CDKL5 Gene Therapy

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

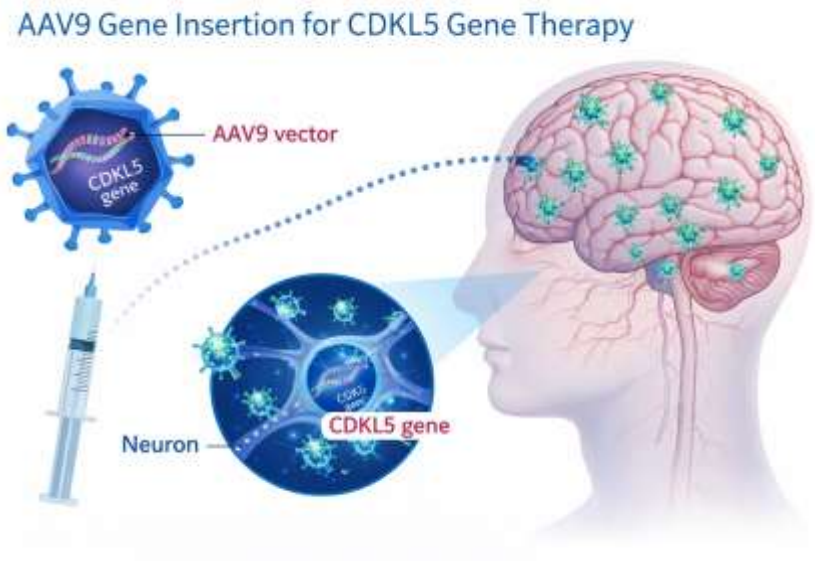
Why CDKL5 Gene Therapy?

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

- Updates will be posted on 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
    - Updates will be posted on www.cdkl5genetherapy.com

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

Pre-Infusion Preparation
Day -1 to Day 0

Day 0 Gene Therapy Administration

Day 0-1 Monitoring (Overnight Stay) Inpatient

Post-Discharge Long-Term Follow-up

Pre-Infusion Preparation

- **Admissions & Baseline Checks**
  Final vitals, 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.

One-Time Infusion

- The gene therapy is typically administie as an ICM (Intractsterna Magna) in a controlled clinical environment.
- **Continuous Monitoring**
  Intensive monitoring by pediatric neurology and nursing teams for any immediate infusion-related reactions.

Safety Surveiliance

- Close observation for common early-phase safety indicators, such as changes in liver enzymes or immune markers

Seizure Management

- Continued monitoring of seizure activity by the UCSF Pediatric Epilepsy team

Family Support

- Care is provided in a family-centered environment at UCSF Benioff Children's Hospital, allowing parents to remain

Long-Term Follow-Up

- 3, months, 6 months
- 12 months, 24 months
- Combination of virtual & in-person
- Evquations
- Safety labs and immune monitoring.

UCSF

- Clinical Stability
- No signs of acute-adverse reactions
- Stability in all primary health markers.

Contact information for reporting any adverse effects.

CDKL5 Gene Therapy Timeline

Pre-Infusion Preparation Day −1 to 0

- **Admissions & Baseline Checks:** Final vitals, blood draws, and weight checks
- **Pre-Medication:** Steroids or anti-inflammatory medications as per protocol to reduce immune response to the viral vector

Gene Therapy Administration

- **One-Time Infusion** ICM administration in a controlled clinical environment
- **Continuous Monitoring** Intensive monitoring by the pediatric neurology and nursing teams for immediate reactions

Inpatient Monitoring (Overnight Stay)

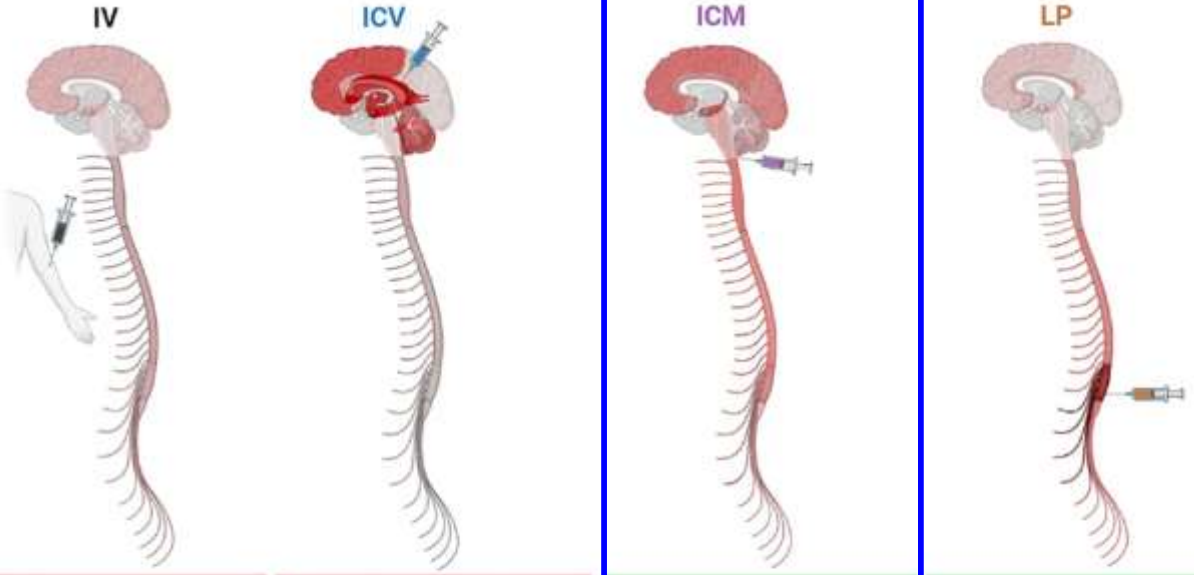
- **Safety Surveillance:** Close observation for safety indicators like liver enzymes or immune markers
- **Seizure Management:** Continued monitoring by UCSF Pediatric Epilepsy team
- **Family Support:** Care provided in a family-centeredenviro at UCSF Benioff Children's Hospital

Discharge Readiness & Transition Home

- **Clinical Stability:** No signs of acute adverse reactions
- **Medication Plan:** Clear ingrainyfor home suge supportive medications (e.g. tapering steroids)
- **Caregiver Instructions:** Emergency contact information
- **Follow-Up Planning:**
  - Combination of in-persion
  - Virtual assessments
  - Developmental and functional

Route of Administration

AAV9 delivery to the CNS



	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			

Trends in Molecular Medicine

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.

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

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.

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

CDKL5GeneTherapy.com/donate