CLIN2 AWARDS

6/25/26

$20,928,438 **GWG RECOMMENDED**

$20,928,438 **CIRM TEAM RECOMMENDED**

$61,000,067 **AMOUNT AVAILABLE**

APP #	TITLE	BUDGET REQ	GWG Recmd	CIRM Recmd	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Previous CIRM Funding	Disease Indication
CLIN2-19848	A Phase 1/2a First-in-Human, Dose-Escalation Study in Subjects with Progressive Multiple Sclerosis	**$8,000,000**	**Y**	**Y**	**94**	92	4	84	95	13	1	Y	multiple sclerosis
CLIN2-19928	Phase 1/ 2 Study of an AAV-9 Gene Therapy in Patients with FOXG1 Syndrome (FS)	**$4,928,664**	**Y**	**Y**	**88**	87	5	75	92	10	3	N	FOXG1 syndrome
CLIN2-19526	AAV Immuno-Gene Therapy for High-Grade Glioma	**$7,999,774**	**Y**	**Y**	**85**	85	2	80	90	12	2	Y	high-grade glioma
CLIN2-20117	A Phase I/IIa, Dose-Escalation Study for the Treatment of Focal Articular Cartilage Defects in the Knee	**$11,193,750**	**N**	**N**	**80**	82	3	77	88	5	9	Y	focal articular cartilage defects
CLIN2-20114	Phase I/IIb Gene Transfer Clinical Trial for CLN6 Disease, Delivering the CLN6 Gene by Self-Complementary AAV9	**$12,597,426**	**N**	**N**	**68**	68	4	60	75	0	14	N	CLN6 disease

Application #	CLIN2-19848
Title (as written by the applicant)	A Phase 1/2a First-in-Human, Dose-Escalation Study to Evaluate [Redacted product name] in Subjects with Progressive Multiple Sclerosis
Therapeutic Candidate (as written by the applicant)	[Redacted product name] is an allogeneic CAR Tr1 Treg cell product designed to eliminate B cells, reduce pathogenic T cell proliferation and dampen inflammation in MS
Indication (as written by the applicant)	Progressive Multiple Sclerosis (primary and secondary)
Unmet Medical Need (as written by the applicant)	In progressive MS, current treatment provides only a modest slowing of disability accumulation and fails to halt neurodegeneration. As a regenerative medicine, [Redacted product name] is designed to replace a defective immune system, regenerate proper immune cell function and help repair the damaged nervous system.
Major Proposed Activities (as written by the applicant)	∉ cGMP Manufacture, Release and Stability Studies of Clinical Product ∉ Clinical Study – Dose Level 1 Cohort 1 ∉ Clinical Study – Dose Level 2 Cohort 2 ∉ Clinical Study – Dose Level 3 Cohort 3 ∉ Clinical Study – Phase 2a Expansion Cohort ∉ Translational (Biomarker) Studies
Statement of Benefit to California (as written by the applicant)	This research offers profound benefits to CA by directly confronting the high unmet medical need of its citizens with progressive MS. By establishing clinical trial sites at leading CA institutions, we provide state residents with early access to a potentially transformative "off-the-shelf" cell therapy. This not only offers new hope but also strengthens CA's leadership in regenerative medicine, bringing advanced clinical research into the state's healthcare ecosystem.
Funds Requested	$8,000,000
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 94

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	92
Median	94
Standard Deviation	4
Highest	95
Lowest	84
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	13
Tier 2 (1-84): Not recommended for funding	1

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Multimodality approach, innovative, potential to halt Multiple Sclerosis (MS).
- No key weaknesses. Key strength was the overall CMC plan and experience.
- The proposal targets a major unmet need in progressive MS, where approved therapies (ocrelizumab, siponimod) slow but do not halt disability progression. [Redacted product name] is positioned as a first-in-class CAR-Treg therapy combining:
  - Deep B-cell depletion (via CD19 CAR).
  - Active immune regulation (via IL-10–secreting Tr1 cells).
  - Potential CNS penetration to address compartmentalized inflammation behind the BBB This dual mechanism is intended to overcome limitations of: anti-CD20 antibodies (incomplete CNS penetration), and autologous effector CAR-T cells (toxicity, logistics, lymphodepletion).
- Robust in vitro data supporting CD19-specific cytotoxicity, IL-10 production, suppression of pathogenic T cells and microglia, and reduced IL-6 release relative to effector CAR-T.
  - In vivo tumor-model data demonstrate B-cell depletion, tissue persistence (including brain), and no major safety signals.
  - Strong CMC readiness, leveraging prior experience with parent product.
  - IND interactions are extensive, detailed, and largely de-risk core regulatory issues.
- This therapy shows great potential to be effective by utilizing multiple mechanisms to target chronic inflammation.
- [Redacted product name] is being developed as an innovative off-the-shelf allogeneic cellular therapy for PMS, a disease with a major unmet medical need for a product with the potential to target CNS inflammation. The multiple modes of action of [Redacted product name] make this an important product to move rapidly through clinical development, starting with this Phase 1/2a FIH dose-escalation study.
- Allo off-the-shelf CAR T-cell regulatory therapy for progressive MS. Fast Track Designation. Engineered CD4+ T-cell that becomes type 1 Treg and treated with lentivirus to overexpress IL-10 and CD19 CAR.
- [Redacted product name] drug product consists of engineered human CD4+ T cells that recapitulate the major regulatory functions of naturally occurring Type 1 regulatory T (Tr1) cells, a subset of CD4+ regulatory T cells (Tregs). [Redacted product name] is generated by isolating CD4+ T cells from a healthy donor and transducing them with a tricistronic lentiviral vector (LVV) encoding human interleukin (IL)-10, a truncated (non-signaling) form of the human nerve growth factor receptor (NGFR, CD271) [ΔNGFR], and CD19 chimeric antigen receptor (CAR). The expression of IL-10 drives the conversion of the transduced CD4+ T cells into Tr1-like cells that are functionally comparable to Tr1 cells. Expression of ΔNGFR allows for the identification and purification of the transduced cells, and expression of the CD19 CAR enables targeted B-cell depletion.
- As an allogeneic product, it avoids the manufacturing and patient burdens of autologous CAR-T.
- Patient uptake likely to be strong given the lack of good alternative treatments and the severity of disease and disability progression in PPMS and SPMS.
- Strong commitment to patient and community engagement in recruiting and supporting patients, and in disseminating results.
- Very strong access and affordability plan.
- Highly innovative product with multiple potential mechanisms of action which may impact disease status in both PPMS and SPMS. Complicated product and CMC which they have addressed well. Excellent access and patient-focused considerations.

Value Proposition

- Potential to halt MS progressive by getting into the brain.

- [Redacted product name] is being developed as an allogeneic, "off-the-shelf" cellular therapy designed to provide a safe, effective, and durable treatment for patients with progressive forms of multiple sclerosis (PMS), for which effective treatment options are limited.
- Primary focus on safety and tolerability; extensive PD, CSF, MRI, and biomarker endpoints.
- Expansion cohort designed to establish optimal biological dose and justify Phase 2b/RMAT.
- Highly Differentiated Therapeutic Concept
  - The CAR-Tr1 fusion strategy is conceptually elegant and well-matched to PMS biology.
  - Unlike autologous CAR-T programs, [Redacted product name] integrates immune regulation, not just immune ablation.
  - Off-the-shelf allogeneic approach significantly improves scalability, cost, and access, all critical for MS.
- Strong Alignment with Unmet Need
  - Progressive MS lacks disease-modifying therapies with meaningful impact on disability.
  - The proposal convincingly frames PMS as driven by CNS-resident B cells, dysfunctional Tregs, and microglial inflammation, all addressed by [Redacted product name].
  - Emphasis on older patients (>45) and non-active SPMS is well justified and differentiated.
- Mature Regulatory and CMC Readiness
  - IND cleared with unusually detailed FDA correspondence for this stage.
  - Fast Track designation enhances downstream regulatory value.
  - Manufacturing yields, consistency, and projected cost of goods are credible and competitive.
  - Risk mitigation (RCL, GvHD, infections, insertional mutagenesis) is thoughtful and aligned with FDA guidance.
- High-Quality Translational Strategy
  - Extensive CSF biomarker work (OCBs, κFLC, IgG index, GFAP, NfL) is appropriate and compelling.
  - PK/PD plan is unusually rigorous for a Phase 1/2a MS study. •Biomarker strategy increases likelihood of biological proof-of-concept even with small N.
- Significant unmet need for treatments for disability progression in progressive MS.
- FDA FastTrack designation; well-designed study.
- [Redacted product name] has been developed to overcome the limitations of other MS therapeutics as an off-the-shelf, single dose therapy with modes of action targeted at both CNS and peripheral nervous system inflammation that may have an improved safety profile over existing treatment options.
- If efficacious and well tolerated, [Redacted product name] is likely to become a standard-of-care treatment for patients with PMS.

Rationale

- Strong data to support efficacy.
- [Redacted product name] is expected to overcome other product limitations, such as: it can act both within the CNS and periphery; ii) it has the potential for single administration; iii) it combines B-cell depletion, T-cell modulation, and microglial inflammation reduction properties in a single agent; and iv) it may induce long term tolerance due to the immuno-regulatory cytokine IL-10; and thus v) it is expected to have an improved safety profile
- Key Weaknesses and Risks -
  1. Reliance on Non-Disease-Specific in vivo Models
     - The in vivo efficacy and safety data rely on xenograft tumor models, not MS-relevant neuroinflammatory models.
     - While limitations are acknowledged, the lack of an in vivo autoimmune or CNS-inflammation model weakens translational confidence.
     - Reviewers may see this as a structural gap rather than a practical inevitability.
  2. Bold Claims of “Immune Reset” and Regeneration
     - Language suggesting immune system “reset,” regeneration, or repair may be perceived as over-aspirational for a phase 1/2a program.
     - Clinical proof of sustained tolerance induction (“infectious tolerance”) remains largely theoretical in MS.

- This creates expectation risk with reviewers focused on feasibility over vision.

3. Clinical Design Limitations
   - Open-label, single-arm design limits interpretability of clinical endpoints (EDSS, cCDP).
   - Small sample size and heterogeneous PMS population increase noise.
   - Heavy biomarker burden (multiple LPs, imaging, extended visits) may affect enrollment and retention despite mitigation plans.
4. Safety Assumptions Require Early Validation
   - Reduced CRS/ICANS risk vs effector CAR-T is plausible but not yet clinically proven in CNS autoimmune disease.
   - Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are serious, potentially fatal immune-related side effects occurring in 57–93% (CRS) and 20–70% (ICANS) of patients after CAR T-cell therapy. They involve widespread inflammation and neurological symptoms, managed primarily with supportive care, tocilizumab (anti-IL-6), and corticosteroids.
   - Allogeneic persistence and repeat dosing introduce cumulative uncertainty (immunogenicity, loss of efficacy, late toxicity).

- ∉ Excellent and thoughtful study design, dose escalation with an expansion phase. Rigorous stopping rules and safety monitoring.
- ∉ Outstanding scientific rationale.
- ∉ The proposed MOA and available data support moving [Redacted product name] into clinical development.

Project Plan and Design

- ∉ The CMC project plan appears sound. Two GMP clinical batches are proposed to support the phase 1 study, including long-term and in-use stability studies. Seven lots have been manufactured to date and release data look excellent.
- ∉ FDA will likely require quantitative acceptance criteria for the potency assays, while currently report results.
- ∉ Realistic budget with excellent visibility into costings. Co-funding provided by applicant which is always appreciated in terms of commitment.
- ∉ The phase 1/2a protocol is well designed and the current version has addressed FDA's input. The inclusion of a P2a expansion cohort should provide sufficient safety and preliminary efficacy data on the selected dose to move into a POC study.
- ∉ The inclusion of up to 12 study sites should allow this study to meet its enrollment goals.

Project Team and Resources

- ∉ The CDMOs for starting materials and GMP manufacturing and testing are reputable and successful.
- ∉ 3 alpha clinics supplemented by an additional 9 sites outside California. Provides for enrollment potential and engagement from well-regarded PIs that are geographically dispersed.
- ∉ This project's leadership and clinical trial vendors/CRO appear well qualified to conduct this study.

Population Impact

- ∉ Strong impact, exciting.
- ∉ Seems appropriate.
- ∉ Good focus on Black population, which has a higher prevalence of progressive MS and often a more severe disease course.
- ∉ Excellent support for patients who enroll, including a daily stipend for patients as well as their caregivers.
- ∉ Potential for dramatic positive impact on MS patients with a patient-focused approach to clinical development
- ∉ The study population is appropriate given the epidemiology of PMS.
- ∉ Addresses an unmet medical need to a community with minimal options.

Application #	CLIN2-19928
Title (as written by the applicant)	Phase 1/ 2 Study of [Redacted], an AAV-9 Gene Therapy, in Patients with FOXG1 Syndrome (FS)
Therapeutic Candidate (as written by the applicant)	[Redacted], an AAV9 viral vector-based gene therapy using a neuron-specific promoter to deliver functional human FOXG1 to target cells
Indication (as written by the applicant)	The target disease for the proposed study is FOXG1 syndrome
Unmet Medical Need (as written by the applicant)	FOXG1 syndrome is a devastating neurodevelopmental pediatric disorder with no approved disease-modifying treatments, as the current standard of care is palliative. Our therapy will address this unmet need by being the first potential disease-modifying, life-altering therapy for FOXG1 syndrome.
Major Proposed Activities (as written by the applicant)	∉ Completion of contracting and clinical site activation ∉ Enroll 12 patients in a Phase 1/2 study to evaluate the safety, tolerability and efficacy of [Redacted] ∉ Pursue regulatory activities to ensure global patient access ∉ Establish safety and efficacy to achieve go/no go decision for BLA filing ∉ Conduct resupplying GMP drug product manufacturing round ∉ Finalize patient access and commercialization strategy
Statement of Benefit to California (as written by the applicant)	Led by FOXG1 Research Foundation's (FRF) California-based executive leadership and biomedical experts, this project advances the state's precision medicine goals by bringing a first-in-class gene therapy for FOXG1 syndrome to the clinic. Out of the 189 US-residing FOXG1 syndrome patients in the FRF registry, 24 live in California. This program offers California citizens diagnosed with FOXG1 syndrome access to a potentially disease-modifying, life-altering treatment.
Funds Requested	$4,928,664
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 88

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	87
Median	88
Standard Deviation	5
Highest	92
Lowest	75
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	10
Tier 2 (1-84): Not recommended for funding	3

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Strong science; guidance and involvement of advisory board. Caregiver involvement that has driven study design and planning is impressive. Strong natural history study (NHS) data and a plan for enrolling patients from the NHS.
- High quality project deserves to be considered for funding.
- Platform therapy, phase 1/2 trial and BLA enabling for this ultra-rare disease. Very high dose of AAV in potentially very young patients puts them at risk of immunologic events later.
- Overall, positive scientific feedback from the panel. Largest concern is with the high potential vector dose; this potentially suggests issues with base plasmid construct and design.
- The applicant has made a compelling case for the use of a targeted AAV construct with a specific promoter to provide a disease-modifying treatment for FOXG1 syndrome, an ultra-rare disease. It is providing a cautious approach by targeting patients that show haploinsufficiency. The team has a good collaboration with Citizen Health and the patient community. It is possible, though, that the therapy may alleviate certain symptoms but not reverse the impact of the disease. A cost-benefit analysis between the effects of this treatment, if successful, and lifetime standard of care will have to be made.
- Strengths: 1) Huge unmet need; no known competing products 2) They have two advanced regulatory designations, plus the IND's proof of concept studies in preclinical models are promising; intracerebroventricular (ICV) delivery plus a neuronal-specific promoter are appropriate and justified 3) Patients have a variety of loss of function (LOF) variants, and the applicant's strategy will be applicable irrespective of the pathogenic variant 4) The timeline of 2 years (with additional 3 years continued safety monitoring) is reasonable 5) Based on their natural history studies, recruitment is feasible even for this ultra-rare condition 6) Strong and committed team at the applicant organization: Commendable actions: global registry, natural history in >100 patients, calibrated outcome measures based on caregiver interviews, licensed IP for the therapeutic.
- Key weaknesses: 1) This is a neurodevelopmental disorder. Will postnatal delivery of FOXG1 correct the developmental component of the phenotype? 2) The phenotype is more severe with truncating variants versus missense variants, plus younger patients will likely respond better – so the mix of patients in their approximately ten patient study will determine how any efficacy is seen 3) For any disease that is caused by "haploinsufficiency" there is the likelihood of dosage sensitivity for the protein product. Protein overdosing did not occur, even in their high-dose mouse; this is a strength. However, this should be carefully monitored in human studies 4) FOXG1 is an ultra-rare disorder (~500 patients in the global registry). So, the potential impact will not involve a large number of Californians,
- The high required dose raises questions about vector design and efficiency of expression. It also raises concerns about potential risk with vector delivery.
- This proposal and team did an exceptional job incorporating the patient voice into every step.
- It's unclear how well a therapy will change outcomes for disorder that is associated with brain malformation.
- The statistical plan is unclear regarding how the external control arm will be used to understand changes in disease trajectories.
- The expanded age range to be included in the study will likely not allow sufficient patient numbers for efficacy analysis.

Value Proposition

- Compelling, well-presented argument for low patient numbers.
- Clear unmet medical need with high potential to result in positive, meaningful clinical outcomes. ICV route enables an improved safety profile and reduced COGS, which will promote patient and payer uptake. As this is an ultra-rare disease, concerns exist about the commercial viability of this product due to relatively low demand and high COGS.

- Even though FOXG1 is an ultra-rare neurodevelopmental disorder, the sponsor of this research has carefully worked with caregivers to show that the proposed therapy would provide significant improvement in all areas of functioning for this severely debilitating illness. There are no other treatments available or in development, and the trials appear to be very well designed for safety and in such a manner as to reduces patient and caregiver burdens.
- The patients and caregivers will be monitored to assess the improvements in cognition, sleep, behavior, speech and digestion. The domains to be measured for the expected improvements were chosen by caregiver groups.
- The plan for feasibility and practicality of uptake was also designed from caregiver input, and it is therefore very detailed including practical considerations involved with traveling with disabled children. The payor research has not yet commenced, so obviously that is quite unclear.
- High unmet medical need; no current disease-modifying treatments exist. Devastating pediatric neurodevelopmental disease.
- Currently, there are no FDA-approved therapies for FOXG1 syndrome, with symptomatic treatment being the standard of care, highlighting the urgent need for a disease-modifying treatment. The existing standard of care is limited to supportive treatments to address symptoms, but these approaches have variable efficacy among patients.
- The off-the-shelf nature enables immediate availability, eliminating the costs associated with multi-stage procedures.
- The team is targeting patients that show haploinsufficiency; this is a cautious approach to the use of gene therapy to treat genetic diseases.
- There is a multilayered mitigation strategy identified to address and manage potential risks associated with the route of administration and any potential product related risks that may lead to serious adverse events.
- Huge unmet need; no known competing products. Advanced regulatory designations. POC studies in preclinical studies are promising, although it will not be possible to reverse all the neuro-developmental phenotypes associated with the condition. The proposal tacitly acknowledges this by expecting reversal of only certain debilitating features. There is good reason to believe that this therapy will benefit recipients, but it may not be transformative. FOXG1 syndrome is an ultra-rare pediatric neurodevelopmental disorder. So, the potential impact will not involve a large number of Californians.
- It's unclear if improving quality of life will result in sufficient benefit for reimbursement.

Rationale

- Clear scientific rationale for a monogenic disease treating loss of function. Controlled gene expression will be critical and is likely addressed in the use of a tissue specific promoter. Proposed dose is very high relative to benchmarks, creating questions on construct design and potency. If this is the therapeutic dose, product may likely have a very high COGS.
- Since the team proposing this work is totally dedicated to this spectrum of disease, and the scientific rationale seems to be quite sound. The applicant appears to have conducted deep research on the illness, its effects and approaches to providing assistance for years. Their global patient research is impressive.
- Strong support and endorsement by FDA. The reviewer is uncertain about the Australian component of the project and if there has been any regulatory interaction thus far with the Therapeutic Goods Administration.
- The rationale for the intervention is reasonable; i.e., to give a one-time ICV delivery of AAV9-FOXG1 driven by a neuronal specific promoter, to correct the haploinsufficiency. This strategy will be applicable irrespective of the pathogenic variant. 2) ICV delivery plus neuronal-specific promoter is appropriate and justified based on preclinical models and biodistribution.
- This is a neurodevelopmental disorder (microcephaly, corpus callosum abnormalities, simplified gyral pattern, hypoplastic basal ganglia and frontal lobes), presenting with developmental delay in achieving key milestones, speech delay, motor abnormalities, moderate/severe intellectual disability, seizures, sleep disturbances, and feeding difficulties. Will postnatal delivery of FOXG1 correct the developmental component of the phenotype? Their expectation of partial phenotypic improvement, especially in seizures, motor skills, muscle tone, cognition, and sleep pattern, is reasonable given the likely irreversible developmental component of the phenotype. 4) The preclinical models showed improvement whether intervention was at P1 or at P30 – which is a strength, given it is a developmental disorder. However, the limited benefit in the W300X mouse, which is a more accurate model for the human condition (compared with the postnatal conditional KO) showed limited response in the dentate gyrus / hippocampal response to therapeutic intervention. 5) For any disease that is caused by "haploinsufficiency" there is the likelihood

dosage sensitivity for the protein product. Protein overdosing did not occur, even in their high-dose mouse, which is a strength. However, this should be carefully monitored in human studies.

- ∉ Very strong preclinical data.
- ∉ There is a duplication (overexpression) syndrome for this same gene. The risk of causing overexpression of FOXG1 was not sufficiently addressed.

Project Plan and Design

- ∉ Overall project plan and design is adequate. Concerns that the proposed patient dose is driving high GMP manufacturing batch requirements (multiple 200L batches). Process includes a purification step that has challenges in empty:full separation, process robustness, and residual impurities. The full capsid specification is generally acceptable but on the low side, likely driven by product yield requirements (higher should be achievable with gradient purification). Unsure of acceptable residual impurity levels from the purification step for intracerebroventricular use.
- ∉ The project plan seems carefully crafted and is clear about what has already been accomplished such as describing the patient journey that is in progress (completing the patient registry) and what is in progress now.
- ∉ The timelines in this grant period seem feasible and working with caregiver groups so closely makes it seem likely that the enrollment targets will be met .
- ∉ Some inconsistency in the proposed number of sites (2 versus 3 versus 4) in the proposal, budget, and enrollment plan. Questionable ROI on opening a site in Australia. Leveraging the NHS for enrollment will be instrumental in enrolling this study in a realistic timeframe.
- ∉ The team's good collaboration with Citizen Health allows them to access real-world data with a retrospective cohort (N=224)
- ∉ 1) The timeline of 2 years (with additional 3 years continued safety monitoring) is reasonable. 2) Based on their natural history studies, recruitment may not be difficult. 3) The patients who will be enrolled in the trial will be consecutive – so they will have an unknown mix of truncating versus missense variants. This may not be a problem for safety/tolerability readout, but for any motor milestones / effectiveness readout(s) it may be noisy given the genotype-phenotype differences. 4) Younger patients will likely benefit more – so any signal for improvement will be predicated on the age distribution of the approximately ten consecutive patients.
- ∉ Excellent trial design to evaluate safety.
- ∉ By allowing multiple genetic subgroups with different developmental trajectories into the trial, this may add phenotypic complexity and limit the interpretation of efficacy outcomes.

Project Team and Resources

- ∉ Generally, no concerns with team. Charles River is a well-established CDMO for GMP manufacture and testing. The team is light on CMC depth, which is my only criticism, and I believe they could benefit from the support of a well-established consulting firm with depth of resources.
- ∉ The team seems to have been devoting their careers to help ameliorate the situation of these affected families.
- ∉ Strong.
- ∉ Excellent Team, sites, key personnel, vendors and consultants.
- ∉ The proposed program will be executed by a multidisciplinary team with extensive experience in neurodevelopmental disorders, including GMP manufacturing, IND maintenance, and clinical trial execution.
- ∉ Manufacturing of the AAV product is being handled by CRL, a well-established and highly reputable AAV manufacturing center. They have previously produced a 200L GMP clinical batch of vector for this first-in-human clinical trial, so manufacturing setbacks are not expected.
- ∉ 1) Strong and committed team at the applicant institution 2) The sponsor has done a lot to make this a feasible study (global registry, natural history in >100 patients, calibrated outcome measures based on caregiver interviews, licensed IP of AAV9-FOXG1 with neuronal-specific promoter).
- ∉ Strong clinical teams.
- ∉ Limited inclusion of CMC experts.
- ∉ Exceptional patient advocate group involvement

Population Impact

- ∉ Strong patient support team involvement, with an impressive number of ready to go participants.

- Generally, no concerns. Disease is not part of prenatal screening so may have challenges in identifying new patients who could benefit from early treatment.
- Since the group has developed the approach that they are taking with the advice and consent of the Patient Advisory Board and have used their worldwide registry to develop a thorough understanding of disease burden, health outcomes and associated factors.
- They were very careful in their research for the parent and caregiver advisory boards to cover all of the relevant demographic and socioeconomic variables of those who might be assisted by their treatment.
- Since the applicant worked so closely with caregiver groups, they seemed to have covered all of the bases for those who might be included in the study while recognizing the challenges imposed by the ultra-rare disease.
- Again, their outreach, engagement, enrollment and retention plans are among the strong points of this proposal. This proposal's use of the Patient Advisory group was exemplary.
- There's limited number of patients identified worldwide, with only 189 patients identified in the US and a total of 24 identified in CA. They seek to enroll 6//24 identified patients in CA.
- Very small population and aggressive estimates in terms of CA enrollment of low numbers, make this less impactful.
- Well-designed study with enough safeguards to allow for go/no go decisions.
- The team has a good collaboration with Citizen Health and patient community.
- 1) The proposed therapy will work for all gene variants 2) The applicant has worked closely with families and caregivers to understand their needs, and to optimize outcomes based on needs. 3) FOXG1 is an ultrarare pediatric neurodevelopmental disorder. So, the potential impact will not involve a large number of Californians.
- Excellent engagement by the applicant team.

Application #	CLIN2-19526
Title (as written by the applicant)	[Redacted] AAV Immuno-Gene Therapy for High-Grade Glioma
Therapeutic Candidate (as written by the applicant)	AAV immuno-gene therapy
Indication (as written by the applicant)	Adult recurrent high-grade glioma
Unmet Medical Need (as written by the applicant)	High-grade glioma is the deadliest brain cancer, with no effective treatments after recurrence and a median survival of only 6-9 months. [Redacted] aims to meet this urgent need by activating the immune system within tumors to destroy cancer cells.
Major Proposed Activities (as written by the applicant)	∉ Activate 3 clinical sites for MRI-guided CED delivery in adult rHGG ∉ Conduct Phase I dose escalation to establish safety and RP2D ∉ Complete Phase II dose expansion to assess safety and preliminary efficacy ∉ Generate integrated clinical, PK/PD, and biomarker datasets ∉ Finalize CSR and complete FDA End-of-Phase 2 meeting ∉ Execute CIRM Access & Affordability planning
Statement of Benefit to California (as written by the applicant)	This project directly benefits Californians by advancing a first-in-class AAV immuno-gene therapy for brain cancer into clinical testing. Nearly 1,200 Californians are diagnosed with high-grade glioma each year, and this trial will offer access to a novel therapy. With [applicant organization] and [redacted] both based in [redacted], the project also strengthens California's biotech and healthcare ecosystem.
Funds Requested	$7,999,774
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 85

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	85
Median	85
Standard Deviation	2
Highest	90
Lowest	80
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	12
Tier 2 (1-84): Not recommended for funding	2

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- This application proposes a phase 1/2 clinical trial for first-in-human evaluation of an adeno-associated virus immuno-gene therapy for adults with recurrent high-grade glioma.
- Despite multimodality therapy, recurrence is universal among patients with high grade glioma. Limited options are available at the time of disease recurrence. Outcomes are particularly dismal for patients with glioblastoma. There is a need for novel survival prolonging therapies for all patients with recurrent gliomas.
- This application represents a novel immunotherapy approach that is agnostic of tumor subtypes and molecular alterations by providing interferon beta driven immune responses generated by use of a viral vector. If effective, this would represent a significant advancement in tumor treatment.
- The treatment itself is administered by convection enhanced delivery, surgically, proposed as a single session. This is a convenient treatment administration for patients even if it is an invasive approach.
- There is an unmet need for this condition and promising preliminary data to advance a product for high grade gliomas.
- Strong rationale.
- Key strengths: Local control and treatment within the tumor with reduced risk to collateral tissues, single administration, good nonclinical results, clinical drug product inventory is ready for use, regulatory designations to facilitate agency interactions, contractors and consultants have required expertise and experience to support study.
- Key strength: The proposed study is feasible from the standpoint of CMC issues. The proposed dosage form is consistent with the proposed method of administration to patients.
- The proposed trial uses a proven phase 1 3+3 approach followed by a phase 2 expansion. It is expected for this overall design to provide useful preliminary data in humans. However, there are some concerns that must be considered in terms of applicability of this therapy.
    - The first and most significant concern is that the proposed treatment is delivered surgically by convection enhanced delivery. This is a highly advanced treatment technique that is not likely to be available outside of major medical centers. Many patients with glioma do receive treatment at community centers. While the product is proposed as a single administration surgically delivered therapeutic, it is unlikely that many patients will have access to delivery. The treatment is much more likely to remain confined to academic centers and available to patients who have the ability to access highly specialized neuro-oncology centers rather than something that will be available to the broader population of glioma patients.
    - Additionally, applicability of the treatment to all patients with recurrent glioma is likely to be limited considering this is a local therapy that requires surgery. Patients with tumors in certain locations may not necessarily be amenable to receive convection enhanced delivery. Patients with multifocal tumors may require multiple administrations or unable to benefit from this therapy. Patients with disseminated tumors, especially leptomeningeal disease related to their gliomas are not likely to be candidates.
    - Per the project plan and the 28 day follow up schedule the investigators propose, the phase 1 portion could take up to 24 months, exceeding their proposed timeline by 6 months. No mitigation strategy is provided for the possibility that the phase 1 portion takes 6 months longer than planned.
    - Overall the statistical analysis plan provided within the protocol document is very superficial and it is unclear how the primary as well as secondary endpoints of the trial will be analyzed. Further, virtually no plan is provided for analysis of exploratory endpoints.
- The proposal would be strengthened with more on (1) the safety and toxicity of using the proposed cytokine and (2) how this approach is positioned relative to other intra-tumoral approaches to enhance tumor cell death and mount a more complete immune response.
- Key weaknesses: The applicant is essentially a virtual company so principals may be spread too thin to properly oversee the project; method of administration is highly technical meaning it can be performed

only in centers of excellence/qualified academic centers, target infusion volume and injection technique is gauged to match lesion size therefore clinicians must be well-trained to deliver therapy consistently, ∉ Key weakness: Clinical issues exist which might require further discussion. ∉ Weakness: clinical design clarity needed.
Value Proposition
∉ Very compelling need. There is no established standard of care for recurrent (high grade) glioma. The median survival is 6-9 months following recurrence, 5% survival rate at 5 yrs. ∉ The treatment proposed within the application has never been tested in humans. However, in this patient population with limited treatment options and no available curative therapies, a treatment that can achieve local disease control, prolong progression free survival, and prolong overall survival would certainly represent a meaningful and substantial improvement. As an example, since 2005, for patients with glioblastoma, the only interventions that were shown in a large clinical trial to prolong survival and lead to a change in clinical practice were temozolomide and tumor treating fields. Even those two interventions are associated with a modest survival benefit. As such, if the product was found to improve survival even modestly among patients with glioblastoma, a very significant advancement in treatment of glioblastoma will be made. This is an excellent value proposition in a patient population with great need. ∉ There are some concerns that must be considered in terms of applicability of this therapy. The first and most significant concern is that the proposed treatment is delivered surgically by convection enhanced delivery. This is a highly advanced treatment technique that is not likely to be available outside of major medical centers. Many patients with glioma do receive treatment at community centers. While the product is proposed as a single administration surgically delivered therapeutic, it is unlikely that many patients will have access to delivery. The treatment is much more likely to remain confined to academic centers and available to patients who have the ability to access highly specialized neuro-oncology centers rather than something that will be available to the broader population of glioma patients. ∉ Applicability of the treatment to all patients with recurrent glioma is likely to be limited considering this is a local therapy that requires surgery. Patients with tumors in certain locations may not necessarily be amenable to receive convection enhanced delivery. Patients with multifocal tumors may require multiple administrations or unable to benefit from this therapy. Patients with disseminated tumors, especially leptomeningeal disease related to their gliomas are not likely to be candidates. ∉ Potentially improved local disease control and increased survival would have a positive impact in clinical outcomes for patients with high grade glioma. With improved local disease control, it is conceivable that patients will also experience longer periods of neurological stability and functional independence, representing a positive impact on patients and their caregivers. ∉ This therapy is not curative, it is life-extending by reducing disease burden and stalling disease progression. ∉ Potentially helpful for a quality improvement for this condition. ∉ High unmet need with a difficult problem. ∉ There is a plausible mechanism of action from intra-tumor delivered drug product that use of an AAV9 gene therapy encoding a cytokine which is expected to drive anti-tumor activity. ∉ The proposed study is feasible from the standpoint of CMC issues. The proposed dosage form is consistent with the proposed method of administration to patients.
Rationale
∉ Scientific rationale for the proposed therapy is scientifically sound (AAV9 delivery of the transgene, body of available nonclinical data). Single administration reduces treatment burden; use of MRI CED should be a precise, reproducible way to deliver therapy to the intended target region(s). ∉ This gene therapy expresses a human cytokine that induces tumor cell death and anti-tumor immune response upon secretion. Once inside tumor cells, the product drives local production and secretion of cytokines, activating the immune system to recognize and destroy cancer cells while minimizing effects on healthy brain tissue. ∉ Investigators provide compelling data indicating efficacy of the treatment based on mouse studies. In one study, higher doses of the treatment are associated with good tumor control. In another study, lower doses are associated with overall poorer tumor control. The combination of this data has allowed investigators to select a dose appropriate to start first-in-human testing. ∉ Investigators also provide compelling data regarding safety of the treatment. They demonstrate feasibility of the administration strategy using pig data. They also demonstrate reasonable safety data based on animal studies.

- Limitations of data presented: (1) A key shortcoming of the overall treatment approach is that per the data provided, it can only achieve local disease control at the site of the infusion. The investigators do not present any evidence that immune system activation achieved by the infusion can have a broader whole tumor effect. This means the approach cannot be applied to cases where multifocal tumor is present and cannot be applied to cases where leptomeningeal dissemination is present. More importantly, adult type high grade gliomas are diffuse infiltrative tumors that spread throughout the brain as disease progresses. Local treatment strategies as a result do have an inherent limitation. (2) It is stated that sensory ganglia damage, decreased neuron cellularity, and neuron necrosis were noted in a pig study. The treatment could potentially lead to nervous system injury in humans based on what the investigators presented. (3) The process in determining the human equivalent dose.
- Additionally, investigators demonstrate that the production process has been reviewed and validated. Overall, presented data does provide robust scientific rationale that the proposed therapeutic approach may be effective in humans and it may be well tolerated.
- Rationale of the proposed CMC approach is consistent with delivery of a gene therapy by intralesional administration. The drug when delivered should function as proposed and may provide proposed therapeutic effect. From a CMC perspective, the proposed work should be able to accomplish the stated goal of advancing the project to an end of Phase 2 meeting with FDA, clinical results permitting.

Project Plan and Design

- The overall plan appears appropriate and reasonable. High-grade glioma is the deadliest brain cancer, with no effective treatments after recurrence and a median survival of only 6-9 months.
- The project plan outlines a phase 1/2 clinical trial. The phase 1 portion includes a traditional 3+3 design where patients are enrolled one at a time and evaluated for dose-limiting toxicities. Phase 2 portion represents an expansion cohort. Conceptually, the overall clinical trial design is fairly standard and can be implemented as it has been for many other studies.
- Given the very traditional design utilized, it is reasonable to expect the phase 1 structure would identify a maximum tolerated dose, assuming the starting dose selection based on animal studies is appropriate. Given the traditional design, the phase 2 portion should provide some preliminary efficacy data while adding to the safety data.
- The clinical protocol was well designed, although the timeline may be a little aggressive.
- Based on review discussion, the clinical study design would benefit from specific modifications but should generate data that will permit determination of dose and DLT in support of a phase 2 dose expansion. Three institutions with significant expertise in neurosurgery and neuro-oncology will have access to the required patient population;
- The proposed project CMC program is conducted at reputable contract manufacturers which have extensive experience with AAV-based gene therapy products and should readily execute the proposed manufacturing and analytical program. The manufacturing and analytical programs proposed are as expected for development of AAV gene therapies and are phase appropriate.
- The drug product has been manufactured and quality-released (is sufficient material to complete the entire trial); IND is cleared; regulatory designations are in place.
- There are multiple potential issues in terms of meeting timelines as intended as well as issues with clinical trial design:
  - The investigators propose a fixed rate of enrolling one patient every 28 days. It is unclear whether this provides sufficient time to evaluate patients appropriately and manage dose limiting toxicities that may emerge. It is also unclear what strategies the team will utilize if the fixed schedule cannot be maintained.
  - There is virtually no statement as to how dose-limiting toxicities will actually be managed. It is somewhat superficially discussed how dose escalation decisions will be made, who will be involved in the decisions, and how disagreements may be handled in the project plan that is provided in the application.
  - Per the project plan and the 28 day follow up schedule the investigators propose, the phase 1 portion could take up to 24 months, exceeding their proposed timeline by 6 months. No mitigation strategy is provided for the possibility that the phase 1 portion takes 6 months longer than planned.
  - Eligibility criteria in the provided clinical trial protocol have the following concerns: It is not clear whether there are any restrictions on type or dose of radiation therapy that has been previously administered. Are patients eligible if they receive hypofractionated protocols as well as 6 weeks of RT? Are patients eligible if they receive proton RT as opposed to conventional photon-based RT? Is it possible for participants to have received a short course of bevacizumab for control of

radiation necrosis? What are the dosing and duration limitations of temozolomide? Are participants eligible regardless of how many adjuvant cycles they received? Why are oligodendroglioma patients who received PCV chemotherapy as opposed to temozolomide ineligible?

- According to the clinical trial protocol, the authors seek to enroll patients with any type of recurrent high-grade glioma both IDH mutant tumors and glioblastoma. It is not clear from the materials available for review how overall survival and progression free survival analysis will be completed in light of enrolling a diverse group of patients. Is there stratification by tumor type? Throughout the application the investigators make a claim that survival for recurrent high-grade glioma is 6-9 months, which is only true for glioblastoma. Patients with recurrent oligodendroglioma or IDH mutant astrocytoma can and do respond to salvage treatments and can live for multiple years. It is critically important that investigators consider the actual diagnosis and tumor grade of the patients to evaluate progression free and overall survival outcomes appropriately. How will they determine whether efficacy data is sufficient to justify a larger phase study?
- Overall, the statistical analysis plan provided within the protocol document is superficial and it is unclear how the primary as well as secondary endpoints of the trial will be analyzed. Further, virtually no plan is provided for analysis of exploratory endpoints.
- For a clinical trial that has a phase 1 and a phase 2 portion, it is unclear why interim analysis is not planned when moving from one phase of the study to another.
- It is unclear what contingency plan is in place if the 2-3 patients per month goal is not being met during the dose expansion portion to ensure completion of the study within the intended period.

- The TRAN grant provides prior data. Clinical design clarity needed. More safety planning is needed.

Project Team and Resources

- The key personnel included in this proposal is composed of basic science researchers as well as neuro-oncologist clinicians. The listed individuals are all accomplished in their fields.
- Study PI is recognized for their work in viral vector studies and has experience in development of the therapeutic strategy that will be utilized as part of the clinical trial.
- Clinical site leaders have experience in conduct of neuro-oncology clinical trials and have extensive experience in treatment of patients with glioma.
- The listed study sites have the capabilities to conduct the type of clinical trial proposed. They also each evaluate large volumes of glioma patients each year.
- Proposed CMC personnel have significant experience managing similar programs over several decades, and the proposed resource level is adequate to oversee the proposed work. Contract manufacturer has necessary facilities, equipment, staff, and systems to execute the proposed program.
- The applicant uses experienced contractors and consultants; the applicant organization is essentially virtual (6 employees) so the main concern is that the principals are spread too thin to properly oversee all aspects of the project.
- Appears to have appropriate experts involved with 3 clinical sites involved. [Named research organization] will oversee the CA portion of the trial.
- Good. Needs neurosurgeon member on team.
- The key concern is that this is fundamentally a surgical clinical trial. The intervention is to be delivered by convection enhanced delivery via a surgical procedure. It is difficult to understand why no neurosurgeons are included in this proposal. All three of the site PIs are clinical neuro-oncologists who would not be responsible for the actual administration of the study intervention. Lack of neurosurgical oversight is a significant gap and could certainly influence successful conduct of the proposed clinical trial.
- Lack of a neurosurgeon on the team is a concern.
- It is unclear whether the CEO should be the PI on this project.
- The justification for salaries seems too pat. The groups listed all have the same base salary even though the scope of their functions differ. That leads me to question how well thought out the budget is in other respects as well. If they truly are paid the same, then that points to a possible management experience issue.

Population Impact

- The applicant appears to understand the target indication, disease burden, care and health outcomes extremely well. In particular, there is no upper age limit for eligibility, in recognition that HGG is a disease of older adults.

- The protocol proposes to enroll a variety of different tumors, some of which have a relatively good prognosis. Therefore, the impact on patients will vary depending on the type of tumor.
- While they do not touch on equity and community outreach, they are including research in three states to include a diverse population. More could be elaborated on with regards to outreach.
- Overall, the application has a global issue in terms of understanding glioma burden. Throughout the application, it is repeatedly stated that survival outcomes for recurrent glioma are dismal and median overall survival is 6-9 months. This is only true for glioblastoma. IDH mutant astrocytoma and oligodendroglioma are associated with far superior outcomes and patients very frequently do respond to salvage treatments, can be expected to live far longer than 9 months at first recurrence. While this does not negate any of the excellent scientific work done by the PI and their team, it does underscore an overall lack of awareness of the disease state, which is important as evaluation of treatment outcomes within this study does require an overall accurate understanding of typical outcomes.
- The proposed study is potentially very meaningful to all patients with recurrent glioma regardless of the above concern since options for treatment are limited and outcomes can be improved for all persons with recurrent glioma.
- The clinical trial as proposed in this application does select for patients with tumor in a single site, relatively small volume of tumor, and in excellent clinical status. This means that patients with multifocal tumors as well as poorer performance status are excluded and the results of the study are not going to be generalizable. While this does represent a limitation, interventions that can improve local tumor control are still very meaningful to this patient population.
- The study does include three sites that represent geographically distinct areas of the country, broadening reach despite the small number of potential participants.
- However, one key limitation is that the intervention being studied, delivery of viral vector based gene therapy using convection enhanced delivery is likely to be very limited in terms of its widespread use. Even if demonstrated to be efficacious, this approach is likely to be available only to those patients who can travel to major academic centers.
- Some concerns but general sentiment is fundable.

Application #	CLIN2-20117
Title (as written by the applicant)	A Phase I/IIa, Dose-Escalation Study of [redacted product name] for the Treatment of Focal Articular Cartilage Defects in the Knee
Therapeutic Candidate (as written by the applicant)	Stem cell derived juvenile chondrocytes
Indication (as written by the applicant)	Focal cartilage defects in the knee
Unmet Medical Need (as written by the applicant)	Articular cartilage lesions do not regenerate in adults. Some clinical solution are available and include microfracture surgery, expanded autologous cartilage cells or osteochondral allografts. Unfortunately none of those solutions are fully efficient for the proposed indication.
Major Proposed Activities (as written by the applicant)	∉ Enrollment of 10-14 patients in a Phase 1/2a clinical trial to demonstrate safety and early efficacy ∉ Conduct clinical and imaging assessment of the outcomes ∉ Complete Accessibility and Affordability strategy and commercialization planning ∉ Manufacturing of new GMP lots ∉ IND maintenance ∉ Identify commercial partner for the next phase
Statement of Benefit to California (as written by the applicant)	Nearly 10% of adult population in California have focal cartilage lesions. If this is not treated, the majority of these patients will develop osteoarthritis, a major degenerative joint disease. Currently, no therapies are available for osteoarthritis and many of those patients will undergo total joint replacement, a very expensive medical procedure. Thus, having an efficient therapy for early stages of cartilage disease will be a major advancement for the State of California and the citizens.
Funds Requested	$11,193,750
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 80

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	82
Median	80
Standard Deviation	3
Highest	88
Lowest	77
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	5*
Tier 2 (1-84): Not recommended for funding	9

* See Minority Report below

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses
∉ The goal of an off the shelf cartilage repair product for one stage surgery creating Type II collagen with "normal" extracellular matrix is the holy grail of cartilage repair. The goal is commendable, but in reality, this is extremely expensive to pursue and will take at least 10 yrs to demonstrate efficacy that will influence payers that we are decreasing incidence of osteoarthritis (OA) and total knee arthroplasty (TKA). ∉ Complicated; conflict of repairing cartilage vs. addressing OA in the project proposal. ∉ Clear, structured approach with outlined value proposition. ∉ Strengths are based on producing an off the shelf allogeneic option to articular cartilage repair. Manufacturing is complete, and the team is very strong. Weakness includes potentially lack of need for this type of approach in light of current interventions. Concern about the use of a stem cell derived product where primary tissues are available. Also, no movement towards a commercially viable (and compliant) manufacturing process and analytics are addressed. ∉ The unmet need was overstated in the application as the number of addressable patients is more in range of 30,000 to 70,000 and is not related to the 27M patients with OA they presented. Microfracture and MACI are available therapies for these patients. ∉ The development plan is conservative and slow, with a small study size and long follow-up that delay meaningful data and increase the risk of loss to follow-up in a competitive enrollment environment. Given the very limited sample size, even minor loss of patients will compromise interpretability and any decision about dose. The lack of any detail on MRI assessment method was notable since that is the most important endpoint for detecting an efficacy signal. ∉ The team is composed of well-known experts in the field of cartilage research. It is an off-the-shelf product that would enable immediate availability, eliminating the costs associated with cell harvest, in vitro expansion, or multi-stage procedures. ∉ A key weakness is the manufacturing process and its lack of refinement based on 2026 standards.
Value Proposition
∉ The stated goal of an off the shelf implant to regrow cartilage using stem cells with the formation of chondrocytes that make normal extracellular matrix is the holy grail of cartilage restoration. This would, in theory, have tremendous societal value. Unfortunately, attaining this goal is a very daunting endeavor. There are many obstacles to achieving this goal. The efficacy and clinical value of this technology will take 10+ yrs to prove, as commercial success and payer acceptance will require 10+ yr data showing prevention of osteoarthritis and decrease in downstream surgery, particularly TKA. There ARE extant technologies that do address this clinical need, albeit each has limitations that theoretically could be superseded by this product. ∉ The proposal conflates osteoarthritis (OA) with focal cartilage lesions. The target patient population represents a subset which may not necessarily have an urgent medical need. ∉ Articular cartilage injuries often progress to osteoarthritis. This affects 27 million Americans and can cost the US $137 billion annually. ∉ Surgical options are limited by poor tissue quality, donor site complications, and multiple surgeries. ∉ The product is an off the shelf cartilage implant designed for a single procedure focused on the knee. Preclinical studies have shown early successes. ∉ Advantages include: single procedure; effective across diverse demographics; low immune risk; could prevent total knee replacement. ∉ Value proposition remains conceptual and lacks pieces for the program to advance. ∉ It is unclear how the determination of "unmet medical need" is determined; reviewers thought that there is little need for another approach at this time. ∉ The proposal conflates osteoarthritis (OA) with focal cartilage lesions, which are very different clinical conditions with different patient populations and treatments. The cited numbers focus on the large

incidence of OA – 27M, but the study targets a much smaller subset: patients with symptomatic focal cartilage defects. The actual addressable population is estimated to be 30,000–70,000 patients per year, mostly sports medicine cases like athletes. ∉ There is already an established therapy available for cartilage lesions, MACI, from Vericel, with reasonable clinical success and market leadership. The advantages for this therapy would be single-stage surgery and potential cost reduction. ∉ While the condition is meaningful and worth treating, it does not constitute a serious unmet medical need. It is niche rather than urgent, and the presentation of the numbers was not transparent. ∉ The product is designed to overcome age-, sex-, and race-related variability in treatment response irrespective of defect size or location, making it suitable for middle-aged adults (40–60 years), who often show suboptimal outcomes with traditional bone marrow stimulation.
Rationale
∉ The preclinical evidence relies primarily on histologic outcomes from a 6-month animal study. No functional endpoints were reported. Histologic staining alone provides evidence of tissue formation, but not functional recovery or durability. ∉ The preclinical evidence shows histologic repair, but there is no functional data. There is a gap between 6-month histology in animals and 24-month clinical outcomes in humans. That gap creates uncertainty around durability. There is nothing in their preclinical work to support that this will have durability nor was there any data on comparative efficacy versus available therapies or MSC therapies to motivate investment in the project. ∉ Articular knee injury is an appropriate indication; OA seems to be outside of the scope of this proposal. Preclinical data is supportive but limited to 6 months maximum which may be insufficient to determine lasting effects. ∉ The approach in the protocol is scientifically robust and rigorous. ∉ A significant number of trials are open currently; advantages of the current program are questionable. ∉ It will take more than 10 years to prove the efficacy and clinical value of this technology.
Project Plan and Design
∉ This is a FIH study, and this project, while quite expensive, appropriately addresses this Phase 1 goal. If funded, this study may, or may not, validate the hypothesis. ∉ A big problem with focal cartilage repair is mission creep. These lesions rapidly progress to OA, even in younger patients and the repair technologies are continually applied to these early OA cases, which are very different than the "simple" focal chondral defect. ∉ The Phase 1/2a study expects to enroll 10 patients, which is very small even for early clinical development. The clinical study includes only 4 patients per dose level, which is not enough to interpret dose–response to inform design of next phase or efficacy signals. ∉ The primary efficacy assessment occurs at 24 months, with no strategy to evaluate or act on 12-month outcomes. The development plan lacks any sense of urgency and does not demonstrate a clear path to clinical validation. Four years to obtain data on 10 patients before advancing the program is slow. ∉ Patient burden in this study is meaningful, and this creates a real risk to study completion and getting interpretable data. This is a very small study with a long follow-up period for a condition that is not life-threatening. Also, the patients are typically younger and more mobile, which makes it easier to lose them to follow-up. ∉ There is very little detail provided on the MRI assessments; they are the most important objective endpoint in the study. ∉ The team may be unable to recruit patients willing to try this new treatment with unknown clinical outcomes within the proposed timeline. ∉ The determination of genetic stability and the mechanical durability of the final product via visual inspection prior and after the thawing procedure is not sufficient. There should be a more robust determination of chromosomal stability, especially since the product is derived from an embryonic stem cell source. ∉ Project plan is adequate and well staffed.
Project Team and Resources
∉ This is an "A team" for cartilage research. If any team can handle this *very* difficult, multi phase trial they are qualified to do so.

- The team appears capable of running the early-stage study. However, if the program moves forward, they will likely need additional help and different expertise to advance beyond early clinical development and move through the regulatory process.
- Resources are adequate for the proposed trial.
- A consulting firm is the main regulatory partner, and they are collaborating with regulatory experts at a CRO.

Population Impact

- The proposal focuses on the burden of osteoarthritis which affects a very large and diverse population. However, the study specifically targets patients with focal cartilage defects without degenerative joint disease.
- The proposal discusses demographic considerations but does not provide detail on how different patient groups will be represented. Since it's a very small study, achieving representation would be challenging.
- The study specifically targets patients with focal cartilage defects without degenerative joint disease which is a small representation of large and diverse population that experiences osteoarthritis.
- This may have an impact on only a small subset of healthy young athletes with recent injuries and strong tissue architecture supporting high likelihood of recovery potential.
- It will be very hard and take 10+ yrs to prove this technology is better than existent methods currently in use. Some of those are very cheap.
- The product has potential, but long-term and other treatment modalities are available.
- Many competing trials are more advanced.
- Limited market options and unmet medical need.
- The proposed Alpha Clinic will be responsible for outreach efforts, starting with a community engagement event focused on developing patient and provider resources, educating stakeholders about CIRM Patient support program and connecting staff with the applicant institution's race and equity center.
- The budget covers transportation, lodging, meals, patient navigators, caregiving, and lost wages for lower-income participants.
- A stipend will also be offered to offset time and lost wages.
- Documents and trial information will be available in English and Spanish (including interpreter services for enrollment and informed consent).

MINORITY REPORT

If an application receives a Final Score of 1-84 and 35% or more of the scientific members of the GWG recommend an application for funding, then a minority report is provided that summarizes the perspective of those scientific members.

The reviewers who supported funding this project agreed the team is strong and the goal of pursuing an off-the-shelf allogeneic product for articular cartilage repair is commendable. The therapy could reduce costs and complexities of current options like MACI, though reviewers questioned whether there is a strong unmet need given the existing treatments. Establishing long-term efficacy, clinical value, payer acceptance and superiority over cheaper existing methods will require more than ten years of data. The clinical protocol and manufacturing are complete, however the preclinical evidence is limited to 6-month histologic outcomes without functional data, and key concerns include conflation of osteoarthritis with focal cartilage lesions, a narrowly defined target population, challenges in patient recruitment, and insufficient assessment of genetic stability for a stem cell–derived product. However, the project is well staffed, appropriately scoped for a first-in-human study, and if funded, could meaningfully test the underlying hypothesis despite its high cost and the likelihood of impact being limited to a small subset of patients.

Application #	CLIN2-20114
Title (as written by the applicant)	Phase I/IIb Gene Transfer Clinical Trial for CLN6 Disease, Delivering the CLN6 Gene by Self-Complementary AAV9
Therapeutic Candidate (as written by the applicant)	A CNS-directed AAV9 gene therapy delivering a functional CLN6 gene via intrathecal administration.
Indication (as written by the applicant)	Variant late infantile neuronal ceroid lipofuscinosis (CLN6 disease), a fatal pediatric neurodegenerative disorder.
Unmet Medical Need (as written by the applicant)	CLN6 disease is a uniformly fatal pediatric neurodegenerative disorder with no approved disease-modifying therapies. Care is purely supportive. This proposal addresses the urgent need for a CNS-directed treatment that targets the underlying genetic cause early in disease progression.
Major Proposed Activities (as written by the applicant)	∉ GMP manufacture of clinical-grade scAAV9.CLN6 to support intrathecal dosing ∉ Complete IND-supporting CMC, biodistribution, and toxicology activities ∉ Obtain regulatory authorization for CNS-directed intrathecal administration ∉ Initiate and conduct a Phase I/IIb clinical trial in pediatric CLN6 patients ∉ Assess safety, tolerability, and preliminary efficacy using clinical endpoints ∉ Evaluate durability of expression and long-term safety to inform next phases
Statement of Benefit to California (as written by the applicant)	This project advances a first-in-class gene therapy for a devastating pediatric disease at California-based clinical sites. It strengthens California's leadership in rare disease gene therapy, supports high-skilled biotech and clinical jobs, and accelerates access to innovative therapies for California families affected by CLN6 disease.
Funds Requested	$12,597,426
GWG Recommendation	**(1-84): Not recommended for funding**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 68

Up to 15 scientific members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Mean	68
Median	68
Standard Deviation	4
Highest	75
Lowest	60
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	0
Tier 2 (1-84): Not recommended for funding	14

FINAL COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

Key Strengths and Weaknesses

- Addresses an ultra-rare disease that would otherwise not have much access to successful intervention.
- The application presents a confusing plan and a poorly assembled project.
- Key issue is CMC and the depth of CMC information provided. The manufacturing plan (who is doing it) and comparability plan are unclear, and no CMC personnel names are provided. Inconsistent information is presented in the proposal.
- The value proposition for this application is not specified in sufficient detail to evaluate it.
- Given the lack of specific information on the number of patients available for this study, one cannot determine if the recruitment timeline and goals are feasible.
- The criteria that will be used to judge the efficacy of this treatment aren't included in the grant application.
- High unmet need.
- Strengths: Unmet medical need and potential therapeutic benefit. Weaknesses, CMC, manufacturing switch, lack of experience, and an apparent conflict of interest in Key personnel related to the PI.
- The FDA correspondence regarding the injection route was confusing. Apparently an intracerebroventricular (ICM) route was chosen to which the FDA agreed. The FDA disagreed with the intrathecal (IT) route and dose until comparability and nonclinical studies are completed.
- Data from the prior study including ages, symptoms, progression, and any autopsy findings regarding expression would have been useful to present in the application to support the rationale.
- Expected enrollment is approximately ten patients; the age of eligibility is 4 to 60 months. Clearly, patients 4 to 12 months of age are not necessarily independently ambulatory. The investigator's brochure really had no inclusion criteria outside of age despite discussions of having "neurologic" or "ambulatory" criteria for entry. The team may have the same problems as seen in the prior trial with patients presenting too late in disease course.
- Related to the above, the team could easily look retrospectively to see how many patients, given their new criteria, would be eligible for the current therapy as written. The reviewer did not see that this was done. This would go a long way in letting the reviewer understand if this trial is enrollable as written.
- The product comparability and manufacturing plan changes are given in the application. There are also analytical methods and potency strategies. Not all these strategies have been agreed upon by the FDA. The FDA pointed out that a potency method should be evaluated, and it should not be an in vivo animal model due to the variability, especially prior to a phase I/IIb trial. In fact, a cell-based model would be better. This reviewer does not see that such a model has been developed. This would be the main criticism regarding the development of a potency assay.
- A reviewer finds this a poorly executed application.
- Building on a prior gene therapy study, the applicant wants to increase the vector dose 10X. What is rationale for this dose? Did the preclinical model data show improvement with the proposed10X dose? Lack of a potency assay. The reviewer questions the route of injection. Team and expertise are fine.
- The team are changing manufacturers with no alignment of assays between the two. Regarding comparability, the application lacks personnel with CMC depth. The team need to focus more on efficacy and potency.
- The applicants wish to deliver a higher dose in younger patients than previously, but they don't show why.

Value Proposition

- Clear unmet medical need with potential to result in positive, meaningful clinical outcomes. IT approach enables an improved safety profile and reduced cost of goods (COGS), which will promote patient and payer uptake (although confusion exists regarding the route of administration). As this is an ultra-rare disease, concerns exist about the commercial viability of this product due to relatively low demand and high COGS.

- CLN6 disease is an ultra-rare genetic disorder that has a devastating impact on children including progressive language loss, motor deterioration, cognitive decline, vision loss, refractory epilepsy and premature death. No treatments are available for this progressive neurological disorder.
- It is difficult to judge the value proposition for this therapy because the application lacks information on the overall incidence of the condition. In reviewing the literature, the true incidence of CLN6 is unknown. The incidence of all forms of neuronal ceroid lipofuscinoses is estimated to be 2-4 per 100,000 live births in the United States.
- While the dose proposed in the current application is higher than the previous dose tested, the investigators do not provide any information on what would be viewed as long-term efficacy of the drug (i.e, a secondary objective).
- Based on the information provided in the access and affordability plan, it is not clear how payors would evaluate this therapy.
- The gene therapy could be curative if it works.
- Solid potential; questionable ability to deliver.
- Regarding impacts on the medical needs on patients, caregivers, and healthcare system, clearly there is no approved therapy for CLN6, and any new therapy would fulfill that need. Whether or not such therapy would be adopted in a widespread manner is not clear to the reviewer. This is an exceptionally rare disease with just a few hundred cases described worldwide. Therefore, very few patients will be involved. Secondarily, the cost of the current application is roughly $12 million, which could be extrapolated to about $1 million per patient being spent. This somewhat diminishes the value proposition in the reviewer's opinion.
- This ultra-rare pediatric neurologic disease leads to death with no good therapies.

Rationale

- Clear scientific rationale for a monogenic disease treating loss of function. Durable gene expression will be critical, and the reviewer is unsure how this is addressed compared to the prior clinical results. The proposed dose is in line with benchmarks and will drive low COGS.
- It's unclear that going to a higher dose will result in better efficacy data than that of the previous trial.
- There may be qualitative issues limiting gene expression and vector targeting that will not be overcome by simply increasing the dose.
- Reasonable rationale.
- Regarding the rationale, not a lot of scientific data are included in the application. This application is building upon a prior trial, but this time they will increase the viral genome dose by tenfold. The authors give two factors important in lack of efficacy in the prior trial: advanced disease at the time of treatment as well as insufficient transgene expression at the given dose. It would have been helpful for the reviewer to see the information regarding the data evidence for insufficient dosing. Prior data about the administration of the virus in the murine model is adequate. There are some murine histological and behavioral outcomes given in the application, which were helpful to review.
- The preclinical data in a relevant model were not given, but three studies were done via the IT route. A referenced article compared 5x1012 vg/kg in a relevant preclinical model and claimed ICM injection could be 100x more effective than the IT route. Another recommendation would have been to repeat the dosing in relevant preclinical model to show that this higher dose allows for better transgene expression in the CNS. Intrathecal injection seems to be a more direct route to the CNS than IV injection in the reviewer's opinion. There was FDA correspondence regarding the injection route that was confusing. Apparently an ICM route was chosen to which the FDA agreed. The FDA disagreed with IT route and dose until comparability and nonclinical studies are completed. There is no clear potency study. The FDA suggested that non-clinical studies may have to be repeated in light of switching manufacturers.
- A reviewer is uncertain it makes sense to simply adjust the vector dose tenfold because the prior trial didn't demonstrate efficacy. It's difficult to rationalize that this adjustment will change the clinical outcome of such a devastating disease. Data from the prior study including ages, symptoms, and progression would have been useful to present in the application to support the rationale.

Project Plan and Design

- This element is lacking in many areas of the project.
- Overall, the project plan timeline is adequate. The proposal states manufacturing will be done by one manufacturer, but the documents show a different manufacturer as the CDMO; this is a major issue. It seems the first manufacturer will outsource testing of the product, but the cost and lab to conduct this are not shown. The initial manufacturer's process uses CsCl, which is an outdated and not scalable technology, although this may not be a concern for an ultra-rare disease.

- ∉ No information is provided on the number of available participants to achieve the recruitment goals for this study.
- ∉ Given that a natural history study exists for this condition, it is unclear why epidemiologic data were not included in this grant application.
- ∉ Due to the absence of information on the potential participants (e.g., number who meet the eligibility criteria, geographic location of the patients), one cannot judge the feasibility of the recruitment plan.
- ∉ The discussion of the planned route of administration with FDA is unclear.
- ∉ CMC and manufacturing are not clear. Who is the CDMO, and will there be a potency assay?
- ∉ The proposal includes an unrealistic clinical development plan, timeline and budget.
- ∉ Regarding the project plan, the authors discuss that they would like to have patients that are independently ambulatory with CLN6 disease, and this will differentiate it from prior trials in which patients may have been later in the disease course. Expected enrollment is approximately ten patients with the age of eligibility being 4 to 60 months. Clearly, patients 4 to 12 months of age are not necessarily independently ambulatory.
- ∉ Their investigator's brochure really had no inclusion criteria outside of age despite discussions of having “neurologic” or “ambulatory” criteria for entry. The authors may may the same problems as the prior trial with patients presenting too late in disease course.
- ∉ The authors could easily look retrospectively to see how many patients, given their new criteria, would be eligible for the current therapy as written. The reviewer did not see a description of this exercise. This would have gone a long way towards helping the reviewer understand if this trial is enrollable as written.
- ∉ The team have a goal of nine months for enrollment. The listed contingency plans seem reasonable.
- ∉ As mentioned, there is a transfer of manufacturers, and there have also been conversations with the FDA to be sure that the potency and product developed at the new manufacturing center meets or beats the criteria from the prior one. The product comparability and manufacturing change plans are given in the application. There are also analytical methods and potency strategies. Not all of these strategies have FDA concurrence. The FDA pointed out that a potency method should be evaluated, and it should not utilize an in vivo animal model due to variability concerns, especially prior to a phase I/IIb trial. A cell-based model would be better. The reviewer does not see that such a model has been developed yet. This is the main criticism regarding the development of a potency model.
- ∉ There are various listed manufacturing risks which seem appropriate as does the mitigation plan. Again, the patient population is to be independently ambulatory. There's also no definition in the investigator's brochure about what is meant by independently ambulatory, whether that includes the use of a walker or other device, and if the authors are really trying to catch patients with early-stage diagnoses. This should be spelled out more clearly.
- ∉ Inconsistencies in the approach were concerning.
- ∉ Failure to provide a comparability assessment plan is a significant issue which makes it difficult to compare any previous non-clinical, clinical, and laboratory data obtained with the previously manufactured product to that obtained with the product from the proposed manufacturer.

Project Team and Resources

- ∉ No major criticisms of the team's leadership or expertise. They will be using a clinical project manager to run the trial, and they have some interactions with Batten disease patient advocacy groups. Though this is a single-center trial, there does seem to be a coordinated effort to get patients as early as they can.
- ∉ The applicants state that the vector manufacturer is an experienced viral vector CDMO with a scalable AAV platform and robust quality system. The reviewer is not familiar with the company but will take the statement at face value. The use of a CIRM Alpha Clinic is a positive attribute and can provide infrastructure, regulatory, operational, and clinical trial expertise. It’s unclear who will be doing the manufacturing, testing, and comparability work. Limited to no CMC depth exists on the internal project team or through a consultant to navigate a complex pathway with a comparability protocol pending execution.
- ∉ Significant concerns; apparent conflicts of interest on the team.
- ∉ Lacking. It’s not clear the team is qualified to conduct the study.

Population Impact

- ∉ The minimal recruitment plan is not realistic given the ultra-rare condition and anticipated challenges accessing patients.
- ∉ Generally, no concerns. This disease is not part of prenatal screening, so the team may have challenges in identifying new patients who could benefit from early treatment.

- The study will enroll children between the ages of 4 to 60 months. However, it is unclear how a 4-month-old would meet the criteria of being ambulatory.
- Some information is provided on outreach activities, including patient advocacy organizations and clinician networks, involvement of pediatric neurology and genetic practices. However, detailed recruitment and retention plans for the patients with this ultra-rare disease are lacking.
- A very brief description is provided about how provisions will be made to support bilingual patients and coordinate support for travel and housing. However, no information is provided on the actual catchment area that will be used for recruitment.
- While a natural history study is noted in the application, no information is provided on the demographic characteristics of the children who have this condition.
- Moderate overall.
- Very hard to determine the extent to which the project will have a potential impact across affected populations. The disease is extremely difficult to diagnose at all versus trying to diagnose it at an early stage. Therefore, impact on disease is difficult to predict, though given the neurodegenerative nature of this type of disease, progression may still occur. The reviewer recognizes this is not known. Overall, a clinical trial for this disease is appropriate for the target indication. The reviewer has no criticism regarding any of the demographics of the populations which have been defined. They have no criticism about outreach, engagement, enrollment, other than what I listed above. No criticisms found for addressing key barriers to care.
- Ultra-rare condition with an unmet medical need, unfortunately lots of scientific concerns.