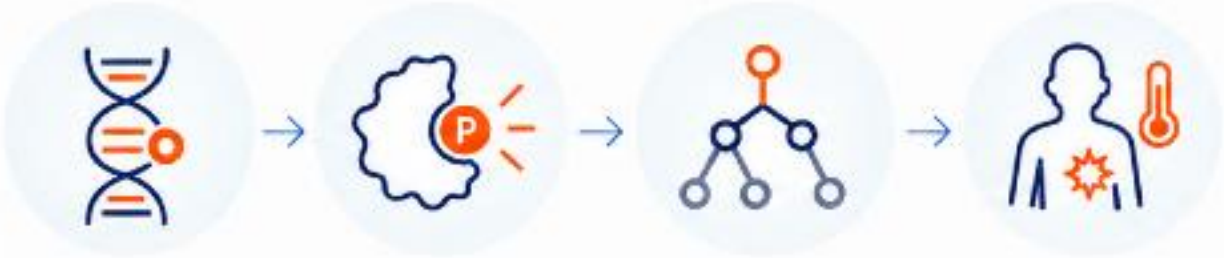
Disease modification and improved long-term safety remain to be demonstrated in CRIA.

[1] Prednisolone SmPC. [2] Lalaoui et al., Nature 2020. [3] Tocilizumab SmPC. Treatment risks are label-derived, not CRIA-specific rates. Full references in notes.

Clinical stage RIPK1 inhibitor enables rapid translation in CRIA

Licence to continue development of selective RIPK1 inhibitor with established human PK/PD and safety package

Mechanistic rationale



1. Causal RIPK1 variants

CRIA is driven by cleavage-resistant RIPK1 variants

2. Persistent RIPK1 activity

Loss of normal cleavage sustains RIPK1 kinase signalling

3. Inflammatory amplification

Persistent signalling promotes TNF-driven inflammation and cell-death pathways

4. Clinical disease

Recurrent fever, lymphadenopathy and multisystem inflammatory flares

Targeting RIPK1 directly addresses the proximal disease mechanism in CRIA.

Licensed development foundation

New chemical entity

Selective oral RIPK1 inhibitor for continued development

400+ participants

Extensive human PK, PD and safety data

>90% target engagement

Robust pathway engagement in prior studies

Clinically de-risked start

First-in-disease development

Why this matters for paediatric development

- Builds on an existing adult clinical data package rather than starting from a new discovery programme
- Supports dose selection and trial design through prior PK/PD knowledge
- Creates a faster path toward a genetically targeted therapy for children with CRIA

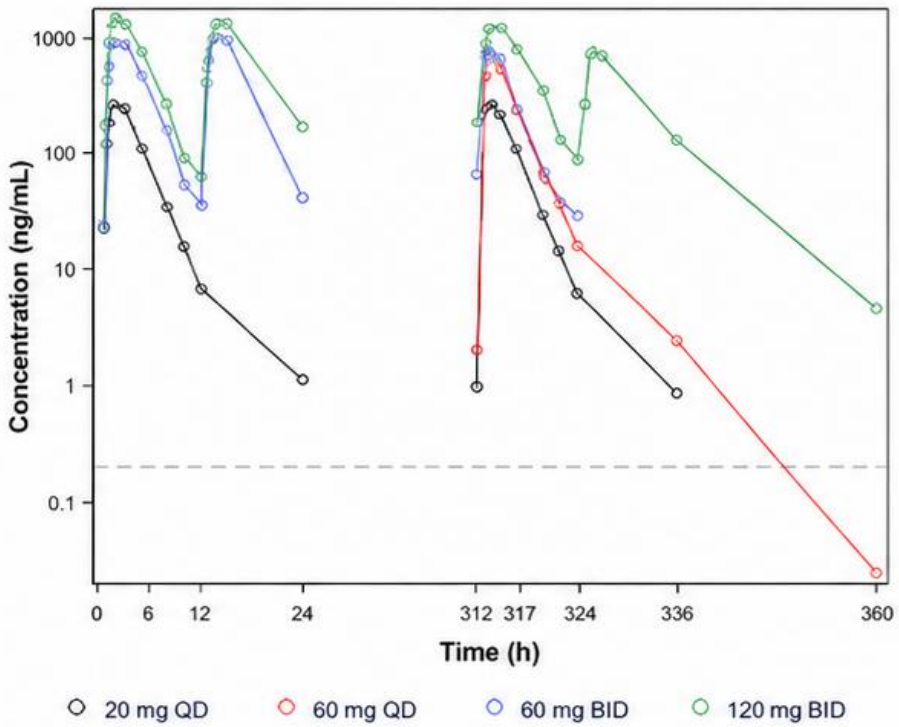
Human clinical data support BID dosing and RIPK1 engagement

Observed adult human clinical data show sustained exposure at 60 mg BID and 120 mg BID, together with strong RIPK1 target engagement

Key translational takeaways

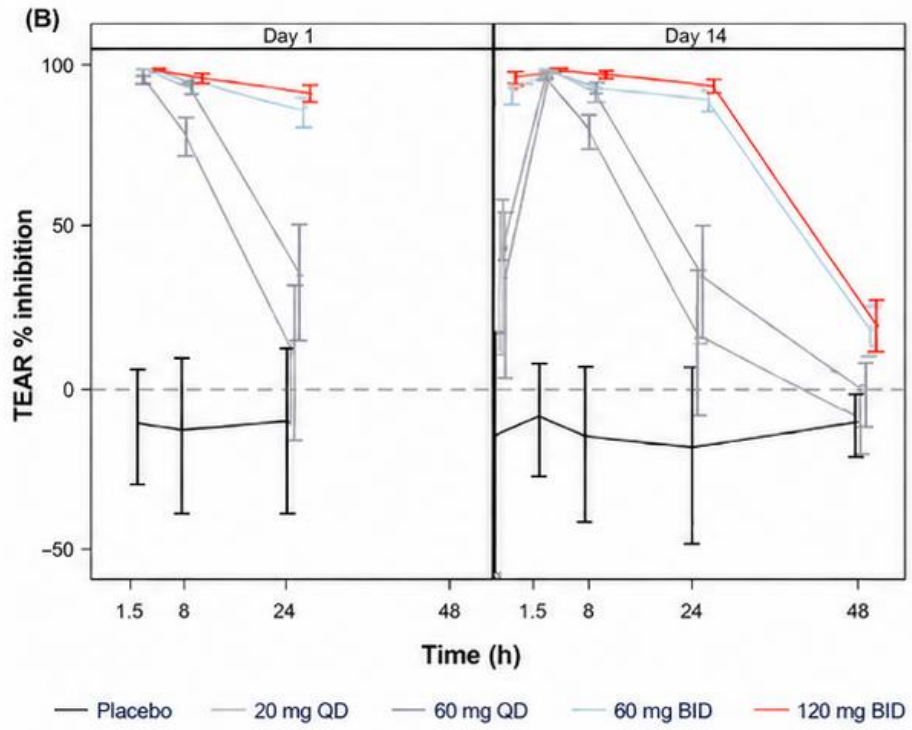
1. **Human clinical dataset**
   Conclusions are based on adult clinical PK/PD data.
2. **Repeat-dose exposure**
   60 mg BID and 120 mg BID provide sustained exposure.
3. **Target engagement**
   RIPK1 inhibition is robust at clinically studied BID doses.
4. **Paediatric translation**
   These human data support PopPK-informed paediatric dose selection.

A. Repeat-dose pharmacokinetics



60 mg BID and 120 mg BID maintain sustained exposure across the dosing interval.

B. RIPK1 target engagement



60 mg BID and 120 mg BID show high target engagement on Day 1 and Day 14.

Translational message: existing adult human PK and target-engagement data support retaining BID dosing and using PopPK to guide peadiatric dose selection in CRIA.

Figures reproduced from the existing adult clinical dataset.

Precedent: NOMID/CAPS supports a feasible ultra-rare study model

Published and regulatory precedent shows that a small, open-label programme with objective biomarkers and withdrawal / rechallenge can support decision-making in monogenic autoinflammation

NOMID/CAPS precedent at a glance

Population
NOMID / CINCA / CAPS

Study type
Prospective, long-term, open-label, uncontrolled

Sample size
43 patients in the regulatory dataset

Age range
0.7–46 years

Study sequence

1. Baseline assessment
- Document symptoms and inflammatory activity
- Clinical symptom score plus CRP, SAA and ESR

→

2. Open-label anakinra
- Start IL-1 blockade in all enrolled patients
- Early symptom and biomarker response assessed

→

3. 3-month evaluation
- Response reviewed after initial treatment period
- Improvement in disease activity and inflammatory markers

→

4. Withdrawal / rechallenge
- 11 patients underwent temporary withdrawal
- Disease worsened off treatment and improved again after restart

→

5. Long-term follow-up
- Continued open-label treatment up to 60 months
- Durability, safety and prevention of damage progression assessed

Key scientific takeaways

Clinical response
- Rapid improvement in systemic symptoms
- Fever, rash, headache and joint symptoms decreased

Objective biomarkers
- CRP, SAA and ESR fell with treatment
- Biomarkers complemented symptom assessment

Within-patient confirmation
- Withdrawal strengthened causal inference
- Rechallenge demonstrated return of response

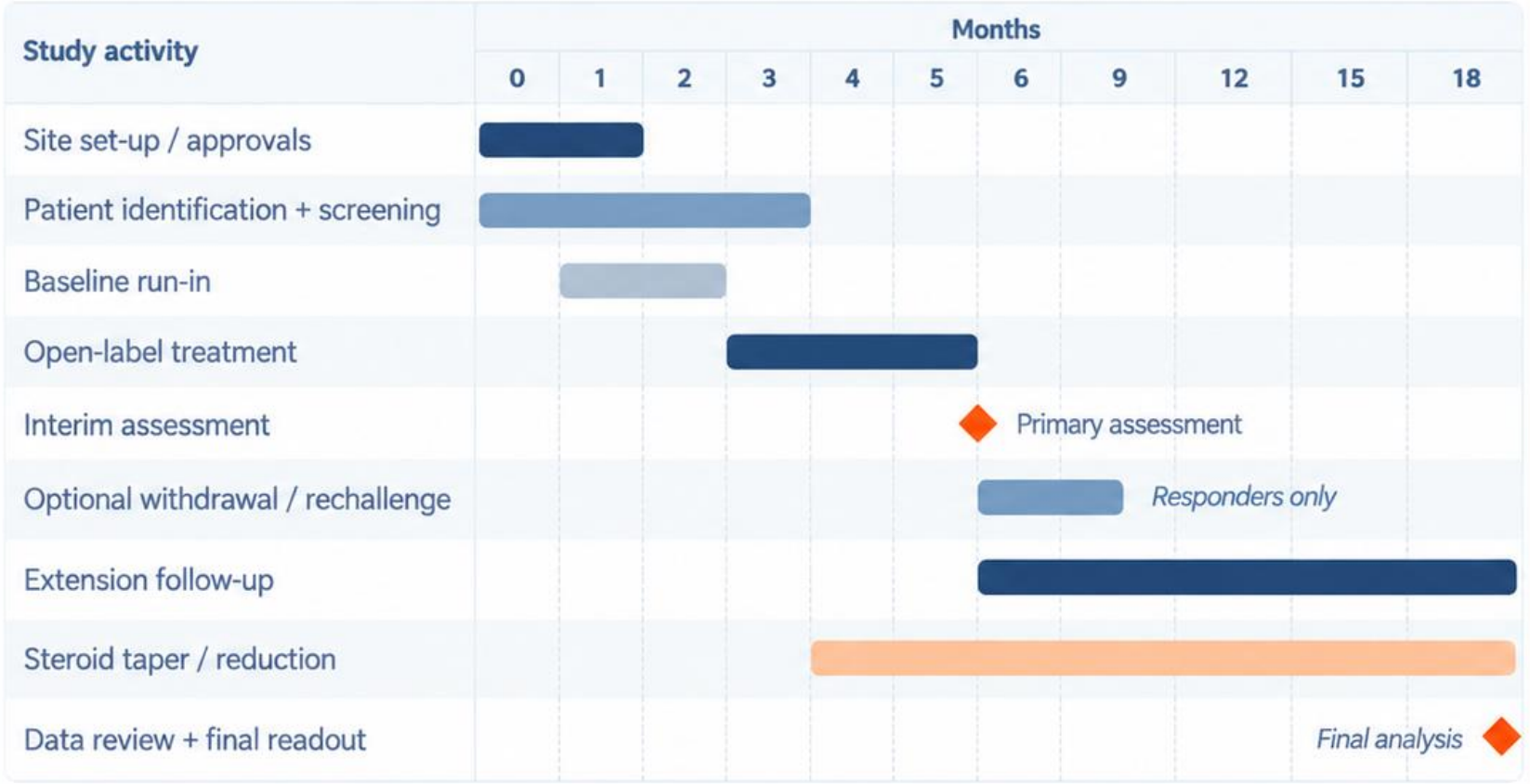
Why this matters for CRIA
- Monogenic autoinflammatory precedent in a very small population
- Supports thinking about open-label treatment plus objective biomarkers and optional withdrawal in responders

Precedent concept: in a very rare inflammatory disease, open-label benefit plus objective biomarkers and withdrawal / rechallenge may provide a persuasive package when randomised trials are difficult.

Based on Goldbach-Mansky et al., NEJM 2006; Sibley et al., Arthritis Rheum 2012; Kineret prescribing information.

ReIGNITE study: inflammatory flair control in CRIA syndrome

Proposed study timeline



Study features and readouts

A — Population
- 10–20 patients
- Adults and children aged 6+
- Genetically confirmed CRIA

B — Design
- Single-arm, open-label
- Biomarker-rich assessment
- Optional withdrawal / rechallenge in responders

C — Key readouts
- Flare frequency, duration and peak fever
- CRP, SAA, IL-6 and symptom burden
- PK / exposure–response and target engagement
- Corticosteroid use and taper success

D — Desired outcomes
- Evidence of clinical control
- Objective inflammatory improvement
- Steroid-sparing effect
- Durability and longer-term safety

Planning concept: combine open-label clinical benefit, objective biomarkers and within-patient confirmation in an ultra-rare disease setting.

Path to CRIA clinical study start

Illustrative programme timeline from Q1 2027 to Q2 2028 study initiation

1. Foundations

Q1–Q2 2027

- Target product profile and evidence-gap review
- Natural-history and patient-identification work
- Regulatory and clinical strategy set-up
- CRO, lab and key partner selection

2. CMC + dose translation

Q3–Q4 2027

- GMP API manufacturing and stability programme
- Bioanalytical and assay readiness
- Population PK modelling to inform paediatric dosing
- Current formulation retained in a child-suitable dosage form; BID dosing maintained

3. Study readiness

Q1 2028

- Protocol, endpoints and operational plan finalised
- CRIA site network and patient-finding refined
- Clinical supply and release preparations
- CTA package assembled for submission

4. Study initiation

Q2 2028

- CTA / ethics review and approvals
- Site activation and screening opens
- Drug available for study use
- First patient in / clinical study starts

What this timeline is designed to achieve

- Mechanism-aligned first-in-disease study
- Paediatric dosing informed by PopPK rather than a new regimen
- Operational readiness for a small, genetically defined trial
- Transition from development work to clinical execution

Formulation principle

Keep the current formulation approalch, adapt the dosage form for peadiatric use, and use BID dosing with PopPK-informed dose selection.

Planning concept: integrate CMC, translational modelling, regulatory preparation and patient-network readiness to reach efficient study start in CRIA.

Supported by leading partners

Enabling the development of a first-in-disease therapy for CRIA.

Anthropic AI for Science

Rare disease research grant recipient.

ANTHROPIC

Selected through Anthropic's AI for Science rare-disease programme to support our research and development efforts within the CoSyne Therapeutics group.

EIS (applied)

Application submitted to the Estonian Research and Development and Innovation Programme.

eis enterprise estonia

Application submitted to support the CRIA development programme through Estonia's research, development and innovation funding.

ERDERA (applied)

Application submitted to the European Rare Diseases Research Alliance.

ERDERA European Rare Diseases Research Alliance

Application submitted to support the first-in-disease clinical study in CRIA through the ERDERA Clinical Trials Call 2026.

ElioSyne Therapeutics – part of the CoSyne Therapeutics group – is working with trusted partners to accelerate innovative therapies for patients with rare diseases.