

# CDKL5 Gene Therapy

Inside the CDKL5 Gene Therapy Journey  
– By Nyesha Bahl & Nicholas Schein

CDKL5 Deficiency Disorder (CDD) is a rare genetic condition affecting about 1 in 40,000 children, leading to severe developmental delays and seizures due to mutations in the CDKL5 gene. For families living with CDKL5 Deficiency Disorder, hope has often arrived with uncertainty. Over the years, many parents have watched promising research programs appear, stall, or quietly disappear, usually for reasons that had little to do with science and everything to do with business priorities of the research institutes and medical offices. That history is precisely why this CDKL5 Gene Therapy effort by the Child's Cure Genetic Research Foundation exists, partnering with the UCSF clinical team to advance a program that builds on established science, brings gene therapy from the lab to the clinic, and communicates every step with careful, responsible, and transparent intent.

On January 15, 2026, families gathered virtually and in person for a UCSF Clinical Dinner, where a "working draft" of the planned Phase I clinical trial was presented. The event featured key members of the UCSF clinical team: Dr. Nalin Gupta, a pediatric neurosurgeon with experience in multiple Phase I studies and serving as a principal investigator; Dr. Adam Numis, a pediatric neurologist and epilepsy specialist; and Dr. Kazim Narsinh, a neurointerventional radiologist. Jainu Jogani, co-founder of Child's Cure Genetic Research Foundation, provided an overview of the CDKL5 gene therapy project, its current status, and next steps. Industry partners from Charles River Laboratories, iXCell Biotechnologies, UCSF Catalyst, and uBrigene also attended, highlighting the collaborative effort behind this initiative. The purpose of the meeting was to explain what is being built, why certain decisions are being made, and what participation in a first-in-human gene therapy trial would truly involve.

The foundation's commitment to the CDKL5 community was emphasized, acknowledging past timeline shifts in clinical development that have challenged families. Milestones are shared only when finalized. Teams are working with urgency, extending schedules to speed the transition from bench to bedside. The presented details remain a "working draft," subject to refinement through ongoing collaboration with the clinical team and FDA guidance during the Investigational New Drug (IND) submission process. Key milestones achieved include successful vector design and development for CDKL5 protein expression, proof-of-concept efficacy studies in CDKL5 mouse models and iPSC cell lines showing functional restoration, completion of pre-IND discussions with the FDA, and finalization of the clinical protocol synopsis outlining the trial's structure and endpoints. Active IND-enabling activities focus on safety and toxicology studies for intracisterna magna (ICM) delivery, development of the Investigator's Brochure (IB) and Informed Consent Forms (ICF) for UCSF review, and compilation of the IND application, including manufacturing controls and quality assessments. CDKL5 gene therapy aims to replace the dysfunctional gene with a healthy copy, addressing the root cause of CDD. The CDKL5 protein supports dendrite branching and synapse formation, and by delivering a functional version via an Adeno-Associated Virus serotype 9 (AAV9) vector, the therapy targets widespread brain networks affected by the disorder. What is different is execution. Previous programs did not reach the clinical trial, often because of shifting corporate priorities or financial models that did not favor rare diseases. This parent-led effort exists to finish the work—to take what science already knows how to do and carry it across the final, difficult threshold into human trials.

The Phase I trial, will involve multi-tiered safety oversight, including the Institutional Review Board (IRB), Data and Safety Monitoring Board (DSMB), and Institutional Biosafety Committee (IBC). These independent committees ensure participant rights, welfare, and safety, with frequent monitoring. Eligibility criteria, still under development and subject to UCSF IRB and FDA review, will ensure a homogeneous study population for reliable data. Categories include demographics (minimum age of 5 years, all genders), confirmed CDKL5 diagnosis, disease severity (e.g., seizure frequency), overall health and comorbidities, prior treatments, and ability to meet study requirements. Details will be available on [ClinicalTrials.UCSF.edu](https://ClinicalTrials.UCSF.edu), [ClinicalTrials.gov](https://ClinicalTrials.gov), and updates on [CDKL5GeneTherapy.com](https://CDKL5GeneTherapy.com). Enrollment is a multi-stage process: initial pre-screening via UCSF's survey for medical history and diagnosis confirmation; formal clinical evaluation of seizure history, developmental status, and health; informed consent discussions on risks and commitments; and final eligibility confirmation with safety clearances. The inpatient journey begins with pre-infusion preparation (Day -1 to 0), including assessments of vital signs, blood draws, weight checks, and pre-medication like steroids to mitigate immune responses to the viral vector. On the day of administration (Day 0), the child is asleep under anesthesia in an interventional suite for the one-time intracisterna magna route (ICM infusion), with continuous monitoring for reactions. Post-infusion (Day 1+), surveillance covers safety indicators like liver enzymes and immune markers, alongside seizure management in a family-centered setting where parents can stay bedside.

Discharge requires clinical stability, no acute reactions, a medication plan (e.g., tapering steroids), emergency protocols, and scheduled post-discharge follow-ups. Long-term monitoring includes 3-month, 6-month, 12-month, and 24-month visits, blending in-person and virtual formats.

Natural history data from 111 patients highlighted demographics (mean age 8.3 years, 93% female), early seizure onset (median 1.5 months), high frequency (82% >16 seizures in first 28 days), polypharmacy (average 2.6 ASMs), comorbidities (e.g., gastrointestinal issues, muscle tone abnormalities, sleep disorders), and functional metrics showing floor effects in motor skills and impacts on independence. Endpoints focus on meaningful outcomes, which vary by patient but center on seizure reduction as the primary measure, tracked via caregiver diaries. Secondary endpoints include the CDKL5 Severity Scale, Vineland scores, CGI/PGI for overall change, and caregiver QI-Disability. Exploratory elements may involve EEG metrics like spike burden. Safety assessments encompass MRI (with anesthesia) at planned timepoints, standard labs, and adverse event recording.

Biomarkers include primary monitoring of CSF p-EB2 levels pre- and post-treatment to confirm CDKL5 expression and function. Exploratory options like CSF CDKL5, blood-based markers (NfL, tubulin), or neuronal extracellular vesicles may be analyzed from stored samples to inform future studies. Routine MRI serves safety but can be archived for post-hoc imaging analyses.

During the Q&A, parents and attendees raised thoughtful questions. On funding, the \$3.5 million goal supports Phase I and II with a small cohort, contrasting with FOXC1's \$22 million for all phases including a larger Phase III. Using a "house" metaphor - you can buy an expensive house with a porch and view, or you can buy a functional home that meets your needs. This program is building a functional house, cost-effective study with essential endpoints and biomarkers, itemizing costs per patient for visits, MRIs, EEGs, and more. Funds may support family travel; participants need to be within a 45-minute drive of the site for a week post-treatment, though details are pending.

Gene therapy was chosen over stem cells because it directly fixes the genetic root cause as a one-time treatment, unlike stem cells, which face integration challenges and lack evidence for CDD.

Another question about dose sensitivity arose; parents wanted to know whether too much or too little of the gene could be harmful. The team explained that this is why extensive animal studies are essential. They guide dose selection so that the first human dose is conservative, small enough to be safe, yet large enough to plausibly have an effect. Early-phase trials proceed cautiously. If safety is established, future groups may receive adjusted doses based on what is learned. This stepwise approach is fundamental to gene therapy.

Perhaps the most emotionally charged question concerned the possibility of regression. Could gene therapy “reset” a child, wiping out hard-won skills?. Gene therapy is not one uniform thing. Each gene has a different role. Effects depend on where and how that gene is expressed. The field is still learning what happens when a working gene is introduced into a brain that has never had it. There is no known pattern of gene therapy causing a universal “system reset,” but variability is real. That uncertainty is exactly why Phase 1 exists, why long-term monitoring matters, and why safety is of utmost importance.

Parents were asked to keep a detailed seizure diary. Stability in baseline data is crucial for measuring change. Maintaining consistent routines and medications unless your clinician directs otherwise during the baseline period will be expected. Stay engaged as the criteria become final. Most importantly - help fund the path to the clinic. This program exists because families decided not to wait passively.

For any clinical or non-clinical questions, families can reach out to [cdkl5@childscure.org](mailto:cdkl5@childscure.org). Those who wish to help accelerate progress can donate at [www.cdkl5genetherapy.com/donate](http://www.cdkl5genetherapy.com/donate).

This meeting was a working session with the people designing a serious clinical study. It reflected determination, realism, and responsibility. The foundation made clear that it welcomes collaboration from any organization willing to help. The UCSF team emphasized its role: to build the safest possible study with the highest likelihood of answering the questions that matter.

# Our Commitment to the CDKL5 Community

**Respecting Community Trust:** We recognize that historic timeline shifts in CDKL5 clinical development timelines have created significant challenges for families. To maintain integrity and trust, we are sharing milestones only as they are finalized.

**Operational Intensity:** Our multidisciplinary teams are operating with a sense of extreme urgency, maintaining extended daily schedules to accelerate the transition from bench to bedside.

**Regulatory Evolution:** The details presented today represent a "Working Draft." These protocols remain subject to refinement based on ongoing collaboration with the clinical team & guidance from the FDA during the Investigational New Drug (IND) submission process.



# CDKL5 Program Evolution: Status and Forward Strategy

## Milestones Achieved

- Vector Design & Development: Successful engineering of the therapeutic cassette for CDKL5 protein expression.
- Efficacy Studies: Documented proof-of-concept in (CDKL5 Mice Model/ CDKL5 iPSCs Cell Lines) demonstrating functional restoration.
- Regulatory Pre-consultation: Completion of the Pre-IND discussion with the FDA to align on study expectations.
- Clinical Framework: Finalization of the Clinical Protocol Synopsis, defining the trial's structure and primary endpoints.

## Path to Clinic (Active IND-Enabling Activities)

- Safety & Toxicology: Formal IND-enabling Tox studies to establish the safety profile for ICM delivery.
- Clinical Documentation: Development of the Investigator's Brochure (IB) & Informed Consent Forms (ICF) for UCSF review.
- Regulatory Submission Package: Compilation of the final IND Application, including manufacturing controls & quality assessments.



# Overview

- Brief introduction to CDKL5 Gene Therapy
- Phase 1 Clinical trial
  - PI profiles
  - Inclusion/exclusion criteria
  - Enrollment
  - Hospital Stay
    - the inpatient journey - what to expect
  - Endpoints and biomarkers
  - Post treatment monitoring
  - Patient Timelines

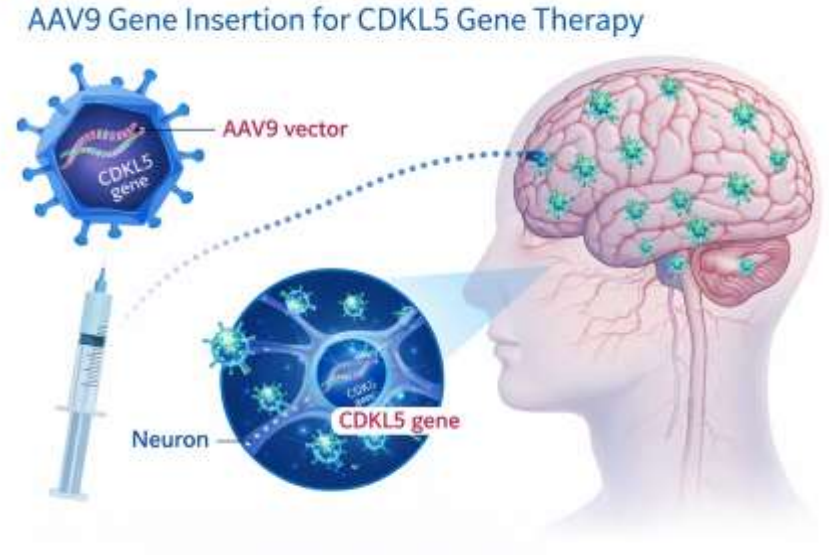
# Why CDKL5 Gene Therapy?

CDKL5 gene mutations cause severely debilitating disorder

- Currently no highly effective FDA approved treatments

CDKL5 protein helps dendrite branching & synapse formation

By replacing the non-functional gene, we are treating the underlying cause of CDKL5 deficiency disorder (CDD) at the root cause level



Representative imagery provided for conceptual context.

# Phase 1 Clinical Trial

# Principal Investigator Profiles



Dr. Nalin Gupta -  
Pediatric  
Neurosurgeon



Dr. Adam Numis -  
Pediatric Neurology &  
Epilepsy



Dr. Kazim Narsinh -  
Neuro Interventional  
Radiology

# Multi-Tiered Safety Oversight

## Independent Oversight Committees

- Institutional Review Board (IRB)
- Data and Safety Monitoring Board (DSMB)
  - High-Risk Designation: Due to the nature of gene transfer, these trials are designated as "high-risk," requiring more frequent monitoring, typically on a quarterly or as-needed basis.
- Institutional Biosafety Committee (IBC)



# Eligibility Framework & Oversight

## Purpose of Criteria

- Required practice for all high-quality research protocols to identify appropriate participants and ensure safety
- To ensure the study population is homogeneous enough to gather reliable data and determine the treatment's true effect
- Criteria help control for variables that might skew the study results or increase participant risk

## Criteria Categories

- Demographic characteristics (age 5 years +, all genders)
- CDKL5 diagnosis confirmation
- Disease state/severity (disease severity & symptoms - eg seizure frequency).
- Overall health status and presence of other significant medical conditions (comorbidities).
- Current or prior medications/treatments that might interfere with the gene therapy.
- Ability to participate in study requirements

This will be reviewed by FDA & UCSF Ethics Committee (IRB) to ensure participant safety & the scientific validity of the results

The details will be available on <https://clinicaltrials.ucsf.edu/> & [ClinicalTrials.gov](https://ClinicalTrials.gov)

- Updates will be posted on [www.cdkl5genetherapy.com](http://www.cdkl5genetherapy.com)



# Enrollment

Enrollment is a multi-stage journey designed to ensure that this investigational gene therapy is both safe & appropriate for each potential participant.

- Step 1: Initial Pre-Screening: Interested families begin by completing the UCSF Clinical Trials Pre-screen Survey, which gathers high-level medical history and diagnostic confirmation.
- Step 2: Formal Clinical Evaluation: If initial criteria are met, the clinical team schedules a comprehensive evaluation to review seizure history, developmental status, and general health.
- Step 3: Informed Consent: Families meet with the Principal Investigator and trial staff to discuss the protocol, potential risks, and the long-term commitment required for gene therapy follow-up.
- Step 4: Final Eligibility Confirmation: Final safety clearances, are completed before a participant is officially enrolled.
- Enrollment details will be available on <https://clinicaltrials.ucsf.edu/> & [ClinicalTrials.gov](https://ClinicalTrials.gov)
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# The Inpatient Journey: What to Expect

## Pre-Infusion Preparation (Day -1 to 0)

- Pre-operative Assessment: Vital signs, blood draws, and weight checks to confirm trial readiness.
- Pre-Medication: Administration of steroids or anti-inflammatory medications (as per protocol) to reduce the risk of immune response to the viral vector.

## Day of Administration (Day 0)

- Admission
- One-Time Infusion: The gene therapy is typically administered as a ICM (Intracisterna Magna) in a controlled clinical environment.
- Continuous Monitoring: Intensive monitoring by the pediatric neurology and nursing teams for any immediate infusion-related reactions.

## Inpatient Monitoring (Day 1+)

- Safety Surveillance: Observation for early-phase safety indicators, such as changes in liver enzymes or immune markers.
- Seizure Management: Continued monitoring of seizure activity by the Pediatric Epilepsy team.
- Family Support: Care is provided in a family-centered environment, with parents able to remain at the bedside.

# The Inpatient Journey: What to Expect

## Discharge Criteria

- Clinical Stability: No signs of acute adverse reactions and stability in all primary health markers.
- Medication Plan: Clear instructions for at-home supportive medications (e.g., tapering steroids) and emergency contact protocols.
- Next Steps: Scheduling of the first "Post-Discharge" virtual/outpatient follow-up.
- Contact information for reporting any adverse effects.

Long term monitoring - 3 months, 6 months, 12 months, and 24 months. Combination of in-person and virtual visits.

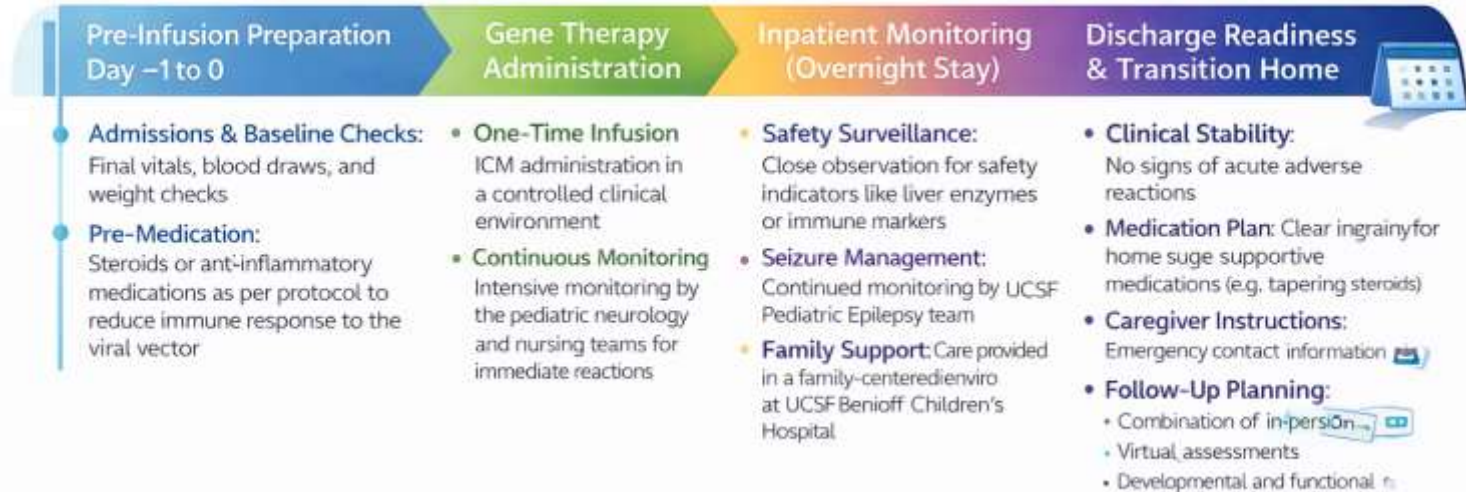


# CDKL5 Gene Therapy Timeline

AAV9 ICM Administration



# CDKL5 Gene Therapy Timeline



## AAV9 delivery to the CNS

### Route of Administration

	IV	ICV	ICM	LP
Spinal cord transduction	Low	Low	High	High
Brain transduction	Low	High	High	Low
Dosage	High	Low	Low	Low
DRG toxicity	Minimal	Not investigated	Moderate	Moderate
Procedural risk	Low	High	High	Moderate
Other	Hepatotoxicity Affected by serum AAV9 Abs			

# End points

- Primary: Reduction in seizure count (reported by trained caregiver diary).
- Secondary: CDKL5 Clinical Severity Scale (multidimensional clinician/parent assessment), Vineland scores, CGI/PGI (overall change), & caregiver QI-Disability.
- Exploratory: EEG metrics (e.g. spike burden) may be collected as an objective adjunct, but not a formal endpoint.
- Safety: MRI (with anesthesia) at planned timepoints, standard labs, & routine recording of any clinical or lab adverse effects.

# Biomarkers

- Primary biomarker: CSF p-EB2 levels pre/post treatment.
- Exploratory biomarkers: CSF CDKL5, Blood-based markers (NfL, tubulin) or neuronal extracellular vesicle contents could be analyzed from stored samples, but are not required for the IND. They may inform future studies if signals emerge.
- Imaging biomarkers: Routine MRI will serve mainly safety (no expected volumetric change), but brain imaging data can be archived for post hoc analyses if needed.

# Meaningful outcomes

- Vary from patient to patient
- Overall - seizures
- Minimum: stability
- Development across areas varies



# Patient Demographics & Seizure History



## Demographics



**Study Population:** 111 included in analysis.



**Age Profile:** Mean age 8.3 years (Range: <1 to 28 years); 9% were adults (≥18 years).



**Gender:** 93% Female.



## Clinical Presentation & Comorbidities



**Top Comorbidities:** Gastrointestinal hypomotility, muscle tone abnormalities, and sleep disorders



**Sleep (Bruni Questionnaire):** Significant disruptions in sleep initiation, sleep-awake transition, and excessive somnolence across all age groups.



**Quality of Life (QI-Disability):** Mean total scores of 53% to 64%, the Independence Domain was identified as the most impacted area of life.



## Seizure Burden

- **Median onset:** 1.5 months (Range: 0–66 months).
- **High frequency:** 82% experienced >16 seizures in the first 28 days
- Six (6) participants were seizure-free at baseline
- **Polypharmacy:** Average of 2.6 Anti-Seizure Medications (ASMs) at baseline



## Developmental & Functional Metrics

- **Gross Motor (GMFM-88):** Observed “floor effect” in crawling, standing, and walking across the entire cohort.
- **Cognition/Behavior (Vineland-3 & Bayley-4):** Scores derived successfully for most participants.

**Receptive language,** interpersonal skills, and fine/gross motor scores showed improvement correlating with age



# Natural History & Baseline Characteristics (n = 111)

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Funding

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*Thank you!*