Application #	CLIN1-14607
Title (as written by the applicant)	Cancer Stem Cell Interception with a Small Molecule Splicing Inhibitor
Therapeutic Candidate (as written by the applicant)	The candidate is a novel small molecule inhibitor of splicing that selectively eradicates therapy-resistant cancer stem cells in blood cancers.
Indication (as written by the applicant)	The target indication is relapsed/refractory secondary acute myeloid leukemia (sAML), or intermediate-2 or high-risk myelofibrosis (HR-MF).
Unmet Medical Need (as written by the applicant)	Despite advances in molecularly targeted and immunotherapeutic strategies, sAML and intermediate-2 or HR-MF patients have a 5-year life expectancy of 25% due to high relapse rates fueled by cancer stem cells harboring splicing-mediated activation of a malignant isoform of an RNA editing enzyme that regulates immune responses; this underscores the unmet medical need for the candidate therapy.
Major Proposed Activities (as written by the applicant)	• Manufacture the candidate small molecule to complete IND studies and GMP manufacturing of the candidate small molecule sufficient for clinical trials. • Complete toxicological, pharmacokinetic and pharmacodynamic studies in rats and rabbits as well as genotoxic and ADME studies. • Submission of IND and completion of phase 1 clinical trial start-up activities with the candidate small molecule for relapsed/refractory myeloid malignancies.
Funds Requested	$3,200,000
GWG Recommendation	Tier 1: warrants 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: 1

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

Highest	1
Lowest	1
Count	15
Votes for Tier 1	15
Votes for Tier 2	0
Votes for Tier 3	0

- A score of “1” means that the application has exceptional merit and warrants funding
- A score of “2” means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement
- A score of “3” means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG’s recommendation

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.

GWG Votes	Does the project hold the necessary significance and potential for impact?

Yes: 14	• The drug is targeting relapsed or refractory myelofibrosis (MF) and secondary acute myeloid leukemia (sAML) in patients for which there is a large unmet clinical need and poor prognosis. The program has considered all aspects of translation from established proof-of concept through early-stage nonclinical development and the studies have identified a safe, feasible dose for patient administration through preliminary toxicology studies in three species. The applicant has liaised with FDA prior to pre-IND and has adhered closely to the feedback and guidance provided. Further studies are planned to evaluate dose range finding, given the short half-life of the active ingredient, to inform on final dose and dosing regimen. The mechanism of action of the drug is novel and potentially impactful for these indications and could possibly extend to the treatment of solid tumors. • Clinical development of this drug would help to address the unmet medical need of recurrence-related mortality in MF and sAML as well as other treatment refractory malignancies. • Cumulative data suggest that this drug's mechanism of action targets hallmarks of MF pre-leukemic stem cell (LSC) transformation into self-renewing sAML LSCs that drive therapeutic resistance to conventional chemotherapy, Venetoclax, Glasdegib, and hematopoietic cell transplantation, thus there is a value proposition to this therapeutic approach. • The target populations are difficult to treat diseases and only a few targeted agents are available. • There is still a need for treatments for sAML.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The proof-of-concept studies have shown that the small molecule has the potential to decrease malignant RNA editing by inhibiting splicing of a specific mRNA isoform, the protein product of which drives immune silencing and malignant regeneration in MF and sAML. In vitro and in vivo studies added to the proof of concept to inform on the potential to target LSCs. Early-stage toxicology studies identified non-toxic drug levels in three species within a targetable therapeutic window. The data from these studies can be leveraged to demonstrate safe clinical dose levels and a dosing regimen with robust, agreed-upon margins of safety per regulatory guidelines. • The preliminary data from completed pre-clinical studies are compelling. In pre-IND studies in three species, the small molecule was well tolerated at doses that eradicated leukemia stem cells and spared normal hematopoietic stem and progenitor cells. • Recently completed CIRM-funded preIND studies combined with ongoing IND-enabling studies have shown that the small molecule is chemically stable and reverses malignant RNA editing by inhibiting splicing of a transcript encoding an RNA editing enzyme at doses that spare normal hematopoietic stem and progenitor cells (HSPCs). • Considering the high prevalence of its activation in sAML and INT-2/high-risk MF as well as other aggressive cancers that are prone to malignant regeneration and immune evasion, a small molecule that inhibits splicing of the malignant isoform of the RNA editing enzyme represents an innovative therapeutic strategy to obviate therapeutic resistance-related relapse and addresses the unmet need for developing effective cancer stem cell inhibitors, with the possibility to extend beyond hematologic malignancies including to solid tumors that activate the malignant isoform. • Standard of care chemotherapy for patients with sAML and long-term JAK2 inhibitor therapy for INT-2 or high-risk MF has a number of associated toxicities including secondary malignancies, and are generally not curative and ultimately lead to hematopoietic stem cell transplantation, which of course has its toxicities and limitations of candidates. • The candidate small molecule has an intravenous formulation with predictable pharmacokinetic and pharmacodynamic properties, favorable bioavailability, and stability, thereby enabling twice-weekly intravenous dosing with no evidence of systemic toxicity. • The biological rationale for the mechanism of action of the small molecule is strong. • The data provided suggest that the drug targets LSCs, although it is not clear how broad this activity is.

	• It is not clear whether additional splicing events are actually responsible for the activity of the drug. • This is a novel treatment modality that has a sound rationale with data to support development.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• There is a major milestone in this application that deals with manufacturing. The proposal indicates that the small molecule is to be manufactured by a vendor which has a track record in GMP manufacturing. Synthesis and manufacturing high level flow charts are provided. This company will also perform release testing. These tests are listed along with other characterization assays. A potency assay is described. The lot failure rate is >0.1%. Handling of the drug product by a contracted pharmacy is described in detail. However, in the FDA interactions table a different vendor is listed as the active pharmaceutical ingredient GMP manufacturer. This should be clarified. • The applicants have an established contract with a vendor who will perform manufacturing, and the application describes a novel, scalable synthesis route to manufacture sufficient material for IND-enabling studies and sufficient GMP material for clinical trials. The design and budget appear appropriate. • The budget requested is appropriate. Primary drivers of the cost for this project revolve around the CMC and analytical activities, animal definitive toxicology studies, ADME and genotoxicity, and clinical components necessary to move this project to the clinical trial stage. • Yes, all aspects of nonclinical development have been considered. The study plan moving forward will utilize the cGMP drug product for pivotal GLP toxicology studies for translation into safe clinical use for the first-in-human clinical trial. The plan considers the timeframe, cost and risk management of all aspects of the program. • A reasonable biomarker strategy is described. • The proposed tasks are appropriate to produce the IND. • The clinical development plan provides information to support the proposed activities. • One area that may need additional information is dose justification for the first-in-human studies. The nonclinical package may address this gap.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• The nonclinical data support feasibility of dose, dose escalation and toxicology parameters required to open an IND. The plan to develop cGMP grade material for use in tox studies and clinical studies is in place prior to receiving funding from CIRM. Plans to conduct tox studies in two species, genotoxicity, ADME, evaluation of metabolites and develop biomarker and bioanalytical methods has been pre-determined at CRO's. Dose range-finding studies will enable safe doses within the therapeutic window to inform on dosing regimen. The nonclinical plans are ready to be implemented for a timely IND submission. Risk mitigation strategies have been considered. • The CMC and Analytical activities include formulation, scale-up, manufacturing process development and optimization, and GMP manufacturing of the small molecule, and these will be performed with a reputable vendor. Definitive toxicology studies in rats and rabbits, ADME, and genotoxicity studies are necessary for IND-enabling studies, and will be conducted by another recognized vendor. Clinical activities include study start-up and initiation, clinical data management, and medical writing and reporting activities. These activities will be primarily managed through a contract with the applicant's institution for regulatory support, Alpha Clinic operations management and Alpha Clinic cancer trial expert management, Alpha Clinic data management services, and clinical writing and protocol development. A portion of the clinical medical writing, reporting, regulatory activities, as well as IND preparation and electronic IND submission will be managed by vendors. • The timeline is appropriate, as are the milestones. • Yes, there are no concerns about feasibility and the project will be executed by an appropriately multidisciplinary team. • The project is feasible based on the preliminary data and the expertise involved. • The nonclinical studies are comprehensive and support the development. • The manufacturing plan appears to be well considered.
No: 0	*none*

GWG Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
Yes: 14	• The proposed cancer stem cell targeting product addresses the unmet medical needs of CA's diverse population, including underserved communities, and is pressing considering that mortality rates for AML are higher than for any other hematologic malignancy in the applicants' county. • The proposed study will be open to anyone regardless of gender, race or ethnicity. • The main clinical study site is in compliance with Title VI of the Civil Rights Act of 1964, Title IX of the Education Amendments of 1972, Section 504 of the Rehabilitation act of 1973, and the Americans with Disabilities Act of 1990, and does not discriminate on the basis of race, color, national origin, religion, sex, disability, or age in any of its policies, procedures, or practices; nor does the University discriminate on the basis of sexual orientation. • The application specifically discusses the importance of and a plan to effectively establish the therapeutic index of the small molecule candidate in a larger group of genetically diverse individuals. • The applicants actively advocate for more inclusion and outreach efforts directed towards underserved and underrepresented communities by adding additional clinical trial coordinators and collaborations with hospitals that serve these communities. • The applicants propose to provide knowledge networks for underrepresented communities, building relationships established on trust, and connecting patients with clinical trial matches. • The proposed cultural sensitivity activities include connecting with community researchers and experts at the applicant institution's School of Public Health. The applicants will also actively work with patient and community groups to understand and study barriers to clinical trial access. • The applicants will form a Community Advisory Board comprised of patient and community advocates from priority populations who will have the opportunity to meet researchers and provide feedback on the recruitment strategy. • The DEI plans discuss the importance of and goals to extend enrollment to pediatric populations and mirror the diversity of the US in larger phase 2 and 3 trials. • All aspects of DEI have been considered.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 9

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	5	• The application includes a well thought out plan that accounted for factors associated with not only recruitment but retention. • The study will recruit from geographic areas near the applicant's institution that serve more underrepresented minority and socioeconomically disadvantaged patients. The applicants are also upfront in acknowledging that with a small phase 1 cohort, that there may not be the opportunity to enroll some groups with less than 5% presences in this area. • There are no expected differences in safety and efficacy by race/ethnicity and gender, but the applicants acknowledge that it will be important to have representation from a diverse population to confirm this. If differences are observed, they can be addressed with follow up studies.

		• Enrollment will be limited by the ability of the participants to also receive care at the primary site; however, the applicants provide patient reimbursement for transportation to and from this site and will be flexible with scheduling where necessary. Personalized follow up mitigation strategies are planned if a trial participant misses a visit. • All community outreach, engagement, and recruitment efforts (patient support group meetings, charitable organization events and diverse media outlets) are performed by dedicated personnel with skill and experience dealing with culturally sensitive approaches. • This team will have both English- and Spanish-speaking staff with access to translation services for other languages. • Planned activities are well thought out and reflect a good-faith effort for outreach and engagement. • The application includes a very well thought out DEI plan. • The DEI plan is strong.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-14068 #2
Title (as written by the applicant)	Treatment of Severe Aplastic Anemia (SAA) by induction of mixed chimerism using CD4+ T cell depleted haploidentical donor stem cell transplant (SCT)
Therapeutic Candidate (as written by the applicant)	A minimally manipulated half-match donor blood stem cell transplant with a low-toxic conditioning regimen of the transplant host
Indication (as written by the applicant)	Older (>40 yrs) Severe Aplastic Anemia (SAA) patients that are ineligible for the potentially curative standard stem cell transplant
Unmet Medical Need (as written by the applicant)	Our product will allow more SAA patients without full match donors access to the potentially curative stem cell transplant. Our method will allow patients to receive less-toxic conditioning regimen before receiving stem cell transplant from half match donors.
Major Proposed Activities (as written by the applicant)	• Donor Cell Manufacturing and Release of Allogeneic Product • Culture Sensitivity Training, Recruitment, Community Engagement and Clinical Trial (Treat 6 Patients) • Assess Safety, feasibility of producing sufficient donor cells, and the ability to induce mixed chimerism
Funds Requested	$9,054,216
GWG Recommendation	Tier 1: warrants 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: 1

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

Highest	1
Lowest	2
Count	13
Votes for Tier 1	11
Votes for Tier 2	2
Votes for Tier 3	0

- A score of "1" means that the application has exceptional merit and warrants funding
- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG's recommendation

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.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• The seriousness of severe aplastic anemia (SAA) in patients > 40 years old refractory to immunosuppressive therapy is a documented unmet medical need. Nonclinical studies and pilot study results in patients with severe sickle cell anemia (SCA) support the potential of this therapy to provide improvement over the standard of care for SAA.

	• This study focuses on individuals over 40 years old with SAA. These individuals have worse outcomes and are at risk for complications from disease and treatment. However, this is a small group of patients. In my opinion, the merit behind this study lies in potential gains for the spectrum of auto-immune disorders. In future discussions, the applicant should compare this potential treatment against novel immune therapies on the market, as these are easy to deliver but have a high financial cost.
	• Patients with SAA may receive either immune therapies or stem cell transplantation (SCT) from a healthy donor. The choice of treatment is swayed by the availability of a matched donor. Matched donors are more difficult to identify in some ancestral/racial/ethnic communities, which creates a health disparity. Exploring treatments like the proposed therapy, that allow mis-matches between patient and donor could potentially reduce health disparities beyond SAA.
	• This is a reasonable population to study, as older SAA patients may have limited treatment options due to difficulty tolerating current regimens. From this perspective the proposal addresses an unmet medical need.
	• The approach should help to increase the number of eligible donors for older SAA patients.
	• The applicant has responded in detail to the GWG's prior comments and their responses are reasonable.
	  ◦ They have added additional study results supporting the removal of total body irradiation (TBI) from the treatment regimen.
	  ◦ They responded to the GWG's request for additional data on older SAA patients treated with PTCy by referencing another literature review. This review supports the overview conclusion that prospective trails are needed.

No: 0	*none*
GWG Votes	**Is the rationale sound?**

Yes:
13
	• The applicant has responded in detail to prior questions from the reviewers. Their responses satisfactorily address the reviewers' questions.
	  ◦ They acknowledge the complexity of defining a human dose based an animal studies.
	  ◦ They point out that their study includes investigations to deepen their understanding of the induction of mixed chimerism in SAA.
	  ◦ They confirm they should be able to recruit six patients within the time available.
	  ◦ They agree that it may be difficult to differentiate between the effects of the conditioning regimen and the graft manipulations, but indicate that the conditioning may be adjusted if required while the manipulation of the graft cannot.
	  ◦ They provide the requested supplementary animal study data with additional time points.
	  ◦ They provide additional information on the potential role of allogeneic transplant in treating SAA and other autoimmune diseases where mixed chimerism is desirable.
	• The applicant provides a sound scientific and clinical rationale based on literature, preliminary (nonclinical) studies, and a pilot study in three adult patients with severe sickle cell anemia (SCA).
	• The responses to the previous critique were strong and clarified outstanding questions.
	• The rationale and plans for the treatment aspects of this study are strong.
	• The rationale is well explained.
	• The bone marrow recovery studies are less well-developed and represent a considerable portion of the budget. The applicant proposes to assess the bone marrow micro-environment of patients using RNA sequencing, mulitplex analyses, in vitro characterization of mesenchymal stem cells, and cytokine analyses, stating this is a unique opportunity to study the bone marrow microenvironment after allogeneic stem cell transplantation (allo-SCT). They have demonstrated the feasibility of some of these assays in the previously halted study of SCA. However, they have not demonstrated the rationale of attaching these studies to this clinical trial specifically versus in any SAA patient recovering from allo-SCT. Bone marrow recovery and the bone marrow microenvironment are important to study, especially in SAA. However, the proposed analysis seems preliminary - it has many variables and will be difficult to interpret in the context of SAA, mixed chimerism more generally, other bone marrow recovery, etc. It is a substantial component of the budget (~$1 million) and requires better justification.

No:	*none*

0	
GWG Votes	**Is the project well planned and designed?**

Yes:
12
	• In response to the prior GWG comments on project design, the applicants explain the following:
	  • Their 3x3 design is for observing toxicity; the trial is not designed to determine maximum tolerated dose
	  • How they would respond to the case where each of three patients has a different outcome (complete chimerism, graft failure and GvHD)
	  • There is a focused primary objective for the study, and all the other variables are either secondary or correlative
	  • They have provided a revised contingency strategy and have reduced the budget as requested.
	• Regulatory correspondence indicates that CMC and clinical study design issues have been appropriately addressed by the applicant and reviewed by FDA.
	• FDA has communicated that the applicant may treat new indication(s) under their IND, given the product has been trialed in humans and and preclinical data support use in the proposed patient population.
	• The applicant submitted their protocol for the SAA trial under the IND in July 2022, and received no additional FDA feedback. From the regulatory perspective, the proposed study can now proceed.
	• The clinical trial and outcome measures are well designed.
	• Overall, yes, but are the animal studies necessary?

No: 1	• The current timeline allows four years for completion of the clinical trial. The timing of data collection may not allow for successful commercialization given the competitive landscape.
GWG Votes	**Is the project feasible?**
Yes: 12	• I maintain my original opinion that the Manufacturing Section is feasible and that the team is experienced in the procedures. • The applicant has addressed previous GWG review questions and FDA concerns. • This team should have no issues achieving the goals of the proposal. • The project is feasible; the team is well qualified; the institution is appropriate and able to offer support. • The institution and investigators are well positioned to recruit patients and safely deliver this therapy.
No: 1	• This set of activities is too ambitious for the timeframe.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• The applicant presents a DEI plan that is attentive to the socio-demographics of the patient population and socio-demographic impacts on the disease outcomes. • The applicant appears to have a strong commitment to DEI and actionable plans are in place. • Yes. A Community Advisory Board, cultural sensitivity training and community dissemination of findings are included in the project plan.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 8

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?

9-10: Outstanding response	0	*none*
6-8: Responsive	5	• A major gap exists for SAA patients without a well-matched donor, who are often racial/ethnic minorities. • The applicant has identified the population at highest risk and has explained their plan in detail to gain recruitment to this population through feasible means that will impact diverse underserved and underrepresented communities. • Planned activities are adequate and reflect a good-faith effort for outreach and engagement. • The applicant provides a very comprehensive DEI plan. • OK DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-14748
Title (as written by the applicant)	Evaluation of Safety and Feasibility of Cytomegalovirus-Specific, Anti-HIV Chimeric Antigen Receptor (CMV/HIV-CAR) T Cells in People with HIV
Therapeutic Candidate (as written by the applicant)	Cytomegalovirus (CMV)-specific T cells that express a chimeric antigen receptor (CAR) which targets and eliminates HIV-infected cells
Indication (as written by the applicant)	Management of human immunodeficiency virus (HIV) & acquired immunodeficiency syndrome (AIDS)
Unmet Medical Need (as written by the applicant)	HIV is still a persistent public health problem in the United States, despite the availability of advanced therapies. An estimated 1.2 million people in the United States were living with HIV in 2019. There is no cure for HIV. A highly effective immunotherapy could significantly improve outcomes for HIV-infected individuals and eliminate the need for anti-retroviral therapy (ART).
Major Proposed Activities (as written by the applicant)	• Manufacture product to supply the proposed trial • Assess clinical safety of the therapeutic product • Data collection, analysis and report
Funds Requested	$11,299,976
GWG Recommendation	Tier 1: warrants 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: 1

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

Highest	1
Lowest	2
Count	13
Votes for Tier 1	12
Votes for Tier 2	1
Votes for Tier 3	0

- A score of "1" means that the application has exceptional merit and warrants funding
- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG's recommendation

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.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• Although HIV infections can be relatively well-controlled in individuals who have access to current therapies, these are life-long therapies with some off-target toxicities. A therapy to eliminate HIV would be impactful in reducing the global burden of this disease. • This is a significant unmet need and this approach is ready to be tried. • Developing an HIV cure would meet a significant unmet medical need.

	• If successful, this approach would offer a substantial improvement over standard of care for people with HIV. • The value proposition of the proposed treatment is high, and if successful would support adoption by patients and healthcare providers.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The investigators provide abundant preclinical data supporting both feasibility of this treatment and a reasonable prospect for control of HIV replication (based on experiments in the humanized mouse model). • The use of CMV-specific T cells as the starting point for generating the HIV-specific CAR T cells and a strategy for stimulating those cells with CMV antigen in order to enhance their survival is highly innovative. • The investigators have meticulously addressed each step necessary for production of the proposed dual CAR T cells. They have had extensive discussion with the FDA regarding the elements that must be in place to proceed with proposed phase 1-2 trial; all elements have been addressed appropriately. • There are minor concerns that HIV (and HIV-infected cells) may escape the N6 antibody through mutations in the viral envelope protein (Env). • It is not clear how many latently infected cells in each HIV patient express Env and would therefore be targeted by the CAR T cells. Ultimately a combination approach may be required: a method of HIV reactivation in order to induce surface expression of Env, followed by targeted of those cells with the proposed CAR T. • Confirming the safety of the cell therapy (the first objective of the proposed study) will meet one regulatory requirement. To support further development, the clinical studies will need to incorporate measurement of antigen activation. • Achieving 'cure' with only one injection is a laudable goal. Justifying the use of a single injection for a durable response with data represents a risk to the program.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• The proposal contains a detailed manufacturing plan summary that was submitted as part of the IND application, which was approved by the FDA. • These facilities are excellent/experienced and are more than capable of performing the tasks. • The release tests are all appropriate, as are the additional characterization assays. There have been no failures during manufacturing of six products. • The applicant has built-in financial mitigation strategies to combat lot failures and delays to the supply chain. • The manufacturing section is well written and is supplemented by the detailed manufacturing plan submitted to the FDA. • The team is experienced and will perform a full scale GMP manufacturing campaign prior to patient enrollment. • The project is appropriately planned and designed to meet the objective of the CLIN2 PA and to achieve meaningful outcomes that will support further development of the therapeutic candidate. • The proposed manufacturing plan is appropriately designed and budgeted for both time and cost. • The experiments, clinical and laboratory evaluations proposed are essential and provide value that advances CIRM's mission. • The project timeline is appropriate. • There may be some confusion in the protocol as to whether an analytic treatment interruption is or is not planned as part of the protocol - the statistical analysis plan includes time to viremia as an endpoint, but this endpoint may have been retained accidentally from a previous version of the protocol.
No: 1	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• The project is eminently feasible and highly likely to achieve the intended objectives within the proposed timeline. • The proposed team has outstanding qualifications to conduct the proposed trial and has access to all the necessary resources to conduct the proposed activities, including manufacturing.

	• The experience of the applicant and the state of industry suggest that activities can be completed within the timeline and budget. • The applicant presents a careful approach, with a staged escalation of dosing to address safety concerns. • Appropriate contingency plans are in place to manage risks and delays.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• The institution is a clear leader in DEI initiatives. • The applicant has presented an appropriate rationale for the proposed trial population, and adequately addressed issues related to DEI. • Plans for trial outreach, engagement, enrollment, and retention address key barriers to trial participation faced by underserved demographic groups and are well-matched to the needs of the proposed trial population. • Activities for building cultural sensitivity on the team are appropriate.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 10.0

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	5	• Superb DEI plan. • The institution has an active DEI program and is ranked within the top ten in the nation on the 2002 Top Hospitals and Health Systems list from Diversity, Inc. • The institution has also been honored by the California Diversity Council as a Diversity Promoter Organization. • The applicant has a 150-member Community Advisory Board made-up of diverse representation that meets monthly to learn about and review new research, and aims to make clinical trials available to underserved populations that are most severely impacted by HIV/AIDS. • Reimbursement procedures exist to overcome obstacles such as lack of transportation, child or dependent care, language barriers and other issues. In addition, participants will receive $150 each for scheduled or unscheduled research and clinical visits to cover the costs of food and other daily expenses. • The institution cultivates partnerships with community organizations serving women and children, Black persons and Latinx persons. • Planned activities are adequate and reflect a good-faith effort for outreach and engagement.
6-8: Responsive	1	• Strong DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-14787
Title (as written by the applicant)	A Phase 2b, Randomized, Assessor-Masked Clinical Trial to Assess the Safety and Efficacy of a Retinal Pigment Epithelium (RPE) Implant in Subjects with Geographic Atrophy (GA)
Therapeutic Candidate (as written by the applicant)	A patch comprised of a layer of stem cell-derived retinal pigmented epithelial (RPE) cells on a supporting matrix that is implanted under the retina
Indication (as written by the applicant)	Geographic atrophy (GA), the late-stage form of age-related macular degeneration (AMD)
Unmet Medical Need (as written by the applicant)	There are currently no therapeutics that are effective in improving vision in geographic atrophy (GA)
Major Proposed Activities (as written by the applicant)	• Manufacture of the cryopreserved formulation of the RPE implant for use in the Phase IIb clinical trial • Completion of a multi-center, randomized Phase IIb clinical trial testing the efficacy and safety of the RPE implant in geographic atrophy (GA)
Funds Requested	$12,373,748
GWG Recommendation	Tier 1: warrants 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: 1

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

Highest	1
Lowest	2
Count	14
Votes for Tier 1	9
Votes for Tier 2	5
Votes for Tier 3	0

- A score of "1" means that the application has exceptional merit and warrants funding
- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG's recommendation

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.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• Strong preliminary data and an established manufacturing process support moving forward with a phase 2b clinical study. • The project holds significant potential as a therapeutic for geographic atrophy (GA). • GA remains an area of significant unmet medical need. • This program should be benchmarked against competitors: • The first drug for GA (a pegcetacoplan C3 inhibitor) was approved in February 2023. Clinical trials showed that the drug lowered the rate of GA lesion growth

	versus placebo, with increased treatment effects over time. The greatest benefit seen - a 36% reduction in lesion growth - was observed between 18 and 24 months (the last timepoint). ● Additional programs are close behind: A C5 agent was granted priority review at the FDA, with an expected decision date in August 2023. ● The applicant's proposed product would still have a potential role in GA, since the recently approved drug appears to slow degeneration but cannot replace lost tissue. ● Another comparison to consider is the four-year follow-up data from a single patient who received iPSC derived RPE sheet autologous transplantation. That graft survived and visual acuity has remained stable. The applicant's proposed product has a scalability advantage over the autologous transplantation approach.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	● Good preliminary data. ● The data are limited but seem supportive. In the participants previously enrolled, 27% (vs. control arm 7%) gained >5 letters of visual acuity. Previous trial designs and processes are largely consistent and supportive.
No: 1	● The protocol has inconsistency in regard to evaluating the placebo, the number of placebo controls across sites, and the comparison at conclusion is to evaluate versus natural history which presents an unclear rationale for evaluation.
GWG Votes	**Is the project well planned and designed?**
Yes: 12	● The manufacturing plan appears acceptable. The intermediate cell banks are already prepared. The institution has experience in generating the monolayers and the shipping vendor is a validated shipper. ● The institution is highly experienced in a wide variety of manufacturing procedures. ● The tests performed seem appropriate and include a potency assay -release of pigment epithelial-derived factor. ● Seventeen lots have been manufactured with one failing based on release specifications - due to an identified technical error. ● The three intermediate cell banks were prepared at the institution from a fully tested working cell bank. One bank was used for the phase 1/2a study, the second will be used in the proposed trial, and the 3rd is in reserve for future trials. There are data to demonstrate stability for at least one year. ● FDA has provisionally approved the cryopreserved formulation and its use in the phase 2b study. ● The clinical sites will be trained in administration of the implants. ● There is some concern about the applicant's choice of cryopreserved implants versus other options, but this concern should not limit the program. ● This is reasonably well-planned and designed. Ideally, the planned trial enrollment would be larger. ● Enrollment of patients with geographic atrophy (GA) can be challenging and slow. A number of competitors are currently enrolling GA patients, plus potential participants will prefer to also receive the approved drug. ● Since not all of the FDA feedback is available, it's difficult to know how the applicant arrived at their current design. ● Ideally, the applicant would have included much more detail regarding their FDA discussions. ● A primary endpoint of at least 18 months (24 months preferred) is recommended ● More biostatistics planning is recommended. ● Preservation of vision and slowing of progression of the lesion are likely the best outcomes. Gaining significant vision would be a difficult bar. Microperimetry is also an endpoint recommended by the FDA.
No: 2	● Conducting a masked, randomized trial is commendable. ● There are several outstanding issues with the clinical plans. ● The Data & Safety Monitoring Board (DSMB) process needs to be detailed in the application. ● According to the application, the trial will include a placebo arm, but this placebo arm will not be a comparator in the primary assessment of efficacy. The applicant's criterion for therapeutic success is efficacy demonstrated in 22% of participants in the treatment arm, with no reference to the placebo arm.

	• If the null hypothesis does not include the placebo group, what is the purpose of the placebo group? If it is to help design the phase III trial, the clinical plans should include an objective estimating variability and difference from placebo.
	• The statistical plans need work as follows:
	  • The primary endpoint is a dichotomous endpoint from a continuous measurement - they could achieve greater power if they used the original endpoint and then translated it to responses later.
	  • If the placebo arm is included in the sample size calculation, the calculation is incorrect, and the study is well under-powered.
	  • In the Objectives section, the applicant states that they are not looking for statistical significance, yet they state an alpha level in their sample size calculation.
	  • The analysis section states that the applicant will assess primary efficacy by comparing treated participants to control participants. This contradicts the sample size calculation, which states that "the primary efficacy assessment may also include comparisons of the results from the treatment group to historical data from control or sham." This requires clarification.

GWG Votes	**Is the project feasible?**
Yes: 14	• The applicant will likely face challenges in trial enrollment. • The technique will be surgically challenging; this is not a commonly performed technique. Measures need to be taken to ensure identical performance across sites. • The planned number of sites represent a challenge. With the small number of participants in the placebo arm, some sites may not have any patients receiving placebo.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• DEI is addressed with a plan developed in conjunction with their institution's Race and Equity Center. • Mostly. The applicant should consider paying patients for participating. • GA is more common in white people. • Gender-equal ratios will be sought. • The study will reimburse participant expenses. • Staff training in DEI factors was incorporated into the proposed plans.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 9.5

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	5	• The outstanding DEI plan was developed in a collaboration between the institutional Race and Equity Center and the collaborating clinical trial sites. • The applicant provides statistics on the occurrence rates for geographic atrophy (GA) in different racial/ethnic groups and sexes. They have plans in place to recruit patients from rural and urban areas. • The outreach plan for recruitment is outstanding and is based on the knowledge and experience of the institutional Race and Equity Center. • The applicant plans to alleviate participant burden - providing prepaid support for transportation, housing and other essential services for the participant and family caregiver.

		• To reduce participant burden, the applicant has thoughtfully planned implementation of this procedure in the outpatient setting. • Cost analysis – once the intervention is scalable - is comparable to other treatments ($2500 to $3500). • Education and training of all staff involved in this project on the principles of DEI will be conducted by the Race and Equity Center. The plan for DEI education includes robust evaluation of its success. • Very well described DEI plan.
6-8: Responsive	1	• The applicant has a good outreach plan, and they are partnering with the trial sites to help with outreach.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN1-14933
Title (as written by the applicant)	Manufacturing an Antisense oligonucleotides for a Phase 1/2 Clinical Trial for Amyotrophic Lateral Sclerosis
Therapeutic Candidate (as written by the applicant)	[Product Name], an antisense oligonucleotide
Indication (as written by the applicant)	Amyotrophic Lateral Sclerosis
Unmet Medical Need (as written by the applicant)	To date, therapeutic options for Amylotrophic Lateral Sclerosis (ALS) have been limited, and disease-modifying drugs remain to be developed. Current FDA approved drugs Riluzole and Edaravone are not effective.
Major Proposed Activities (as written by the applicant)	• cGMP Manufacturing of sufficient drug substance for the phase I/II clinical trial • Analytic method development and qualification for drug substance and stability studies • cGMP manufacturing of placebo and drug product
Funds Requested	$2,199,782
GWG Recommendation	Tier 1: warrants 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: 1

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

Highest	1
Lowest	2
Count	14
Votes for Tier 1	13
Votes for Tier 2	1
Votes for Tier 3	0

- A score of "1" means that the application has exceptional merit and warrants funding
- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG's recommendation

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.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• ALS is the most common adult motor neuron disease with an incidence of 2 per 100,000 and prevalence of 5.4 per 100,000 individuals. The lack of therapeutics in ALS is a significant unmet need. Riluzole and Edavarone are two FDA approved drugs used in the standard of care. Both drugs have minor effects on improving the quality of life of patients

	or appreciably extending survival. A therapeutic that could significantly alter disease course and be used across both familial and sporadic forms of ALS is greatly needed. The administration of antisense oligonucleotides (ASOs) intrathecally has demonstrated a good safety profile in general. The applicants have also demonstrated target validation in a large animal study. If successful, this therapeutic could substantially alter the disease course for a variety of patients with ALS. This therapeutic could potentially offer patents an improved value proposition over the current, minimally effective FDA-approved drugs for ALS. ● The program offers a unique opportunity to treat ALS patients with various underlying causes. If successful, this would be a direct benefit and provide an opportunity for patients with a devastating disease. ● The approach proposed to clinically develop a drug product for treatment of ALS is suitable based on the experience and process history provided for the antisense oligonucleotide product. ● This candidate has a novel mechanism of action for this devastating disease. ● The proposal addresses a very clear area of unmet need. ● The treatment seems to offer significant value based on the cost per unit of product lot and expected treatment volume for the ALS indication. ● The value proposition is likely to be favorable, although on the higher end the cost-to-benefit ratio.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	● The rational is seemingly sound. There is currently very good mechanistic data demonstrating that inhibition of the target of this ASO product can induce exosomal secretion, which clears misfolded proteins including C9ORF72 dipeptide repeat proteins (DPRs) and TDP-43 from neurons. Inhibition was achieved first using a small molecule tool compound, and then more effectively using the ASO strategies that are the focus of this proposal. ● The ASO product has been shown to be effective in both patient-derived induced motor neurons and in vivo mouse experiments. Target validation in large animals and initial safety data have been established. The mechanism of action would suggest broad applicability across a number of ALS patients. ● The application includes sound preclinical data in the tested models. Inhibition of the target kinase with a small molecule has been shown, and the ASO is effective in vivo and in vitro. Data from the large animal study supports continued development. The product has the potential to be broadly applicable across the various forms of ALS. ● The proof of concept data in the application are convincing. ● Data demonstrating lowering of SOD1 with another ASO in development is supportive of the rationale. ● Overall, the scientific rationale and development plan is sound, and the data collected to date support continued development. ● The body of data supports the continued development based on the discovery data provided that supported the nonclinical studies and the consistency of the manufacturing process. ● Specific to the request to use funding to support manufacturing, the manufacturing and testing (release criteria) followed well-established procedures and analytical methods for an ASO. Of note, novelty and invention are not required or appropriate for this phase of the development. ● The proposed manufacturing strategy is based on sound scientific rationale, considering that the synthesis of the ASO is well established and the use of these synthetic products are continuing to show clinical success. ● Exosomal activation may be a potential unwanted consequence. Long term tolerability studies were not discussed and could be considered to address this. ● The preclinical studies in animal models is not ideal. The over-expression model used in some of these studies is a rapidly progressive model that doesn't mimic ALS in patients. In addition, a second repeat expansion model does not account for effects of loss of function of the disrupted gene. It is acceptable to use these models to achieve protein misfolding to some extent, but questions remain as to why the SOD1 mouse model or FUS models were not used to test in vivo efficacy. This part of the application was lacking given that the SOD1 model is industry standard and easily accessible. No data on evidence of Tau clearing was reported, although this was mentioned multiple times in the

	proposal. Despite this, there is sound rationale for the mechanism of action of the therapeutic. ● One criticism is the lack of data using the SOD1 G93A pre-clinical mouse model. This model is industry standard, and since misfolded protein clearance is the proposed mechanism of action, this model should have been included. ● The chosen mouse model may not be ideal. This model is rapidly progressive, which helps with experiments but is not necessarily reflective of the disease course in patients. It was surprising that neither the SOD1-G93A model nor FUS transgenic models were included. Longer-term models such as these would be needed to understand tolerability and the effect of the extruded exosomal content.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	● The project seems very well planned as outlined in the proposal with a strong project management team and careful attention to timelines, expertise in manufacturing and purification, as well as timelines and trial outcome measures. It appears the manufacturing plan is well documented with appropriate expertise. A key person on the team with deep technical expertise relating to ASO synthesis, analysis, formulation, development, and regulatory affairs has been taking the lead on negotiating requests for proposals and contracting with vendors. It would appear that all of the proposed experiments are in line with IND enabling studies and clinical trial design. There doesn't appear to be any unnecessary proposed experiments or inefficiencies, and timelines seem appropriate. ● The project is well designed and planned suitably, if not a bit aggressively, to achieve meaningful delivery on expectations for product availability to support the IND filing. Key to completion is having the developed and qualified assays available as projected to support drug product disposition and establish early reads on stability with any stability indicating methods. ● The proposed plan is predominantly orienting requested funds to support manufacturing activities of both the drug product and drug substance, including budgets for assay development and qualification. The budget is appropriate for the materials, methods, and facilities anticipated to be fit for clinical development use. ● Ultimately the program cannot proceed without high quality drug substance and acceptable fill/finish of the drug product, justifying investment in these activities. ● Composition of the data and electronic filing are required for IND submission and the transition from non-clinical development to clinical trials. The selected contractor for these efforts appears to be qualified for the task at hand. ● Both the CMC plan and proposed preclinical studies should support a successful IND. ● The applicant has already had a detailed preIND discussion with FDA. ● The manufacturing and testing procedures are well planned and appropriate. The budget and timelines appear to be rationale and reasonable.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	● The applicant has met with the FDA on a pre-IND meeting that was well received. Based on the FDA feedback, they are looking to embark on a phase I/II trial. ● The management team is strong. ● The manufacturing of an ASO is well established and the process/procedures are well-known. The risk of failure is modest and within the bounds of acceptability. ● The team has a reasonable contingency plan for delays once the manufacturing plan has been initiated. ● Contingency plans are described and demonstrate a suitable level of product understanding to mitigate and prevent delays. ● Considering the experience of the team proposed and the nature of an oligo based product, development timelines seem suitable with a perfect execution. Some assays have significant development times, especially those involving cell culture, and delays in assay qualification are of some concern in regard to the amount of time provided to support development and qualification. Overall the project is feasible. ● Risk assessment on some materials used to support drug product formulation and the continued supply of these key materials is not straightforward to understand with the information provided, and may present some novel production control concerns. The agency preIND review of the process and materials provided did not raise any initial concerns of significance which also supports establishment of a feasible regulatory path.

	• The plan to address potential delays prior to formal initiation of work with vendors is not clear. For example, the commitment to manufacture is (usually) not finalized until a contract is signed and first payment is made. There is a risk that the slot available at the selected manufacturing site and/or fill/finish site will not be acceptable for the timeline (and possibly the budget) described to the program.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**

Yes: 14	• The applicant provides evidence for the demographics of the indication with a plan to match race, ethnicity, sex, and age-based demographics to set the trial populations goals.
	• The project plan includes early descriptions for community engagement, including hiring a consultant with expertise in effective decentralized clinical trials to assist the team in reaching the targeted demographic trial participants.
	• The application goes into considerable detail in its inclusion of diversity and distribution of patients and plans for outreach and advertisement:
	  ◦ The applicant plans to hire a community engagement & outreach consultant, who will work with the community network of each clinical trial site and community advisory board members to reach out to underserved communities.
	  ◦ The clinical team will incorporate participants' race, ethnicity, and culture sensitivity while treating patients, incorporating cultural competence into treatment service.
	  ◦ The proposal includes additional plans to work with the ALS Association for advice on patient recruitment and advertisement.
	  ◦ The applicant plans to work with community leaders to educate minority patient about their study, and will also work with ALS Association chapter leaders to reach out to underserved populations.
	• The program appears to adequately capture DEI principles and goals.

No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 7.0

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	4	• The trial population goals are adequate and based on the CDC's National ALS Registry statistics and published studies. Based on what is known about ALS, the goals for the trial population are well matched with the afflicted population. • The applicant plans on using the location of trial sites to organically recruit patients in surrounding areas based on known demographics. They also plan to work with the National ALS Registry and ALS Association to recruit patients throughout the United States and utilize the extensive ALS clinics network. • Some later planned activities for outreach and engagement will include making flyers and brochures for the study and distribute them among Alpha Clinic network sites. These will leverage the Alpha Clinics network sites, as each has built infrastructure to reach out to underserved communities for patient education and recruitment.

		• The applicant noted several specific plans to address potential barriers to participation:
		  • 1st: Flexible followup visits. Scheduled visits are completed in person, virtually, or by sending an in-home nurse.
		  • 2nd: Cover cost for travel and lodging, food and provide a gift card for each visit.
		  • 3rd: Hire a bilingual patient navigator to coordinate patient study visits and care.
		• The applicants will work with a vendor to assist with cultural sensitivity training for the applicant's team as well as staff as needed at clinical trial sites.
		• The applicants are not planning any early-state DEI engagement activities to be conducted under this CLIN1 award.
		• It is unclear specifically in the applicant's projects plans how the success of this project would likely lead to a therapy that positively impacts underserved or disproportionately affected communities.

3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-15087
Title (as written by the applicant)	Phase I Study of Chimeric Antigen Receptor Engineered T Cells for the Treatment of Relapsed/Refractory Acute Myeloid Leukemia
Therapeutic Candidate (as written by the applicant)	Immune T cells from a patient's transplant donor engineered to express chimeric antigen receptors for targeted leukemia killing
Indication (as written by the applicant)	Relapsed or refractory acute myeloid leukemia
Unmet Medical Need (as written by the applicant)	This proposal seeks to address the unmet medical need for more effective therapy against acute myeloid leukemia by engineering de novo anti-leukemia activity using patient-specific chimeric antigen receptor modified T cells.
Major Proposed Activities (as written by the applicant)	• Manufacture and clinically evaluate CAR T cells in a diverse population • Evaluate the safety and preliminary evidence of efficacy • Prepare for a phase 2 clinical trial
Funds Requested	$11,983,547
GWG Recommendation	Tier 1: warrants 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: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

Highest	1
Lowest	2
Count	15
Votes for Tier 1	13
Votes for Tier 2	2
Votes for Tier 3	0

- A score of "1" means that the application has exceptional merit and warrants funding
- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG's recommendation

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.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• The proposal addresses clear unmet need for effective therapies for relapsed acute myeloid leukemia (AML). Previous CAR studies have produced low response rates. Here, the investigators propose a new target and the use of allogeneic cells to improve outcomes. • Available treatments for AML have poor survival in refractory disease or following relapse. This approach, if successful, would address a significant unmet medical need. The proposed treatment has the potential to significantly improve patient outcomes (including

	survival) over current standard of care approaches in relapsed/refractory AML patients. If this treatment improves patient outcomes it would be a significant step forward in the treatment of this patient population and would be incorporated into the treatment path for patients with relapsed/refractory AML. ● The therapeutic options for refractory AML remain very limited, and there is currently no approved CAR T. ● The proposal addresses an important area of unmet need. ● The applicants report interesting preclinical findings that pretreatment with a hypomethylating agent, followed by the candidate CAR T, led to more effective targeted AML killing. This finding will be tested in the clinic.
No: 1	● The process supply chain is concerning in regard to the donor requirements for continued product availability. Although the project does show potential for impact, this issue may cause long-term constraints towards commercialization and thereby limit the significance.
GWG Votes	**Is the rationale sound?**
Yes: 13	● The proposed target antigen should lead to specific killing of myeloid blast cells without significant off-target killing of normal hematopoietic stem cells or non-hematopoietic cells/tissues. The preclinical data support this approach. This phase I study is the next logical step in determining the safety of this treatment, and should provide preliminary efficacy data. ● AML has been a challenging target for CAR T, but the preliminary data are compelling to test this approach clinically. ● The application includes strong preclinical data to support clinical evaluation of the proposed target. ● There is a strong rationale for using donor cells, as they likely have improved fitness. ● It is possible that the use of a hypomethylating agent may improve outcomes. ● The applicants present a good rationale for the target of their CAR T therapy, but the risk of alloreactivity was not discussed.
No: 1	● Questions remain around whether the target antigen is sufficiently selective. There was also a recent death in a trial for a product targeting the same antigen that may need consideration.
GWG Votes	**Is the project well planned and designed?**
Yes: 14	● The protocol is well written with appropriate aims that will provide both safety and preliminary efficacy data regarding this approach. The design of the CAR construct should (although this hasn't been proven) allow an important safety switch for the product. Proof of this concept is included in this application as an exploratory endpoint. The clinical trial includes evaluations (both clinical and scientific) that should further clarify the role of the product in the treatment of relapsed/refractory AML, which is in line with CIRM's mission. The proposed timeline is ambitious but should be feasible through the plan of utilizing the applicant institution's network for recruitment of subjects. ● The cell population in a current clinical trial is the same as the CAR T cells targeting AML undertaken by these investigators. The applicant institution's GMP facility has extensive experience with manufacturing CAR T cells and manufacturing is feasible with clear budgeting justification. ● The trial is well designed with appropriate endpoints and correlative studies to inform future directions. ● The inclusion of a suicide gene reflects good planning. ● One concern is that there is relatively little discussion of the risks of alloreactivity. While this has not been an issue with previous studies using transplant donor blood, this is a first in human allogeneic product with a relatively short manufacturing time. The use of the included suicide gene is not discussed.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	● With robust attention to recruitment goals, this project and the related objectives should be feasible to complete within the proposed timeline. The team and the institution have significant experience conducting this type of research and have access to the necessary resources required to conduct this protocol. The risks as outlined in the proposal and the contingency plans included to address those risks appear to be complete. Several of the risks are unlikely but as noted by the investigators would be catastrophic and management of those risks is difficult if not impossible. ● The applicant's institution has a large heme malignancies program and have sufficient AML patients to complete this study. AML patients can be challenging to enroll to CAR T studies and the use of an allogeneic product may help accrual.

	• The applicant's track record of accrual to previous study supports feasibility of this trial and there is thoughtful consideration of the risk of manufactured products not being infused due to rapid progression of AML. • The track record of the GMP facility supports the ability to manufacture the product. There is thorough consideration of future requirements including stability testing and potency assays should this product proceed to later phase testing. • It is unclear why the matched donor source is warranted for this program. There is a concern that this may complicate treatment over autologous approaches. • There are some issues of discrepancy around the manufacturing process and quality assurance. It is also not entirely clear what the commercialization process for this product would be.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• The investigators have addressed DEI issues and point out that their cachement area will recruit a diverse population. They have included in this application resources to help identify/recruit individuals from under-served communities in Southern California. The proposal includes plans for overcoming obstacles such as transportation, lodging, food, and even patient navigation systems to assist patients on treatment days as well as follow up visits. They specify that some of the navigators are bilingual. • The applicants have a clear understanding of the catchment area population and barriers to enrollment. • The proposal leverages strong institutional efforts to include underserved populations.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate and nurse members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 10.0

Up to 7 patient advocate and nurse 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.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	4	• There is a significant AML survival disparity for Black and Hispanic patients compared to non-Hispanic White patients. While the incidence of acute leukemia in Black and Hispanic populations in the United States is lower than that of the non-Hispanic White population, their mortality rates are notably higher by comparison. One reason for this is access to clinical trials. Therefore, expanding access of novel, potentially curative therapies, including the clinical trial in this proposal, to diverse populations may address the disparities observed in patients with AML. • The applicant has a clinical network that includes 35 sites in 5 counties in Southern California that are integrated with the main campus and provide a diverse source of patients including Hispanic, Asian, African Americans and others. They will be recruiting patients from all these sites. The applicants have created a new position, Director of Clinical Trial Diversity and Inclusion, to manage this effort. The Director works with the study teams, community organizations, DEI leaders, and other cancer center departments to implement initiatives to identify, engage, recruit, and retain study participants from diverse communities more efficiently. • The applicant is using Alpha Clinic resources to help engage patients from underserved communities and help navigate the complex

		treatment plan associated with clinical trials, including working with the community benefit office and the CCARE (Center for Compassion and Altruism Research and Education) program, which provides free education, training, and screenings throughout the community. The Alpha Clinic will fund patient navigators at satellite sites, who will disseminate information and educate the community about biospecimen donation, clinical trials, and research participation, which aids in the promotion of minority participation in research. Participants will be compensated for daily meals and for scheduled or unscheduled clinic visits.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*