CLIN2 AWARDS

3/26/26

$31,000,000 GWG RECOMMENDED

$31,000,000 CIRM TEAM RECOMMENDED

$92,000,067 AMOUNT AVAILABLE

								Score Range		Number of GWG Votes			
APP #	TITLE	BUDGET REQ	GWG Recmd	CIRM Recmd	SCORE (MEDIAN)	Mean	SD	Low	High	Y	N	Previous CIRM Funding	Disease Indication
CLIN2-19270	Advancing [redacted] for Mucopolysaccharidosis I: Clinical Expansion, Clinical Manufacturing and Release Testing	**$15,000,000**	**Y**	**Y**	**85**	86	2	84	90	13	1	Y	mucopolysaccharidosis I
CLIN2-19119	Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of a gene therapy for Pitt Hopkins Syndrome	**$8,000,000**	**Y**	**Y**	**85**	84	2	80	88	10	3	Y	Pitt-Hopkins syndrome
CLIN2-19416	Autologous iPSC-derived Retinal Pigment Epithelium Cell Therapy to Restore Vision in Blinding Eye Disease	**$8,000,000**	**Y**	**Y**	**85**	84	5	70	89	9	5	Y	blinding eye disease
CLIN2-19378	First-in-human trial for a novel epigenetic gene therapy for FSHD targeting D4Z4 epigenome	**$8,000,000**	**N**	**N**	**84**	83	3	80	88	5	10	Y	facioscapulohumeral muscular dystrophy (FSHD)
CLIN2-19191	A first in human trial of an engineered autologous vaccine to enhance relapse free survival in AML patients.	**$12,000,000**	**N**	**N**	**80**	81	4	70	86	4	11	Y	acute myeloid leukemia

Application #	CLIN2-19270
Title (as written by the applicant)	Advancing [redacted] for Mucopolysaccharidosis I: Clinical Expansion, Clinical Manufacturing and Release Testing
Therapeutic Candidate (as written by the applicant)	B cells will be isolated from patients with MPS I. These will be transposed with a normal copy of the gene and re-introduced into the patient.
Indication (as written by the applicant)	Mucopolysaccharidosis I (MPS I) is a rare disease that affects predominantly children. Untreated, these patients typically die by the age of 10.
Unmet Medical Need (as written by the applicant)	The approach of turning the patient's B cells into drug-producing B cells offers the promise of continuous and sustained delivery of therapeutic levels of alpha-L-iduronidase (IDUA). The resulting drug levels mimic normal physiological conditions, and can penetrate tissues that do not receive sufficient levels of IDUA.
Major Proposed Activities (as written by the applicant)	• Enroll 4 adults and 5 pediatric patients as part of a clinical expansion of an ongoing trial • Clinical manufacturing of drug product and release testing
Statement of Benefit to California (as written by the applicant)	Proposed research will advance a novel gene-modified B cell therapy for MPS I, a rare, fatal disorder with high unmet need. By supporting clinical expansion and manufacturing development, this work accelerates patient access to potentially transformative treatment. California benefits through improved public health, leadership in regenerative medicine, and economic growth from biotech innovation.
Funds Requested	$15,000,000
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: 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	86
Median	85
Standard Deviation	2
Highest	90
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

KEY QUESTIONS AND 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

- A key strength is that they are building on an already successful program.
- Key Strengths include: potential improvement over current enzyme replacement (ERT) therapy, significant preclinical mouse model data and the experience in the patients dosed thus far, favorable interactions with the FDA, approval by FDA for planned study, staged approach to increasing adult patients and then, if safe based on adult patient experience, moving to pediatric patients. The two institutions and PIs are experts in the field and pose the best chance for recruiting patients.
- Two adult patients have been dosed with the investigational product and it has been well tolerated, with only minor adverse events (AEs) to date.
- Key strengths:
    - Value proposition and unmet medical need are strong.
    - Non-viral gene transfer.
    - Established relationships with FDA.
    - Some clinical data from the first and second patient are presented.
- Strengths include:
    - A novel therapeutic strategy.
    - An experienced team.
    - Good preclinical data.
    - Solid CMC.
    - Significant and successful FDA interactions
    - Two subject first-in-man initiation of a Phase 1, thus far safe.
- Pre-clinical data, addressing of unmet medical need, FDA endorsement, positive initial clinical data, established clinical development endpoints and pathway.
- Last fall, the FDA granted Fast Track designation to the product for MPS I (Hurler-Scheie or Scheie phenotypes)
- The product uses autologous B cells to secrete IDUA continuously using a non-viral, scalable platform which would enable a favorable safety profile and practicality for broader clinical adoption since no myeloablative preconditioning and immunosuppression is required.
- A Type C meeting was held to address CMC manufacturing and safety concerns and another planned Type C meeting will be requested before BLA application. FDA Type C meeting last year endorsed the amended safety monitoring plan.
- Due to the rarity of patients having MPS I, the trial may serve primarily as a proof of concept that may be applied to other more common diseases.
- Weaknesses include: the ultra-rarity of the disease and thus the potential difficulty in recruiting patients; the fact that this therapy will not treat the central nervous system (CNS) component of the disease which is a major limitation, the potential for oncologic changes secondary to random insertion although this weakness is slightly mitigated by the preclinical mouse data, the clonal analysis in one patients and the literature review supporting the increased safety of the gene transfer system compared to other approaches.
- Key weaknesses:
    - There is no evidence that the B-cells can migrate through the blood-brain barrier and restore enzyme function in the brain tissue.
    - Due to ultra rare nature of the disease, the commercialization is risky.
    - With the market size of <100 patients per year, the commercialization is not attractive and may not be a profitable business.
- Weaknesses include:
    - Persistent concern with regard to potential for insertional mutagenesis.
    - Need for more detailed description of insertion site and clonal analysis of transduced cells.
    - Lack of strong cardiac and CNS efficacy data.
    - Lack of CNS access of cells or enzyme.
    - Potential for autoantibody formation against wild type IDUA.
    - Rarity of condition, narrow inclusion criteria, potential recruitment difficulty.
- Recruitment problems.

Value Proposition

- The proposal seeks to complete a Phase 1 clinical trial evaluating an engineered B cell therapy cleared for human clinical study, as a treatment for mucopolysaccharidosis type I (MPS I) (Hurler-Sheie and Sheie). The product inserts of IDUA in the genome of B cells ex vivo with subsequent intravenous infusion into patients. It does not require myeloablation or immunosuppression.
- The proposal seeks support for clinical expansion and completion of existing Phase 1 study in which two adult patients have been dosed by adding 4 additional adults and 5 pediatric
- Current standard of care is weekly ERT or hematopoietic stem-cell transplantation (HSCT) for Hurler with experimental approaches evaluating gene therapy and ex vivo modified autologous HSCT.
- There remains a considerable unmet medical need for MPS I despite current standard of care because of the ineffectiveness of standard of care for some disease manifestations which the product may improve upon.
- Value is present for MPS I as the current standard of care is not consistent across patients and have not shown long term improvement.
- Current therapies have shown to have limitations such as limited tissue exposure and weekly IV infusions for ERT and progressive respiratory and cardiac changes despite HSCT.
- This is a transduced autologous B cell product, expressing alpha-L-iduronidase (IDUA) for the treatment of the Hurler-Scheie and Scheie forms of MPS I. This plan is presented as an improvement over current standard of care, enzyme replacement therapy, which is prohibitively expensive, requires weekly infusions and has little therapeutic effect on the brain. It is also presented, reasonably so, as an improvement over hematopoietic stem cell transplant, in that myeloablative conditioning is not needed, and hence morbidity avoided.
- The value proposition of the proposed cell therapy is the improvement of clinical outcomes in patients with MPS I. Existing standard treatments (enzyme replacement therapy and HSC transplant) are not very effective, associated with toxicities and costly. Unmet medical need for new therapies remains significant for these patients. Since the proposed cell therapy does not require conditioning (myeloablation/lymphodepletion or immunosuppression), it is more feasible and it could not be limited to the large specialized medical centers.
- Given the current standard of care for MPS I patients - weekly ERT infusions or HSCT, it is expected that the proposed therapy would be acceptable and readily taken up by patients if it is proven safe and effective since the current therapy offers potentially less complications than myeloablative HSCT and is less of a burden on lifestyle as compared to weekly infusions for 3-4 hours for ERT.
- Current proposal has possibility of being a significant improvement of current standard of care because it offers the possibility of the therapeutic reaching difficult to access tissues (heart, musculoskeletal, but NOT brain) because of its consistent high level of enzyme expression as compared to ERT with its peak and troughs and inability to treat the difficult to reach organs.
- The product also does not require frequent weekly doses and could be potentially doses biannually or even longer.
- The product does not require immunosuppression or myeloablation.
- Lack of need for immunosuppression/myeloablation, a nonviral delivery approach and no need for frequent treatments (compared to ERT) means the current therapy may be more affordable and be able to be given to more patients.
- The product has potential as a proof of concept, addresses an unmet medical need, and also as a potential delivery platform for other disease states.
- The proposed therapy will not affect the brain or CNS pathology.
- Rare condition - recruitment is an issue.

Rationale

- The scientific rationale is sound. Experimental data support clinical development. The IND is cleared by FDA. The current study is an expansion of ongoing clinical trial.
- Two adult patients have been dosed, with the investigational product has been well tolerated, with only minor adverse events (AEs) to date.
- With prior CIRM funding, the sponsor was able to perform convincing rodent proof-of-concept studies that established limited efficacy in decreasing GAG burden in liver and musculoskeletal structures, but not in brain or heart. The sponsor then established CMC procedures and produced GMP-compliant product, obtained an IND approval and progress to a 2-patient safety trial, which revealed no sever AEs after initial, single dose administration, and decreased urinary GAG excretion. Sponsor now seeks funding for a 9 subject follow-on trial, comprising 4 adults and 5 pediatric (>10 years old) patients. They have already obtained FDA Fast Track designation to this effect.

- Under an FDA IND and through support from CIRM the group has dosed 2 adult patients with encouraging safety and some efficacy results which support the current proposal for expansion of the study to more adults and a pediatric cohort.
- Continued evaluation in additional patients to broaden what has been successful so far, encouraging expansion.
- The therapy is based on strong preclinical and a limited amount of clinical data previously supported by CIRM.
- The B cells are selectively enriched, activated, and electroporated with a transposon containing the IDUA gene. The transposed cells are differentiated toward plasmablasts capable of continuous high-level IDUA protein secretion which are then infused intravenously into the patient. This provides a systemic distribution to other organs although the penetration into the brain is hindered by the blood-brain barrier and the treatment may not reverse the disease-related harm on cognitive brain activity.
- In the MPS I mouse model, the group has performed extensive studies including toxicity studies, dose-range finding studies, long-term persistence of therapeutic effect studies and studies demonstrating the ability of the product to mitigate disease including: (1) Sustained tissue IDUA activity 6 months post treatment BUT they failed to show increased IDUA activity levels in the brain and heart – two of the important hard to reach organs with current therapy; (2) Reduction in GAG levels in key organs including heart but not brain; (3) Improvement in musculoskeletal phenotype.
- Sound. Older technology, not novel. Does not treat the brain defect.
- Solid approach with some manufacturing challenges.

Project Plan and Design

- The clinical study design to complete the Phase 1 to provide additional supportive evidence to move into pediatric population as well.
- The proposed studies are necessary and appropriate to drive clinical development and completion of a Phase 1 study. Specifically, the overarching objective of this CLIN2 program is to complete the clinical trial, expanding adult enrollment and initiating a pediatric cohort, clinical manufacturing and release testing. Under the prior award, 2 adults were enrolled and treated. This CLIN2 project will enroll 4 additional adults and 5 pediatric patients, complete the one-year primary/secondary endpoints, and maintain long-term follow-up.
- The project plan is straightforward and the product of long discussions with FDA. Sponsor proposes a 9-subject trial with a year's close follow-up of safety and efficacy parameters, with an extended 15-year follow-up of critical safety metrics.
- The project plan looks reasonable.
- Well-vetted group of vendors and consultants; sites and investigators are excellent.
- Concerns include: Random insertion still permits 3% of insertions into coding regions, and higher proportions into regulatory regions, both within and beyond the regions assessed by the sponsor. At the proposed dose and expected person size, roughly 10E8 cells might be expected to have transgene insertion in coding regions. Caution is thus in order. While the safety profile of the preclinical rodent studies, which reported no evidence of plasmacytoma or myeloma, is encouraging, as is that of the first 2 patients, much longer time courses of observation are needed to be sure of the benign nature of the transposition, especially as delivered to mitotically active plasmablasts prior to their plasma cell maturation. At the very least, the informed consent needs to be clear on this point.
- Long-term monitoring for autoantibodies against wild-type IDUA are needed; depending upon the subject's loss-of-function mutation, the expressed transgene might be immunogenic, and efficacy lost as a function of time.
- The lack of brain access of either the transduced B cells, their derived plasma cells or their expressed IDUA, limits enthusiasm for this strategy. This is presumably the reason for the sponsor's limitation of the study to Hurler-Scheie and Scheie, rather than the more severe Hurler form of MPS I, which is earlier onset and has more pronounced neurocognitive deficiencies. Nonetheless, Hurler-Scheie patients may also manifest cognitive deterioration, and a brain penetrant vector would be preferable to the proposed strategy.
- Recruitment may be a significant limitation, notwithstanding the centrality of the proposed clinical specialty sites. Because of the limitation for the study to Hurler-Scheie and Scheie, most MPS I patients will not be appropriate for this study. Since most studies estimate that 60-70% of MPS I cases are the more severe Hurler form, only 30% of an already rare population (generally estimated at appx. 0.7:100,000 births) would be potentially covered by this study's inclusion criteria; one may thus estimate incidence of 1-2/million live births, or <10 nationally per year.
- Minor point: The events table lists periodic optional CSF examinations, but there is no indication of what test will be done on that CSF. Since B cells can colonize the choroid plexus in normal subjects, the investigators may wish to seek evidence of B cell markers or released cytokines, as well as CSF IDUA activity and GAG

levels. • Appropriate risks have been identified and mitigation strategies also identified.
Project Team and Resources
• The sites and oversight is with Key Opinion Leaders in MPS and a top site for research that will ensure key feedback throughout the study. It would be good to consider additional sites for geographical availability to patients as rare disease can be difficult for caregivers as well to plan for travel. • The team is qualified and has all the necessary resources to perform the proposed work. • The team has the appropriate expertise and resources as is evident by the completion of the IND enabling work and the enrollment, dosing and following of two adult patients at the current time. • The team has shown the appropriate expertise and resources with an approved IND which allowed for the enrollment, infusion and substantial follow up data of 2 adult patients. • Good team. • Some budget concerns but overall positive review. • Team has done a good job of coordinating CRO resources to accomplish IND-enabling studies, IND approval and initiation of Phase 1. Team is largely based on contract research organizations and consultants; little in-house expertise, only modest in-house capability for validating or confirming CRO descriptions of product. Some budget redundancy by virtue of multiple CROs with sometimes overlapping functions. Descriptions or respective scopes of work could be clearer.
Population Impact
• The team appears to try to optimize patient enrollment and recruitment from California and beyond via, among other things, hiring a CRO that specializes in facilitating transport and housing of patients that would need to travel for treatment. • Target Population has high unmet long-term need for stabilization and improvement if disease progression is addressed early on. • The amended protocol incorporates FDA recommendations on pediatric dosing, functional endpoints. • The team is very cognizant that limitations of current therapies include the disruption of daily life required for weekly ERT and the costs of manufacturing viral based therapies. As such they highlight their belief that the nonviral approach and lack of need for weekly infusions associated with ISP-001 would make this therapy more accessible to patients. • Minimal. As noted, the Hurler-Scheie and Scheie forms of MPS I are extremely rare. At appx. 400,000 live births in California annually, one might expect a new case every year, so a state-wide prevalence in the low double digits, and a national prevalence of several score. The value of this study may lie more in its potential proof-of-principle of using transduced plasma cells as secretory sources for enzymatic disorders with predominantly peripheral visceral organ involvement. A focus on such disorders with less CNS involvement would be welcome. • Because the disease is ultra-rare, there is a high risk that the enrollment goal will not be achieved on time. • Somewhat limited impact for this very rare disease but broader platform usage has the potential for great population impact. • Concern exists because this subset of MPS I is an ultra-rare population. • Limited sites are proposed, and there was discussion on site expansion for better outcome data.

Application #	CLIN2-19119
Title (as written by the applicant)	Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of [redacted candidate name], a gene therapy for Pitt Hopkins Syndrome.
Therapeutic Candidate (as written by the applicant)	[redacted candidate name], an AAV9 gene therapy delivered by intracerebroventricular (ICV) injection.
Indication (as written by the applicant)	Pitt Hopkins Syndrome (PTHS)
Unmet Medical Need (as written by the applicant)	PTHS is a severe disorder characterized by intellectual disability, autism-like behavior, absent speech, motor impairment, seizures, constipation, and breathing abnormalities. Current care is symptomatic with modest benefits. Patients experience lifelong dependence and significant caregiver burden.
Major Proposed Activities (as written by the applicant)	• Phase 1-2 study enrollment • Phase 1-2 study conduct (first patient in through last patient out) • Phase 1-2 database lock and topline study outputs • Biomarker identification and validation • Early payor pricing research and updated revenue forecast model
Statement of Benefit to California (as written by the applicant)	It's estimated that 1:50,000 children are born with Pitt Hopkins syndrome To date, with the help of the [redacted foundation name], [redacted company name] has identified more than 60 in CA with an ongoing effort to diagnose additional patients in CA. [redacted company name], a California company is collaborating with partner organizations & vendors in our state and selected clinical trial sites in California. Our efforts will support identification and inclusion of California families in the pursuit of a therapy.
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: 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	84
Median	85
Standard Deviation	2
Highest	88
Lowest	80
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

KEY QUESTIONS AND 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

- There is presently no disease-modifying therapy for TCF4-related (Transcription Factor 4) neurodevelopmental disorder (NDD), and no on-label treatments for this disorder aside from symptomatic treatments. Therapies currently in clinical trials do not address the fundamental genetic mechanism of the disorder.
- Like many rare diseases, it appears the therapeutic landscape is symptom based and nothing currently available to treat the root cause of the disorder – TCF4 deficiency, by directly augmenting TCF4 protein levels, which this product can potentially provide.
- TCF4-NDD is caused by haploinsufficiency; therefore, an AAV9 based gene replacement strategy is compelling for treatment of this disorder. The proposed product is particularly interesting given the auto regulatory nature of its promoter. TCF expression would be expected to down regulate mRNA production from the transgene, as was seen in the preclinical studies; therefore, over expression risks should be minimized.
- Strengths include- AAV9 is an established delivery system and DP uses an established Route of Administration (RoA). [redacted candidate name] is a product that restores TCF4 expression, treating the cause of Pitt Hopkins Syndrome (PTHS). Single administration with possibility of long term, persistent repair. Use of an autoregulatory E box promoter DP inventory for clinical study is quality released and available for distribution. IND is cleared to proceed.
- Readiness for the Phase I portion and having sufficient team and resource brings strength to the program.
- Very rare but have access to sufficient patients.
- Clear value in treating patients with an unmet medical need; sound CMC approach and potential for lower cost of goods sold (COGS); key concern was around expression, but experts viewed this as a positive approach with the e-box element.
- Given the absence of natural history study data or biomarkers in this disorder, more objective measures of neurological functioning (for example, GMFM-88) at baseline and in follow up would be helpful for assessing neurodevelopmental efficacy in addition to the proposed patient reported outcome measures. The chosen measures should not suffer from floor or ceiling effects based upon the developmental capabilities of the average patient with this disorder.
- This is a disorder with great clinical need, but potentially higher risk in the ability to regulate dosage.
- The concerns about risk/benefit for this patient population were powerful and should be part of the consideration and planning process for this product candidate.
- Weaknesses include that AAV9 is a vector that carries risks such as pre-existing immunity and off-target effects. Product carries the risks of the potential for insertional mutagenesis and over expression of TCF4 protein.

Value Proposition

- Since current therapies address symptoms, there isn't a reprieve for patients, caregivers, or the healthcare system managing and taking care of this patient population. This therapy is also a single administration, so there would not be any repeat or prolonged treatment burden. If efficacious, this could be a great relief to the burden and severity of symptoms that affect this population and those who care for them.
- There are no FDA-approved disease modifying therapies, therefore a treatment that reverses a loss of function genetic defect can fill this need. Patients with restored TCF4 expression would incur a reduced treatment burden from caregivers and providers. Payors would cover fewer services and medications although the upfront cost for a single-administration gene therapy will have to be compared to/offset by the economics otherwise incurred by an afflicted patient.
- Unmet need along with proof of concept for AAV9 already being in place would give way to improvement in healthcare utilization if successful.
- [redacted candidate name] is an experimental one-time gene therapy designed to fix the underlying genetic problem in PTHS. Early laboratory studies suggest it could improve communication, movement, learning, and behavior. Even small improvements could greatly increase independence and quality of life for individuals with PTHS and reduce the lifelong caregiving burden on families. Given the severity of PTHS and the lack of effective treatments, the potential benefits are considered meaningful and important.

- Compelling value.
- Very well designed study to rescue haploinsufficiency in Pitt-Hopkins syndrome, a rare neurodevelopmental disorder with profound structural and synaptic defects that lead to cognitive, neurobehavioral and seizure manifestations.
- Importantly, the investigators make a strong case that post-natal rescue (through the delivery of a regulated transcription cassette expressing TCF4B which is the transcription factor that is haploinsufficient) could lead to meaningful functional improvement. Note that the lack of TCF4B leads to pre-natal structural abnormalities in the brain and systemically (classic facial abnormalities). So, these aspects of the disease cannot be corrected with post-natal restoration. But the synaptic simplification could. And the delivery of the expression cassette that autoregulates the transcription factor (not too high, not too low) is smart.
- The therapy has the potential to provide a meaningful and substantial improvement to the intended population with a demonstrated approach for safety and efficacy using an AAV9 vector; a question remains on the safety of the gene being delivered. There is a clear unmet medical need as I could not find any treatments to treat the underlying cause; the disease does create a high burden on patient, caregivers, and the health system. I do believe the therapy can potentially have sufficient uptake with patients, caregivers, and health providers based on the anticipated lower cost relative to other gene therapies due to the intracerebroventricular (ICV) RoA; the open question will be the benefit observed in relation to patient age and the practicality of developing/approving this therapy as it will be a small patient population that (for rare disease) has historically been troubled with creating a viable product.
- There is presently no disease-modifying therapy for TCF4-related neurodevelopmental disorder (NDD), and no on-label treatments for this disorder. Therapies currently in clinical trials do not address the fundamental genetic mechanism of the disorder.
- There is significant unmet need in this patient population, with the average patient requiring lifelong care given the significant disabilities associated with this disorder
- Any therapy in this space would be welcome. Unfortunately, the foundational natural history knowledge is insufficient to safely plan a trial in this rare disease.
- Reference in the clinical rational section of the proposal to Zolgensma leaves me uncertain about the uptake feasibility of the payors.

Rationale

- The Pre-IND had positive feedback and agreement from FDA. Since they received the ok to proceed notice from the FDA post IND review, it is assumed the rationale and study results met requirements and are appropriate to justify the proposed therapeutic approach and route of administration. This reviewer would like to see the response to Pre-IND material that point to how they addressed FDA feedback within the IND application.
- The scientific rationale is sound because [redacted candidate name] uses a gene replacement strategy to eliminate the impact of a loss of function mutation by normalization of TCF4 expression. The design of [redacted candidate name] is rational, using a known vector, known route of administration (ICV/CNS) and payload that contains a promoter that restricts expression to TCF4-responsive cells. Animal data (TCF4 mouse model, a large animal model) and patient-derived organoids constitute a data set that demonstrate safety and disease amelioration.
- Clear unmet need with severe cognitive impairment and high seizures that modifying the disease vs addressing the symptoms is a clinical rationale.
- ICV one time injection of this AAV9 based therapy is smart. Maximizes local CNS delivery and minimizes delivery outside the brain.
- Sound clinical trial design, including immunosuppression. Good safety profile in large animal model.
- Scientific approach seems sound and this reviewer appreciates the lower doses due to the ICV RoA, however regulation of expression will be important for safety and efficacy. Precedent established in approach (ex. Rett syndrome by Taysha) using AAV however this reviewer is not a clinical expert. *In vitro* and *in vivo* mouse study outcomes provided supporting potential for therapy.
- TCF4-NDD is caused by haploinsufficiency; therefore, an AAV9 based gene replacement strategy is compelling for treatment of this disorder. The proposed product is particularly exciting given the autoregulatory nature of its promoter. TCF expression would be expected to downregulate mRNA production from the transgene, as was seen in the preclinical studies; therefore, overexpression risks should be minimized.
- The efficacy measures were insufficiently supported by natural history. It is unknown how these measures change over time.

Project Plan and Design

- N=12 enrolled in one year could be a challenge. The at home health assessments to reduce travel to surgical sites is a good strategy to lessen the burden of participation for the caregivers and study

participants.

- Data from twelve patients should be sufficient to assess safety however, given the rarity of the disease, completing enrollment within 1 year may be a challenge. Use of multiple clinical sites should mitigate risk of slow enrollment. There are no DP supply constraints for Phase 1 since all clinical inventory is available for treatment use. It's unclear whether a qualified potency assay will be in place (satisfactorily accepted by FDA) when DP for Phase 2 / 3 patients is planned for release not later than Q3 '27. The ex-US regulatory strategy lacks detail, in particular, whether there will be a fast follow-on or parallel MAA.
- Project Plan and design is appropriate for starting in Phase I.
- No natural history studies. Not enough infrastructure/rationale for the planned Phase 2 work.
- Overall, little concern with proposed activities; timeline may be delayed due to clinical enrollment as this is a rare disease with a potential additional impact of drug product stability.
- The majority of individuals with TCF4-NDD eventually achieve independent ambulation or ambulation with assistance; therefore, the chosen measures should not encounter a floor effect when assessing motor skills, as plagues some complex genetically based NDDs.
- Given the absence of natural history study data in this disorder, more objective measures of neurological functioning (for example, GMFM-88) at baseline and in follow up would be helpful for assessing improvement in addition to the proposed patient reported outcome measures.
- Concerns about the close spacing in dosing. This will affect both immune response monitoring as well as the broader concerns with dose-effects in this rare disease.
- Unclear if there is any reasonable expectation of benefit in symptomatic patients.
- It is unclear how target engagement will be measured. This is critical.

Project Team and Resources

- Experienced team with relevant experience.
- [redacted company name] appears to have the appropriate team and expertise and is reliant on experienced vendors for CMC, analytics and Clinical Operations, supplementing their intellectual resources.
- There are no concerns about the Team and resources.
- Good team, well resourced.
- No concerns with the team or staffing, however, would be good to understand agreement with manufacturing party if a resupply is required as current vendor is not available. Expertise heavily in the gene therapy space amongst leadership with a proven track record, which is a strong positive. Sound, well established testing partners; unsure of the status of CMO.
- This reviewer does not have concerns about the sponsor’s potential for being able to conduct this study. The gene therapy product has already been manufactured in a quantity sufficient for this study. A CRO has been identified, as have trial sites and PIs, all of whom have appropriate expertise in TCF4 and/or gene therapies. The FDA has signaled approval for the general study design and for the design of the preclinical studies and their results.
- Well poised team and engaged advocacy partners.

Population Impact

- Well planned. Access and Affordability well addressed.
- This therapy appears to move the treatment options from symptom management only to symptom improvement or reduction in severity or progression of symptoms if efficacy is successful. This would be a great achievement for this patient population and the caregivers. It will be interesting to see the differences in outcomes between early and mid-childhood participants, the adolescence, and the young adults.
- Applicant understands the target indication and patient population.
- This seems to be something that would improve patient and family day to day care which would have a significant impact.
- Because PTHS is so rare (fewer than 500 cases in the US, 60 in California identified to date), there isn't much detailed population data available. The team understands that they will allow anyone who meets qualifications to take part.
- The study is going to record who enrolls, not as a means of joining, but to learn more about the population/demographics of the indication. Enrollment info will be used to improve future studies and the outreach.
- Team will work with a foundation and include community meetings, materials and a website.
- Two protocol advisory board meetings provided input into study design - worked with community to raise awareness of the trial. More community meetings were planned for late 2025 (not sure if these happened).
- Travel, lodging and meal support will be covered, using prepaid arrangements whenever possible.

- Home health vendor will conduct study visits in participant's homes for medically complex participants.
- Navigation - each family will be assigned a study coordinator and travel concierge.
- Reimburse reasonable out-of-pocket costs related to participation (e.g., local transportation, meals, dependent care, lost wages). These measures are designed to mitigate the logistical and financial challenges commonly faced by caregivers participating in complex gene therapy studies.
- Primary concerns exist in patient population size, diagnosis of patients, access to patients, and window to practically treat. It is uncertain how long patient enrollment will occur and at what window (of age), therapeutic effect will take. It will be difficult, long term, to identify the right patients early to then treat and allow a scientifically successful product.
- The sponsor appears to have a reasonable understanding of the disease process and co-morbidities, as evidenced by the preclinical data and the conduct of a disease concept model through structured interviews with 30 caregivers in partnership with the Pitt Hopkins Research foundation
- Therapies would be welcome in this space.

Application #	CLIN2-19416
Title (as written by the applicant)	Autologous iPSC-derived Retinal Pigment Epithelium Cell Therapy to Restore Vision in Blinding Eye Disease
Therapeutic Candidate (as written by the applicant)	Autologous iPSC-derived retinal pigment epithelium cells in suspension
Indication (as written by the applicant)	Retinal conditions resulting in dysfunction or death of the retinal pigment epithelium in the macula (e.g. GA-AMD, Stargardt, Reticular Pseudodrusen)
Unmet Medical Need (as written by the applicant)	About 300 million people worldwide suffer from vision loss from RPE-mediated maculopathies (RMMs), leading to reduced independence, higher rates of depression, dementia, and fall-related injury, and major socioeconomic costs. No approved therapy currently improves vision for these diseases.
Major Proposed Activities (as written by the applicant)	• Conduct first-in-human safety study in patients with RPE-mediated maculopathies (RMM) • GMP manufacturing for FIH study
Statement of Benefit to California (as written by the applicant)	This research will advance a novel regenerative therapy for vision loss, fostering California's leadership in stem cell innovation. It will create high-skill biotech jobs, strengthen academic–industry collaboration, and ultimately benefit Californians by addressing blindness that limits independence and quality of life.
Funds Requested	$7,886,551
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	84
Median	85
Standard Deviation	5
Highest	89
Lowest	70
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	9
Tier 2 (1-84): Not recommended for funding	5

KEY QUESTIONS AND 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

- Scientific rationale and preliminary data clearly support this proposed clinical trial.
- The trial will extend to a greater number of patients with RPE-mediated maculopathies (RMM).
- Strengths: Strong science and differentiating aspects of technology making it a very promising therapy for patients with RMM.
- Significant disease.
- Key strength is including the extensive endpoints and data gathered.
- Excellent safety and durability plans.
- The product is a single dose therapy.
- Well-designed Phase 1 clinical trial.
- Appreciated the use of the contralateral eye as a control.
- Team is highly qualified to carry out the Phase 1 trial.
- External data safety monitoring committee will be established to do real time monitoring of safety, as well as monitoring at appropriate intervals.
- The very long manufacturing process raises questions about feasibility. It is unclear what the manufacturing success rate will be. Product release failures will have a severe adverse impact on the timeline.
- Weakness is their timelines and ensuring that all is completed and have consistency in capture and review. I don't believe there is readiness for what is actually needed for execution and management.
- Weaknesses: challenges with autologous manufacturing and associated long timelines may mean that some patients will drop out.
- Manufacturing of the drug product involves three GMP-compliant steps. According to the timetable presented, these activities will take anywhere from a year to a year and a half to produce. There is no allowance for manufacturing failures/patient drop-off due to progression of disease. No interim disease management is proposed.
- No plans for comparability to shift to a second clinical trial site, but this may not be a show stopper for this early stage project.

Value Proposition

- Degenerative diseases of the macula are significant clinical conditions that effect more than 300 million people worldwide. Approximately, 1.2 million people will have retinal pigment epithelium-mediated maculopathy.
- This condition is one of the leading causes of irreversible blindness.
- Condition has a significant negative impact on patients' ability to function and quality of life.
- The proposal contains an extensive access and affordability plan done by SciVida. Findings suggest that the two prioritized rare indications (i.e., Stargardt disease and Best disease) will have an easier path to market access.
- No information was provided on an evaluation of patients' acceptance of the study protocol. The investigators should consider meeting with patients to discuss retention strategies for the time between the skin biopsy and the intervention.
- Value proposition is high. If successful, this approach has potential to treat many patients with RPE-related degenerative macular disease (RMM) - which represent a clear unmet medical need. Key differentiating factor is strong science and an approach which uses autologous iPSC-RPE therapy, reducing the need for immunosuppression - greater patient uptake.
- No current curative Standard of Care so to be able to at a minimum preserve is value
- This program could help with more than vision but also falls and ability to better self care which adds value to healthcare overall
- Large target patient group.
- Long manufacturing time may limit retention.
- AiPSC-RPE represents an advanced approach to supporting patients with RMM. If successful, this product could prevent disease progression in patients with RMM, which could prevent permanent blindness. There are currently no approved therapies to prevent disease progression in these patients, and therefore this product would be a significant advancement over the current standards of care.
- RPE-mediated maculopathies represent a major public health burden, affecting an estimated 300 million individuals worldwide by 2040.
- The current standard of care for patients with advanced maculopathy and RPE loss remains limited to

disease monitoring and rehabilitation through optical aids.
Rationale
• Scientific rationale is clearly stated in the proposal. • This Phase I safety trial is supported by findings from studies that received previous CIRM funding. • Clear and robust scientific rationale. First-in-class and best-in-class product - very promising. Strong pre-clinical data is presented in multiple rodent models including good safety profile, demonstration of RPE integration (correct polarity) and potentially some functional benefit. Appropriate route of administration - sub-retinal delivery. Minor concern - Specify that patients will undergo a surgical procedure including a vitrectomy throughout the proposal (At times it is called an 'office' procedure. No need to downplay.) Previously funded by CIRM Translational Grant and early clinical grant (CLIN1). FDA approval to proceed to next stage. • Translational feasibility is present and shown ready for clinical development If successful it could provide treatment for additional blinding disorders. • Strong science and pre-clinical data with safety and efficacy. • Appreciate the repeated pre-treatment data during the prolonged manufacturing period. • Very strong rationale and good nonclinical program. • The rationale appears sound and the IND was accepted such that the Phase 1 study may proceed. • In vitro potency assays confirm high transepithelial resistance, polarized secretion of VEGF and PEDF, and robust phagocytic activity toward labeled photoreceptor outer segments, demonstrating that AiPSC-RPE cells retain the structural and functional properties of native RPE required for retinal homeostasis. • In vivo studies demonstrate that transplanted AiPSC-RPE cells survive long term in the subretinal space, integrate with the host RPE layer, and form a stable, pigmented monolayer that supports photoreceptor preservation. • The inclusion of a supratherapeutic dose equivalent to more than four times the proposed clinical level using immunocompromised nude rats provides robust preclinical justification for the safety of the intended human dosing regimen. • Animals injected with 100% RPE cells or with RPE-dominant mixtures (≥90% RPE) showed no tumor formation, demonstrating the non-tumorigenic, terminally differentiated nature of the AiPSC-RPE product.
Project Plan and Design
• Well-designed Phase 1 clinical trial. • Team is highly qualified to carry out the Phase 1 clinical trial. • This is a Phase I trial with an IND that has been reviewed by FDA and received a “safe to proceed” clearance to advance toward clinical testing. • Complex study, but nonetheless well designed. Phase 1 trial - appropriate dose escalation, number of patients (12), initially one site - all good. Endpoints are sound - appropriate safety measures and secondary outcomes. Objectives are achievable within the proposed timeline. The idea to recruit patients initially who then have to wait >12 months for treatment due to the cell manufacturing timeline may result in some dropouts. • Risks and contingency plans are detailed and appropriate. • Minor concern: Is 3-weeks safety data long enough? I would suggest extending this period to 6-8 weeks when early signs of fibrosis/retinal scarring could also be picked-up. I would also suggest DSM to review all data up to that point not just 3-week safety data for that cohort. • The CRO readiness time seems short (2 months) with lab readiness, database, and any specialty vendors needed for endpoint collection or to read it would typically be 3-8 months. • External data safety monitoring committee will be established to evaluate the conduct and safety of the trial at appropriate intervals. • Strong emphasis on safety monitoring and detailed inclusion of DSM plans. • The safety plan for oversight and dose escalation needs to be more robust with external subject matter experts for the DSMB. With three subjects being dosed before a DSMB review, there should be criteria other than dose limiting toxicity that would trigger abnormal response if any that would bring the DSMB together sooner if needed. • Indicated in title that it would be multicenter but only one center planned, what is the plan for additional sites and when? • Will there be a stagger in the first 3 patients and if so will there be an internal safety review after the first patient dosed? • The endpoints will need planning for parameters for imaging and central read so there is consistency in the

data captured.

- Aggressive timelines.
- Challenges with the prolonged manufacturing.
- It would be useful to define in process testing and CQAs so that products that are destined to fail can be defined early and additional participants enrolled.
- Manufacturing of the drug product is long and tedious which may result in patient drop-off. No contingency for manufacturing failures.
- Manufacturing is intended to be extended to two sites during the course of the trial. Biocomparability of the drug products from the two sites has to be established and it is not clear in the proposal on how and when this will be done.
- At a high level, the activities appear appropriate however the details and timing are problematic. Six autologous lots are slated to be manufactured at one site, while the timeline does not indicate this. With a manufacturing process that takes approximately 10-11 months, it is unclear if these will be manufactured simultaneously or concurrently, and how this may affect the overall timeline for patient treatment.
- In addition, 6 additional lots are slated to be manufactured at a second site. There is no detailed plan to perform a comparability study for the site change, nor how this activity will impact the timing for treating the final 6 patients.
- It is advised that if the first dose level is expected to be efficacious then the term would be Dose Level 1, 2, 3, and avoid low, medium, and high.

Project Team and Resources

- The approach to conducting this complex trial is clearly described.
- Appropriate resources are available to conduct the trial.
- Contingency plans for potential problems are clearly specified.
- Excellent team and resources. No doubt of their ability to execute this project.
- The Core Team seems established and will be good to ensure a diverse DSMB, a CRO that can centralize the data and provide vendor oversight to ensure real time data availability. A training plan will be important for all personnel.
- Well poised team.
- The inclusion of expertise from both named institutions would be very beneficial to the Phase 1 trial.
- Really only one center is planned. CMC team is weak.
- The proposed teams have proven capabilities in manufacturing and testing, however the applicant may be somewhat naive in the aggressive plans and timelines.
- CMC challenges are noted, and perhaps more detail to increase confidence that they can successfully deliver on manufacturing the product would be beneficial.
- Timeline leaves no room for error. May need to define alternative pathways in case of manufacturing failures.

Population Impact

- The epidemiology of the target condition is clearly described.
- Huge impact.
- Macular disease-RPE with first in class product.
- It would be ideal in future phases to evaluate who would be eligible (responders vs non-responders). With the prolonged observation period during manufacturing, this is a natural time period to capture for trajectory comparability.
- This product could prevent disease progression in patients with RMM, which could thereby prevent permanent blindness. There are currently no approved therapies to prevent disease progression in these patients, and therefore this product would be a significant advancement over the current standards of care.
- Targeted recruitment is appropriate for a Phase 1 study.
- Investigators will provide resources to patients and family caregivers during the trial (i.e., transportation, lodging, meals).
- Applicants demonstrated good understanding of the affected population, and macular degeneration burden on health-care and society. The trial aims to address this.
- Expanding to a second manufacturing site and other clinical sites is timely and appropriate for the trial stage to increase access and demographic groups.
- Patients will be appropriately genotyped for diagnosis where indicated.
- Exclusion criteria for ocular disease is wide but appropriate. Point 34 - what is the rationale for 3 months

window? (Participation in another experimental therapeutic protocol within 3 months before baseline and during the study period). Should any patients with previous cell, gene or RNA therapy to that eye be included?

- The population goal approach is good but the applicant should consider a pediatric approach once first in human in adult is established.
- Comparison of product manufacturing at a second site will address early on biocomparability studies which would prove to be helpful for the BLA application.
- The trial will provide the ability to select 3-4 orphan indications for next registrational trial.
- Early development of potency assays addressing both structural and functional properties of the product will be beneficial for BLA application success.

Application #	CLIN2-19378
Title (as written by the applicant)	First-in-human trial for a novel epigenetic gene therapy for Facioscapulohumeral Muscular Dystrophy (FSHD) targeting D4Z4 epigenome
Therapeutic Candidate (as written by the applicant)	The therapeutic candidate is a gene therapy designed to modulate the expression of the DUX4 gene, a gene involved in the development of Facioscapulohumeral Muscular Dystrophy (FSHD)
Indication (as written by the applicant)	Facioscapulohumeral Muscular Dystrophy (FSHD)
Unmet Medical Need (as written by the applicant)	Facioscapulohumeral Muscular Dystrophy (FSHD) is a rare, complex, and disabling neuromuscular disorder characterized by progressive skeletal muscle degeneration and weakness, significantly impairing the patient's quality of life. Currently there is no cure for FSHD and only palliative care is available
Major Proposed Activities (as written by the applicant)	• Manufacture a cGMP batch and complete Chemistry, Manufacturing, and Controls activities. • Develop and validate a potency assay and biomarker assays to support clinical development • Complete a Phase 1/2 study in FSHD Patients
Statement of Benefit to California (as written by the applicant)	Developing the proposed therapy will strengthen California's leadership in gene-therapy innovation, create high-skill biotech jobs, and attract new investment to state labs and manufacturing sites. Success will give Californians affected by FSHD a first disease-modifying treatment, reduce lifelong healthcare costs, and expand the state's tax base through commercialization revenues.
Funds Requested	$-9,157,394
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: 84

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	83
Median	84
Standard Deviation	3
Highest	88
Lowest	80
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	5
Tier 2 (1-84): Not recommended for funding	10

KEY QUESTIONS AND 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 is an AAV approach for Facioscapulohumeral muscular dystrophy (FSHD) with a novel epigenetic approach.
- This is a very thorough plan with excellent sites and oversight.
- The first in human work is a strength.
- Unique technology is worthy of support.
- Potential concern for low efficiency with proposed approach given dose limiting toxicity in preclinical data.
- Nonclinical tox findings may limit dosing.

Value Proposition

- FSHD is a rare disease with high unmet need. The proposed epigenetic silencing CRISPR-based gene therapy is a novel approach that, if successful, would have a compelling value proposition. The high proposed manufacturing cost of $5M/1000L, which generates 7 doses, coupled with the anticipated $3M per-treatment pricing, does raise concerns about the ability of this product to be accessible to patients.
- Currently, only invasive procedures can provide some improvement, and only for select patients, so the value is high if there is the possibility of slowing or halting disease progression to avoid being wheelchair bound, which increases healthcare and caregiver costs.
- FSHD has high unmet need and there are no curative therapies; numerous investigational therapies appear to be under development.
- Significant patient group.
- FSHD is a genetic neuromuscular disorder characterized by contraction of a genetic region upstream of DUX-4, leading to de-repression of DUX4. DUX4 should only be expressed in early development, and its aberrant expression in myofibers and satellite cells in muscle leads to muscle injury, aberrant differentiation, and the clinical manifestations.
- This approach seeks to re-repress DUX4 by using an AAV with a dead Cas9 and an epigenetic silencer to methylate and silence the promoter. It has the advantage that it is a "hit-and-run" AAV approach, meaning that once the new methylation pattern has been achieved, the silencing construct is no longer needed and that methylation status is likely to be maintained through cell division. This is beneficial because muscle is a mitotic tissue, and if the silencing construct were required to be active for long periods, cell division would impact efficacy.
- A safe, targeted therapy for this rare progressive disease would be of incredible value for the community.
- CIRM should be supportive of novel technologies like this. This has potential as a one-time therapy.
- There do not seem to be any other epigenetic approaches for treating this disease.

Rationale

- Due to only palliative care being available for this disease, this novel therapeutic gives an opportunity for improvement in progression by targeting the gene itself.
- From a CMC perspective, the manufacturing schema is sound. A reputable manufacturing CDMO is being used with a standard AAV process. A large part of the requested grant funds will be used to fund a 1000L clinical production lot at the CDMO, to set up and execute process development in house to improve yield and therefore reduce cost, and to design and receive regulatory feedback on a comparability plan for material generated with the new process. There are very few details given on what parameters will be the focus to improve yield and therefore decrease cost.
- The rationale is sound.
- Several limitations: first, the AAV is likely to transduce only a fraction of muscle fibers. Since DUX4 reactivation is a stochastic process, any untransduced cells will continue the disease process and will not be "protected." In terms of the number of myofibers transduced, literature suggests ~50% or so in mice, which is probably a high-water mark (and may be lower in humans), and this limits enthusiasm.
- The AAV the applicants will use does not get into satellite cells, and this is a problem in that asymmetric division of satellite cells is impaired in this disease.
- In order to get even that myofiber coverage, they have to go to >10^{14}/kg, which is clearly associated with

toxicity and safety liabilities. Their tox does not support that, and the clinical doses are in the 10^{13} range, which is more likely to be safe but less likely to achieve the myofiber coverage needed to be disease modifying. • They had a complete response letter with the initial IND and had to redo tox studies to find a more relevant NOAEL, which they did with immunosuppression. This still suggests a narrow therapeutic window, limited to lower doses. • Appreciate the muscle biopsies to look at target engagement and distribution. • It is unclear how or which safety and biopsy go/no-go criteria will be applied. • Strong selection of clinical outcome assessments. • The applicant conducted robust nonclinical development program and extensive interactions with FDA; applicant successfully addressed all FDA concerns and was able to open an IND. • Preclinical pharmacology investigations are limited by lack of suitable animal model; the applicant pursued studies in a humanized xenograft mouse model as well as numerous in vitro studies; approach appears sufficient and FDA cleared proposed clinical trial to proceed. • There are some concerns across entire class of intravenously administered high-dose AAV products. The proposed dose level range in clinic appears to be relatively low and not at the upper limit. The applicant conducted a relatively robust nonclinical toxicology program including 6-month IND-enabling study and is below NOAEL. • There are sufficient data to support scientific rationale and initiation of human clinical testing
Project Plan and Design
• This program has a robust study design and plan along with solid selection of specialty labs and oversight. • The CMC plan appears reasonable, however activities (and therefore cost) are predominantly in the first two years of the grant. Staff funding is requested for all three years. Given that two patients have already been treated at the first dose level it might be better to have some CMC activities gated on clinical read-outs if feasible. • Overall, the plan is good. Gene delivery seems to be an issue. • The clinical trial is ongoing with the first three patients already dosed. There is no report of the status of those individuals (safety and/or efficacy); reviewers should see some evaluation of those data prior to funding.
Project Team and Resources
• It would be good to see a training plan and a lead that will coordinate between the CRO and labs. • Assurance that any data protection is included in the plan as outside-US sites are being used. • The project team appears appropriate. • Good team and resources. • Excellent teams and expertise.
Population Impact
• With over a million patients potentially being treated once shown safe and efficacious it would be a first for this disease to stabilize or slow disease progression. • The population is typically challenging for a rare disease. The trial does have a large number of sites proposed including two in Australia with no information given about the regulatory/clinical plan for those sites and if the cost is included in the CIRM budget. • High impact. • Progressive, severe disease with no therapeutic options.

Application #	CLIN2-19191
Title (as written by the applicant)	A first in human trial of an engineered autologous vaccine to enhance relapse free survival in AML patients.
Therapeutic Candidate (as written by the applicant)	A universally applicable AML vaccine made by genetic engineering of patient AML and designed to boost anti-leukemic immunity and reduce relapse.
Indication (as written by the applicant)	AML in patients in remission, ineligible for intensive chemotherapy or stem cell transplantation, who face frequent relapse and poor overall survival.
Unmet Medical Need (as written by the applicant)	There is an unmet need for safe and effective immunotherapies to prevent relapse in AML patients ineligible for high-dose therapy. The candidate is a personalized vaccine designed to target residual AML that could be used to treat outpatients, thereby increasing access for Californians without other options.
Major Proposed Activities (as written by the applicant)	• Clinical Trial Execution and Oversight • GMP Manufacturing of the candidate • Patient Outreach, Enrollment, and Retention • Immune Monitoring and Potency Assay Development • Data Management and Regulatory Support • Strategic and Commercial Readiness Planning
Statement of Benefit to California (as written by the applicant)	Our vaccine candidate for AML offers a scientifically rigorous, practical and economically sustainable solution to an urgent unmet need in AML care. Developed for the varied patient population in California, our vaccine meets CIRM goals by delivering an innovative, accessible, and scalable regenerative medicine therapy ready for clinical evaluation. CLIN2 support will enable a first-in-human study of this therapeutic candidate, advancing CIRM's mission to accelerate therapies that improve lives and build a stronger regenerative medicine infrastructure.
Funds Requested	$12,000,000
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	81
Median	80
Standard Deviation	4
Highest	86
Lowest	70
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	4
Tier 2 (1-84): Not recommended for funding	11

KEY QUESTIONS AND 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

- Key Strengths: The autologous approach serves a population with limited options for staying in remission (there are no approved immunotherapies). It leverages known post-HSCT biology for measurable residual disease (MRD) eradication. The drug design contributes to T cell activation and stimulation of NK/T cytolytic activity.
- Key Weaknesses: Autologous patient screening failure rate based upon transduction results may be higher than expected. CMC is complicated and variable in yield. The single institution study may not scale. Potency assay strategy and related tasks lack detail.
- The targeted condition, acute myelogenous leukemia (AML), is in need of novel therapies, and the preliminary data are supportive of the product. However, the limited clinical efficacy of other autologous vaccine approaches for this disease raises concerns. It is not clear that this candidate provides significant advantages over these other products.
- The clinical trial is limited by the omission of discussion around possible allogeneic bone marrow transplant following induction of remission, with up to 30-40% of patients becoming eligible for this curative procedure based on studies at other institutions.
- It is clear that there will be a no-go if the product is deemed unsafe, but it is not unclear what a go signal would be. The immune monitoring studies should not be used as a surrogate for clinical activity; these have failed to have clinical relevance in many other immunotherapy trials. One potential approach could be a small safety run-in trial (as is already proposed) followed by a randomized trial with no vaccination as the control.
- Key strengths: Well-outlined value proposition - Increasing patient access through engagement of oncology community clinics - Solid rationale, and convincing preliminary data.
- Key weaknesses: Deployment of the proposed cell therapy looks complex at the clinical site. The final DP requires re-packaging and irradiation at the administration site.
- There are already vaccines for AML.
- Concerns about interpretability of the data and enrollment.
- The proposed dose levels are likely to be well-tolerated, so that the study is unlikely to identify a maximum tolerated dose. A randomized control group should be feasible, and could substantially improve the interpretability of the study efficacy results. As the study is currently designed, the study results will probably offer little evidence to support a subsequent go / no-go decision regarding further development of the product.

Value Proposition

- Finding new therapies that do not require chemo and or invasive procedures would be an advance for the community and healthcare overall.
- While AML has had some success in being treated or mitigated, older patients and those ineligible for transplant are particularly impacted with no real solutions in relapse cases. There is therefore a strong case for benefit for an autologous vaccine that could prevent relapse. HSCT ineligible patients also experience more frequent relapse due to persistence of minimal residual disease (MRD) and the absence of leukemia-specific immune surveillance.
- The proposal will clinically investigate a tumor cell-based vaccine to prevent relapse in patients with AML. The median age of AML diagnosis is about 70 years, and due to the aging of the population, it is increasing in incidence. Improvements in cytotoxic chemotherapy, including hypomethylating agents and BCL2 inhibitors, have improved remission rates for newly diagnosed AML patients. However, most patients, especially elderly patients with elderly AML relapse, die of their disease. Therefore, novel strategies to prevent relapse are needed.
- Compelling need to serve a rare, orphan patient population with no approved immunotherapy - a very plausible mechanism of action - realistic possibility of prolonged remission, extended progression free survival / overall survival, improved patient quality of life, and reduced caregiver burden. Payor cost of care TBD.
- Several targeted agents have been approved for AML, but their curative potential is not clear. Currently, the only standard curative approach for most patients is high-dose chemotherapy for AML cases with favorable

genetic profiles or allogeneic bone marrow transplantation for high-risk disease. Given increased age and co-morbidities, these therapies may be too toxic for elderly patients.

- The proposed therapy addresses unmet medical need in elderly AML patients with residual disease and risk of relapse after the first line of therapy. The value proposition for the healthcare systems is mostly two-fold: (1) pharmacoeconomic impact by preventing the relapses and (2) administration in the outpatient settings in oncology community clinics. Both are significant cost-saving strategies.
- It's unclear if the data from the trial will inform the decision to proceed to phase 2.
- This vaccine has the potential to improve survival for patients with AML who are not eligible for intensive induction therapy. The product could have a substantial impact on the treatment of AML patients, particularly older patients who are often ineligible for intensive chemotherapy, due to the treatment-related risks of morbidity and mortality.
- There are curative approaches for AML, including allogeneic hematopoietic stem cell transplantation (allo-HSCT). Therefore, there is no absolute unmet need in AML. However, safer and more effective therapies would be significant.
- The ability of the immune system to control AML is evident through the graft-versus-leukemia effects of allo-HSCT, but many efforts have sought to generate anti-tumor immunity through vaccines, including autologous tumor cell products. None of these products has been approved, and it is unclear whether the candidate product has distinct advantages over these other approaches.
- Autologous cellular engineering approaches will likely be costly to produce, but if this becomes a standard approach, it may be competitive to allo-HSCT, which is also costly.
- If successful in preventing relapse, the product may represent a major advance in AML therapy.

Rationale

- Scientific rationale makes sense. The candidate AML vaccine is transduced autologous AML cells that co-express proteins that activate leukemia-specific cytotoxic T cells to mimic graft versus leukemia (GvL), which is well-known biology for disease eradication after allo HSCT. Mouse studies have demonstrated durable remission after treatment with this vaccine candidate. When added to Azacytidine/Venetoclax low intensity conditioning, the vaccine candidate should be effective against MRD.
- The applicant's strategy may provide lower risk to patients and better long term survival.
- The candidate is a dual-function vaccine that enhances the breadth of immune responses by presenting both leukemia-associated antigens and immune-stimulatory signals intrinsic to the vaccine. In preclinical studies, this treatment induced potent anti-leukemic responses eradicating AML in most leukemia-bearing mice.
- Co-culture of post-remission AML patient T cells with the vaccine candidate also induced robust, leukemia-specific cytolytic responses.
- The scientific rationale is sound. The experimental data presented in the proposal support further clinical development.
- Engineering runs at a university manufacturing facility with patient diagnostic bone marrow mononuclear cells established GMP manufacturing feasibility with consistent transduction efficiency, cell viability, and product release metrics. A final GMP qualification run was completed.
- The proposal will study a lentiviral vector to transduce AML cells and induce expression of proteins selected to promote the development of anti-tumor immunity. The overall scientific rationale is supported by published studies in mice. The value of animal studies is questionable, but no other experimental system exists to test efficacy.
- Other products, including AML cell/DC fusions and GVAX, have been developed as autologous cellular vaccines for AML, but have not demonstrated meaningful clinical activity. The PI provides some analysis of these agents, but the arguments for distinguishing this candidate from these other products are limited. The reasons for these other products' failures are also not well understood. It is not entirely clear that this approach will be significantly more effective.
- Previous studies provide a rationale for the dosing of autologous vaccine from a safety standpoint. However, it is not clear that they can provide guidance to maximize efficacy since these alternative vaccine approaches have failed to demonstrate clinical benefit.
- The rationale is fairly sound, but other vaccines in AML have failed.
- This is a first-in-human study, so there is no previous clinical experience with this vaccine. However, an autologous AML vaccine expressing one of the same immune stimulating proteins and IL-2 was administered to some number of patients at King's College London (NCT# NCT02493829).

Project Plan and Design

- Manufacturing the vaccine candidate for approximately 20 patients will provide useful experience and data to drive decisions about and improvements for a scale-out process. AML referral numbers suggest that the

applicant will have sufficient patients to achieve enrollment. The timing for potency assay development and FDA interactions lack detail and seem to be late in the clinical development cycle, given there should be timing and interaction advantages of Fast Track designation. Engaging with commercial CDMOs based on Phase 1 data is reasonable. A US product approval timeline that includes a commercial CDMO should be included in planning during Phase 1, in anticipation of positive outcomes. Onboarding a commercial manufacturer is a complicated, long lead time item. Relatedly, it's unclear if the applicant will be the BLA sponsor.

- The project and plan are sufficient to complete the Phase 1 trial.
- The project plan is appropriate for the first-in-human trials and benefits from the completion of a GMP-run.
- The trial combines frontline Azacitidine and Venetoclax therapy used for unfit patients with post-remission vaccination with the candidate, to increase relapse free and overall survival.
- The decision process for dose expansion and/or dose titration wasn't clear.
- A pilot trial is proposed as a necessary step in clinical development to evaluate feasibility and safety. However, it will be impossible to evaluate whether the vaccine has any clinical activity given the small sample size. Correlative studies examining anti-tumor immunity may suggest activity, but these are not reliable in predicting clinical success for most immunotherapies. How the results of specific correlative studies and the vast amount of data generated will impact go / no-go decisions or future modifications to the clinical approach is not well described.
- Although there are no clinical data with the approach, the approved IND application suggests the production, packaging, and administration of the drug will be feasible.
- Overall, the trial design is reasonable as a first-in-human study examining the safety and tolerability of the candidate. Rationale for the dose, timing, and route of administration are reasonable. The use of a rapid dose-escalation scheme with a 3+3 design as a backup is reasonable, given that the agent is unlikely to cause meaningful toxicity based on other clinical autologous vaccine studies.
- Enrollment will involve patients at a single clinical site. It is not clear whether there are enough patients to complete enrollment within the timeline presented. It is clear that AML patients are seen at the applicant institution, but data beyond the number of potentially available patients seen each year, including current or planned future trials competing for this patient population and evidence of recruitment success for this patient population, could increase confidence that the trial will be completed.
- There will be outreach to other clinical facilities in California, but it is not clear how potential patients will be evaluated for potential enrollment. Given that newly diagnosed AML patients typically need immediate care, it may be difficult to carry out referrals from these sites.
- The trial will target AML patients ineligible for intensive chemotherapy or allogeneic transplant. However, transplant eligibility may change if patients achieve a remission, and there is no mention in the protocol that these patients will have the opportunity to undergo an allo-HSCT evaluation, which remains the only curative modality for these patients. Although myeloablative allo-HSCT would be limited in this population, patients who achieve remission may be able to undergo reduced-intensity conditioning allo-HSCT
- The contingency plans are reasonable.
- The project plan and design look reasonable.
- There is concern that the flexibility in the number of cycles of Azacytidine and Venetoclax in the clinical protocol will lead to substantial variability in the treatments received by the study participants. This variability could make the study results difficult to interpret. This would limit the ability of the trial to enable subsequent go / no-go decisions.
- There is concern regarding the dose escalation and de-escalation plans, noting that the plans may not elucidate a maximum tolerated dose and if the lowest dose is unsafe, the proposed de escalation doses may also be unsafe. It appears that Applicant may have received questionable advice from FDA review team regarding this issue.
- To make these proposed efficacy outcome assessments more clinically relevant, the applicant is advised to consider using time from consent to initiate manufacture as the starting point to measure survival outcomes.
- Given the dose escalation and de-escalation plans and the study's data safety monitoring board, the plan to stop the study in the event of any dose limiting toxicity (DLT) is unnecessarily conservative. This has the potential to substantially delay study completion, particularly when the protocol requires that DLTs be presented to FDA to consider re-initiation of enrollment.
- There is a risk that all three dose levels will appear to have similar efficacy outcomes in this study. In that setting, it can be difficult to assess whether all three dose levels appear to be effective for the treatment of AML, or all three dose levels appear to be ineffective to treat AML. To generate study results that are more likely to be interpretable and support a subsequent go / no-go decision, the applicant should consider revising the protocol to include a concurrent standard-of-care (possibly Aza/Ven) control arm.

Project Team and Resources

- The PI is a deep subject matter expert. The strategic planning committee brings both business and scientific acumen and clinical, medical, manufacturing and analytical staff appropriate expertise to complete the phase 1. Details beyond phase 1 (CDMO, BLA sponsor, potency assay delivery and regulatory strategy) are lacking.
- The team has leaders, sites, and resources they require to complete the phase 1 study.
- The team is well-qualified to initiate, conduct and monitor the trial and follow-up work.
- The leadership and team members are appropriate for the studies proposed.
- The resources for vector and vaccine production, clinical care of AML patients, and the correlative studies are adequate for the proposed studies.
- Institutional guidance on commercialization is available.
- The team is qualified, and it has all the necessary resources to perform the work.
- Good team.
- Leadership and staffing appear to be experienced and appropriate for a first-in-human study.

Population Impact

- The applicant has a deep understanding of the afflicted patients and their disease journey. The trial population is appropriate because they have limited options for eradication of minimal residual disease. The applicant's letters of support demonstrate breadth of outreach and engagement (patient advocates and philanthropy, affiliated medical establishments and long standing manufacturing support).
- While a tough target population, the team understands the unmet need in AML.
- AML remains a devastating hematologic malignancy, particularly for older adults and medically unfit patients who are ineligible for high dose induction chemotherapy and HSCT. Estimates suggest 2500 patients per year in California annually with initially 450-480 patients annually would be eligible for the therapy.
- The economic burden of relapsed/refractory (R/R) AML is substantial, driven by repeated hospitalizations, high-cost salvage treatments, and prolonged supportive care. The candidate vaccine is specifically designed to stimulate the immune system to target residual disease and prevent relapse when combined with current best-practice standard of care therapy with Azacitidine/Venetoclax. As a potentially curative addition, the candidate could improve patient outcomes and quality of life, while reducing side-effects and off-target toxicities in a target population often excluded from intensive or novel treatments.
- Outpatient administration supports the feasibility of community-based vaccine delivery programs. While the current manufacturing strategy requires collection of AML cells at diagnosis at a medical center with cell banking capabilities, once AML cells are collected from patients, engineered and cryopreserved, subsequent TLV therapy could be administered in local community oncology practices that already administer Azacytidine/Venetoclax.
- Current post-remission standard of care has failed to deliver durable disease control, resulting in frequent relapses, hospitalization, and high end-of-life care costs. This approach seeks to shift this paradigm by inducing broad, patient specific immune responses capable of long-term disease control, without restrictions on AML subtype, donor or HLA matching.
- The applicants assess the potential impact on the patient population and have a good understanding of different patient groups. They have a plan for outreach to community oncology groups.
- The applicant appears to have an excellent understanding of the disease and the target population. The distribution of subjects appears to be appropriate for a first-in-human study.