Application #	CLIN1-14792 #3
Title (as written by the applicant)	Superior forward-oriented b-globin vector for treating Sickle Cell Disease
Therapeutic Candidate (as written by the applicant)	Forward-oriented globin-expressing vector CD34+ HSCs
Indication (as written by the applicant)	Severe Sickle Cell Disease (SCD)
Unmet Medical Need (as written by the applicant)	This improvement in transduction efficiency and potency will allow optimization of the apheresis process (wherein HSCs are harvested), allowing for lower CD34+ cells/kg for transduction and this achieving a better clinical outcome for more patients enrolled in SCD gene therapy trials
Major Proposed Activities (as written by the applicant)	• Measure in vivo toxicity of lentiviral vector and success of secondary transplant of CD34+ HSC • Manufacture of clinical lentiviral vector and perform clinical dry runs • IND Preparation and submission
Statement of Benefit to California (as written by the applicant)	Our protocol is designed to address multiple shortfalls that have hindered the prospects of widespread use of gene therapy for sickle cell disease (SCD). The vector design results in an improved HSC product, and a decrease in the cost of vector & cell manufacturing. Through our collaborations the goal is to bring a cost-effective approach for treatment of SCD, that can be used even in financially distressed communities leading to potential long-term benefits for Californians suffering with SCD.
Funds Requested	$4,619,455
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	3
Count	15
Votes for Tier 1	12
Votes for Tier 2	0
Votes for Tier 3	3

- 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.

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: 11 **No:** 4	• Sickle cell disease (SCD) is an underserved disease and potentially curative therapies are urgently needed. Several autologous approaches are currently in development and two recently got FDA approval. These have been priced around $2-3 million each making them one of the most expensive drugs and potentially inaccessible to most. This proposal offers the prospect of a low-cost option developed with a non-profit organization, which if successful would be a game changer in the field. • Yes, project holds potential for significant impact. Applicant is proposing to develop therapy for sickle cell disease, which continues to be associated with high morbidity and mortality. • The only current therapy that is curative is allogeneic hematopoietic stem cell transplantation (HSCT), however access to this therapy is limited by donor availability. Per the applicant, only 10% of patients with severe SCD have a suitable donor for potential HSCT. Of course, even if/when a donor is available, HSCT itself carries risk of graft rejection and acute and chronic GvHD. Thus, remains significant unmet medical need for new therapies. • The currently available commercially approved gene-modified cell therapies for SCD have major barriers limiting their overall accessibility and impact. The applicant plans to address these barriers through the pursuit of a point of care manufacturing approach. • Sickle cell therapies are critically needed, affordable ones even more so. This has the potential to be both. • Excellent scientific team; addresses an unmet need in an underprivileged population. • As clarified in the proposal, the point of care manufacturing is beyond the scope of this grant. While point of care manufacturing would be extremely attractive value proposition, reduced cost is still attractive enough. • Potential to help drive down costs of existing therapies, though there are already two commercially available therapies. Whether or not this will translate into significant cost savings is unknown. There is significant concern about whether this concept is too late given the commercial products available and the relatively small patient population in the US. Would it be more relevant to target a genetic disorder that does not have an existing therapy? Overall, I do think it's important to advance technologies that will drive down cost and increase access. • There is concern about the ability of the investigators to conduct this trial of an unproven product given that there already are two approved products and several that will be approved by the time this trial is initiated. Would patients want an experimental therapy that performs just as well as others that are FDA approved? Would the investigators be able to recruit enough patients for this clinical trial in a competitive landscape? All these remain unanswered questions, which are beyond the scope of this pre-clinical application. • The product comes across as redundant in today's CGT field of SCD approved therapeutics and other approaches also in clinical development. The proposed treatment for SCD may not hold the necessary significance and potential for impact due to external factors, the applicant group and their science are extraordinarily strong. • Concern that by the time this therapy is approved, the landscape will be different with several other and potentially more attractive therapies. There is a question of redundancy. • The value question remains given several competing therapies further along in the pipeline. It appears to be less expensive, which may be a huge advantage outside of the US, but it is also likely the other therapies price will come down over time. • Concerned about the innovative aspects of this disease if the major value proposition is cost reduction. • Given the competitive landscape and time to approval in even the best case, the potential impact on patients appears to be low. Additionally, there are numerous uncertainties regarding the commercial availability of the product at the quoted prices. • While scientifically sound & well planned, given the current availability of three commercial gene therapies for sickle cell and the current pre-clinical stage of the proposed program it is unclear if the program will have sufficient impact for funding. Also, given sickle cell is a rare disease, it may be challenging to recruit patients when this therapy makes it to the clinic. There will be three commercial gene therapies likely achieving standard of care and many patients have a concern receiving a lentiviral vector-based therapy. • The field is rapidly changing and agree with the reviewers' comments that patients will be reluctant to use a lentiviral product associated with HIV when there are alternatives.
GWG Votes	**Is the rationale sound?**
Yes: 15	• The applicant proposes to develop a product for autologous HSC utilizing a "forward-oriented beta-globin-expressing vector", which the applicant hypothesizes will address current shortcomings of other approaches, specifically increased manufacturability, and

No: 0	greater transduction efficiency/ potency (resulting in lower required dose levels and further increase manufacturability). ● Applicant has conducted several promising proof of concept studies in multiple species, comparing their proposed methods to more traditional products; data appear promising and are sufficient to justify continued development of program. ● Autologous HSC with ex vivo modified cells to correct the SCD mutation has rich history of nonclinical and clinical data supporting this conceptual approach and mechanism of action. ● Very good rationale, the forward-oriented vector is innovative and may lead to less need for CD34 collection. The proof of concept is very much needed and reducing costs is fundamental if we want this transformative therapy to be more widely available. ● Project continues to have sound rationale for proposed approach. ● Although there are two commercially approved ex vivo gene modified HSPC based therapies for sickle cell disease, these treatments remain challenging from a cost and manufacturing logistics perspective. The pre-clinical pipeline is rapidly growing with novel in vivo gene editing approaches that target HSPCs. These approaches may ultimately supersede current ex vivo approaches including the one proposed by the current application. However, these in vivo approaches are many years away from becoming a commercial reality for sickle cell disease. In the interim, there remains a significant need for new models and approaches for expanding the ex vivo gene modified cell therapy pipeline of drugs for sickle cell patients. ● The applicant submitted expanded rationale and description for the feasibility of reduced manufacturing costs, which appear reasonable for this stage of product development. It may be appropriate to incorporate interim milestones relating to realizing these reductions in costs to ensure that the overall value proposition of project continues to be favorable. ● The rationale of the forward-oriented vector has been shown in several preclinical studies and the likelihood of it being successful is high. However, it is unclear that it would make much of a difference in the clinical setting. ● Yes, the rationale is sound, though the increased transduction efficiency has been called into question. ● Unclear understanding of ultimate value proposition; recommend discussion of the application at board level.
GWG Votes	**Is the project well planned and designed?**
Yes: 15 **No:** 0	● The clinical trial design is analogous to most other ongoing clinical trials in the field and seems appropriate. ● Well-designed, added new collaborations that make it stronger. ● This is an excellent team with a track-record with CIRM. ● The applicant proposes a fairly extensive nonclinical development program, which builds on nonclinical studies conducted to-date. ● The nonclinical development program has been discussed extensively with the FDA; FDA did not raise any major issues and gave detailed feedback on the types of studies and information that they'd want to see in an IND application. Comments seem addressable and recommendations for study designs have been incorporated into the applicant's proposed studies; granted the applicant proposes an ambitious timeline which may be challenging to address. ● Agree with the applicant that FDA does historically utilize some discretion when considering the GLP status of a study; it is more important that a study is well-conducted and controlled with high degree of independence and data integrity, which can sometimes be achieved outside of GLP compliance. Indeed, it is not always possible to maintain GLP compliance in certain study designs. ● Any potential concerns on long-term follow-up can be resolved with FDA; I don't see this as a major area of concern for this stage. ● In this resubmission, the applicant has addressed all prior critiques and has included a viable path to point of care manufacturing. Importantly, the applicant has brought in additional collaborators and has firmed up their prior collaborations and partnerships through supportive letters. Collectively, these partnerships provide important capabilities that increase the probability of success in the path toward point of care manufacturing. Additionally, the applicant has addressed some of the outstanding issues regarding mechanism of action of the proposed product and has provided a sound rationale justifying the overall target product profile relative to commercially approved products.
GWG Votes	**Is the project feasible?**
Yes: 15	● Appreciate how the applicant positioned the planned nonclinical studies as gating further investment (i.e., Go/No-go). Studies as they read out should give sufficient (and interpretable) data to inform probability of success of an IND submission.

No: 0	• The scientific team is strong and can conduct this project as described. • The applicant is proposing a lot of work, which may be at risk of delay which would push the IND submission out beyond two years potentially. Timelines are fairly aggressive. • I was concerned about the point of care manufacturing. In their response, the investigators have clarified that the point of care manufacturing is beyond the scope of this grant. While that is an attractive addition to the proposal, even without point-of-care manufacturing the proposal holds significance in light of the reduced costs of production. • I remain a little concerned about the possibility of the investigators being able to recruit enough patients to this trial and for this value proposition (low cost) to still remain possible when the product is eventually clinically approved, but that is several years in the future and remains to be seen. • Aspects of the project are feasible, but it is unclear that the applicants have the capability to see this product through all the way to a commercially approved product.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 15 **No:** 0	• SCD primarily affects people of African ancestry. The investigators are addressing a critical underserved illness. • It addresses needs in an underserved population, primarily non-caucasian. • Yes, this application does a good job considering DEI criteria as part of the overall application.

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: 9.0

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	• Strong track record related to patient enrollment. Ability to leverage Alpha Clinic and network. Excellent interactions with patient advocacy groups. Awareness of barriers to participation. • Strong DEI plan. • Alpha Clinics inclusion is a strength. Good DEI plan.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN1-14825 #3
Title (as written by the applicant)	Development of a Gene Therapy for the Treatment of WWOX related epileptic encephalopathy (WOREE)
Therapeutic Candidate (as written by the applicant)	An AAV gene therapy
Indication (as written by the applicant)	WWOX-related epileptic encephalopathy
Unmet Medical Need (as written by the applicant)	WOREE is a severe epileptic disorder resulting in dramatically shortened survival of patients. There are no therapies approved for WOREE and most patients do not respond to anti-epileptic drugs. MZ-9138 may improve symptoms and would be the first disease-modifying treatment for WOREE syndrome.
Major Proposed Activities (as written by the applicant)	• Completion of GLP studies in mouse and nonhuman primate • Manufacture of cGMP gene therapy to support the Phase 1-2 study • Clinical activities including Phase 1-2 start up and the initiation of a natural history study.
Statement of Benefit to California (as written by the applicant)	It's estimated that 1:160,000 children are born with WOREE syndrome. To date, with the help of the WWOX Foundation, the applicant has identified 4 children in California. The California company will collaborate with partner organizations & vendors in our state, including a Children's Consortium for newborn screening at a major medical center in the state and will select clinical trial sites in California. Our efforts will support identification and inclusion of California families in the pursuit of a therapy.
Funds Requested	$4,000,000
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 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	3
Count	15
Votes for Tier 1	12
Votes for Tier 2	1
Votes for Tier 3	2

- 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.

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: 12 **No:** 1	• The significant unmet medical need remains, and while it is not known how the timing of a gene therapy treatment may alter disease severity, there are no other adequate treatments. • The applicant's previous revisions of the proposal provides more context for the proposed construct. With more information provided, it is more clear how the corrections around the rescued phenotypes of the diseased mouse model can be controlled batch to batch. • The demonstration of treatment shows effectiveness based on the composite animal data. For a disease with an unmet need, the project does hold potential to provide a therapeutic. • A reviewer expressed concern that the disease's extreme rarity (less than 50 patients worldwide) presents a significant hurdle for commercial viability. Despite the unmet medical need, the limited market potential would impede the ability to bring this product to patients in the future. • Regrettably, investing in the development of this product has virtually no chance of yielding a commercial product that can reach patients. While there may be more creative solutions, the company did not present any alternatives.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 1	• The additional POC study provided in the revision showed a dose-dependent impact on overall survival and a statistically significant improvement in blood glucose. Neurological behavioral assessments showed a trend of improvement with treatment, but most assessments were not statistically significant. However, it is unlikely that additional efficacy can be demonstrated in this animal model due to the limitations of the dosing window. • The previously updated proposal addressed original concerns around the expected expression based on early discovery data. But the updated proposal includes production changes in the manufacturer, analytical comparability plans, and budgeting for potential additional animal studies. A robust analytical comparability exercise should be prepared for, and there is some concern relying on animal data at this stage of development. Ideally characterization assays, including deep-characterization, are included to support comparability in addition to assays used for release of the product. Relying only upon tests used for release may be an insufficient package, and the applicant would benefit including additional considerations when it comes to characterizing the product for comparability. • Attention to product characterization assays described and their advancement would benefit the program's activities associated with changing product comparability.
GWG Votes	**Is the project well planned and designed?**
Yes: 8 **No:** 5	• The project plan for CMC activities has been modified since last submission. The applicant plans to change manufacturers from the CDMO originally used to produce prior nonclinical materials. The current plan now has up to three different CDMOs to be used for manufacture of the AAV in the selection phase. The applicant recognizes the associated risks with changing manufacturers and has planned engagement with the agency to review the comparability protocol as outlined in the project plan. • The manufacturing comparability needs to be detailed including a functional assay as there is a major manufacturing change proposed in this application. • The proposal includes demonstrating analytical comparability between the first CDMO and the eventual new one, but the application has limited characterization assays described to support a comprehensive comparability package. Currently, the proposal describes the ongoing development of "a functional potency method which will be used for characterization" with no updates from the previous application. Considering the change in manufacturer, an assurance of potency with a qualified characterization assay would help in achieving a favorable agency review from an analytical assessment of the two products without additional animal studies. Considering the manufacturing changes, the functional potency method in development described by the applicant should be prioritized over planning, and budgeting, for a potential animal study. • The revised application contains additional data meant to address the FDA questions around the prospect of direct benefit (PDV). However, the change in manufacturing is concerning, and there was not a strong plan to address comparability. The new 'backup' animal study was not fully designed and could potentially be avoided if manufacturing and analytical comparability were properly addressed as part of the change in manufacturing. • Manufacturing issues remain in terms of comparability and functional testing of lots beyond animal studies. • The applicants seem to underestimate the significant amount of work needed for comparability and lack the necessary test methods (assays) to execute the comparison effectively. Additionally, their limited experience with manufacturing further highlights the challenges of developing a product at such a small, restricted scale.

GWG Votes	Is the project feasible?
Yes: 12 **No:** 1	• The project does have the appropriate subject matter experts, access, and contingencies described to support a feasible project. • The applicant provided suitable description of the virtual development needed just for a product specific assay, including mitigating risks with the contract vendor. They appropriately contextualize how fundamental leveraging resources are to clinically develop a therapeutic for any rare disease. • Most of the animal work is complete. • The proposal outlines an appropriate adjustment of manufacturing plans for the development of the rAAV vector based therapeutic considering the events with the first manufacturer. That said, the proposal may have less than ideal descriptions for analytical characterization of the products to support comparability without relying on a possible animal study. The overall strategy is appropriate with agency feedback planned for the eventual comparability protocol and the associated analytics. However, the limited amount of characterization assays described as available from the proposal, including the ongoing development of a functionality method, may provide for a less thorough assessment of functional comparability. Demonstration of comparable safety is likely achievable from the methods described in the CMC portion of the proposal. • The product addresses a very rare population, thus will be difficult to enroll patients. The applicants do have detailed plans to overcome these hurdles.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• The DEI plan appears responsive. • The project addresses DEI principles appropriately, but the proposed disease indication is ultra-rare with limited demographics available as described. The applicants plan to make the effort to advance the program to broaden inclusion with proposed surveys and explorations of clinical delivery to reach outside of proposed sites. • The project plans to include updated DEI strategies to build cultural sensitivity that match the stages of development for the organization. Included in their development are descriptions of participation in educational workshops that address issues of healthcare disparities with continued education planned for staff to participate in similar workshops focusing on DEI principles.

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: 8.0

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 application presents a strong DEI plan • Demographic assessment is complicated by limited data availability. Partner and clinical site plans are in place with a focus on overcoming barriers to enrollment. • With such small patient numbers – under 50 total in US and a few in California – it is often difficult to determine what a good DEI plan/ community engagement strategy should be. I think this is an area where we should develop different metrics about inclusion in trials when it comes to rare indications. • A reviewer appreciated the following aspects of the DEI plan: The applicant will seek to better understand the sex, race and ethnic demographics of this ultra rare disease. They will collect suvey data, genetic testing outreach campaigns and conduct a natural history study. They have relevant partnerships with patient serving groups, including

		those for diagnosis to identify patients earlier with free genetic testing. They leverage key opinion leaders to identify trial sites early, and they will partner with institutions' outreach offices to address disparity issues. The team will resolve barriers to enrollment by incorporating remote tools and home health visits. Finally, patient and caregiver travel, multi lingual services and cultural sensitivity will all be covered by the sponsor.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN1-16244 #2
Title (as written by the applicant)	Novel Gene Therapy Targeting Multiple Pathological Drivers of Desmoplakin Associated Arrhythmogenic Cardiomyopathy
Therapeutic Candidate (as written by the applicant)	A liver-targeting adeno-associated virus vector-based gene therapy that drives over expression of FGF21.
Indication (as written by the applicant)	Desmoplakin-related arrhythmogenic cardiomyopathy (DSP ACM) at high risk of life-threatening ventricular arrhythmias and sudden cardiac death.
Unmet Medical Need (as written by the applicant)	Despite treatment with ICDs, antiarrhythmic therapies, and heart failure medications, disease progresses and patients remain symptomatic and at high-risk. There are no disease-modifying treatments for ACM, other than cardiac transplant, for late-stage disease.
Major Proposed Activities (as written by the applicant)	• Complete IND enabling nonclinical studies • Manufacture drug product to support the proposed first-in-human trial • Complete study startup for a natural history study to support the proposed first-in-human trial
Statement of Benefit to California (as written by the applicant)	The aim of this project is to complete IND-enabling activities for development of our candidate therapy for the treatment of DSP ACM. We are confident that the candidate, a pleiotropic one-time gene therapy, holds great promise as a transformative regenerative medicine, to meet the unmet medical need of DSP ACM patients in California and beyond, as the first disease modifying therapy for this rare disease.
Funds Requested	$4,000,000
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 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	1
Count	14
Votes for Tier 1	14
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.

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 **No:** 0	• There is great potential impact even beyond that of the intended disease, if successful. • Yes, the project holds necessary significance and potential for impact. • This project continues to hold necessary significance and potential for impact. • The proposed product has the potential to offer a one-time drug product dose for a rare disease (DSP ACM), which may provide an improvement over the current standards of care. • While some treatment options exist for these types of arrhythmogenic cardiomyopathies, none are perfect. This product, if durability and safety concerns are not an issue, would add significant value. • Desmoplakin arrhythmogenic cardiomyopathy (DSP ASM) continues to be associated with significant morbidity and mortality (ventricular ectopy and arrhythmias, ventricular tachycardia, LV systolic dysfunction, heart failure, inability to exercise, decreased quality of life, decreased survival), with no disease-modifying therapies available. • The existing standard of care is inadequate. • The applicants provided updated data from nonclinical study that was pending at the time of prior submission showing efficacy in mouse model that more clearly resembles target patient population (e.g., existing disease at the time of administration). This provides additional data to support the scientific rationale. • The candidate is a systemically administered AAV gene therapy that will drive liver-specific expression of Fibroblast Growth Factor 21 (FGF21). This treatment doesn't target the mutation in Desmoplakin causing arrhythmogenic cardiomyopathy directly but rather pathways that may contribute to the disease progression. • No new issues or concerns arise based upon the re-submission.
GWG Votes	**Is the rationale sound?**
Yes: 14 **No:** 0	• Yes, the rationale is sound. Existing data in the scientific literature regarding pathophysiology of disease and bioactivity of similar products provide support for this therapeutic approach. • The rationale is sound, and applicants strengthened their rationale based on new data from nonclinical study that was pending at the time of last submission. • New nonclinical data provided by the applicant confirms bioactivity and efficacy of product when administered days post-disease onset (with comparable to outcomes when administered at prior to onset on at least one measure). Data were less compelling when the candidate was administered weeks after disease onset. Nonetheless, data provide important connection to the target patient population. • The information provided indicates early evidence of in vivo efficacy, and therefore, the proposed project appears based on sound scientific rationale. • The application presents sound rationale. • Dosing prior to disease onset was a primary concern of the first review. The applicants have since completed an additional study starting treatment after disease onset and it appears to be effective, but less so. Given that the treatment was initiated only days to weeks post tamoxifen induction in their mouse model, this may only be a partial answer. • The applicants have partly addressed the durability issue citing an animal model with a similar therapy but a different indication. They will further address durability with a planned mouse experiment. • They have partly addressed the safety/side effects issue citing an animal model with a similar therapy but a different indication. They will further address safety with a planned primate experiment.
GWG Votes	**Is the project well planned and designed?**
Yes: 14 **No:** 0	• The applicant has completed a successful preIND meeting with FDA. This was a good meeting, and FDA provided detailed feedback on the path to IND including suggested modifications to the applicant's planned animal studies. The applicant appropriately incorporated FDA feedback into the planned animal studies. • FDA agreed with planned safety/toxicity study in a relevant animal model. • Yes, the project is well planned and designed, although there are some concerns regarding aggressiveness of timelines and their feasibility. • The project is well planned and designed despite difficulties associated with the animal model. • Information provided by the applicant adequately addresses concerns regarding biological relevancy of animal model and the relevance of underlying proof-of-concept data. • The project appears well-designed with a detailed timeline that includes, most notably, many specific CMC activities required to achieve a phase 1 study initiation. The proposed CMC plans appear appropriate to support a phase 1 trial. • The CMC budget is unclear, regarding what funds will be used for which CMC activities. The

	detailed activity budget includes all CMC activities, while the manufacturing plan text indicates that funds are only required for the engineering batch. The Excel budget should match the requested funds. ● Applicants should note that most of the tests listed as "additional characterization" will be required to be on the drug substance and/or drug product specifications. For example, the process-related impurities should be on your drug substance specification. ● They also plan a dose finding study in which the treatment will be given prior to disease onset. This may not be the best way to determine the dose, given what appears to be a reduction in efficacy when therapy started post disease onset. ● It is not clear why they chose an intermediate dose in the long-term mouse study. Since this study will be started after the dose finding study why not use the optimal dose? ● They provided additional mechanistic data in the resubmission which adds some strength.
GWG Votes	**Is the project feasible?**
Yes: 14 **No:** 0	● The internal and external teams are appropriate for an AAV drug product, with a high chance of CMC success. ● This appears to be a solid team who has established strong partnerships with subject matter experts, consultants and others. ● Applicants provided expanded discussion of risks and potential mitigations, which is welcome. It's important also to note that the team overseeing regulatory and nonclinical testing is very good and appropriately qualified to navigate risk. ● The project is feasible; although, the timeline may be overly aggressive. ● The applicant presents a reasonable, albeit ambitious, project timeline for their path to IND. ● The project as proposed seems feasible. ● An aggressive timeline is proposed, but applicants did move up dose finding earlier. ● The applicant is proposing to conduct the IND-enabling dose ranging study in parallel with the IND-enabling GLP tox study, as well as the exercise study in mouse model of disease. This introduces non-trivial amount of additional risk in that learnings from one study cannot be easily applied to subsequent studies. This risk may be justifiable, but a panelist would appreciate greater description of this potential risk and related contingency plans, particularly given the stage of the program. ● Nineteen staff remain to be hired, which applicants address by saying they have experience with rapid scale up.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	● Yes, responsiveness to DEI principles appears sufficient. ● The applicant presents a very strong DEI plan ● The applicant has considered race, ethnicity, sex, gender and age when designing the studies and clinical trials. The company appears to have a strong DEI commitment.

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: 9.0

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	3	● Applicants describe a robust institutional commitment to DEI, as reflected in all sections of their application. ● A reviewer appreciated the applicants plans to work with patient advisory boards that include a diversity of patients as well as patient serving groups, outreach to partner organizations, clinicians and patients, cultural sensitivity training plans, plans to address barriers to participation and recruitment, as well as their plans for communicating results of the study back in a culturally sensitive way. ● Applicants will have mechanisms in place to hold the company and sites accountable for meeting health equity and inclusion goals.

		• Some enrollment goals are well below prevalence (Latino/Asian), while others (White/Black) are well above
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-15218 #2
Title (as written by the applicant)	A Phase 2 Study Evaluating the Efficacy and Safety of IV Administered rAAV Gene Therapy in Male Patients with Danon Disease
Therapeutic Candidate (as written by the applicant)	A recombinant Adeno-Associated Virus containing the LAMP2B transgene
Indication (as written by the applicant)	Danon Disease
Unmet Medical Need (as written by the applicant)	The candidate therapy, if successful, will address the unmet clinical need by serving as a disease-modifying therapy with curative potential for Danon Disease patients at high risk for disease complications.
Major Proposed Activities (as written by the applicant)	• Manufacture product to supply the proposed Phase 2 trial at a major California medical center • Assess clinical safety and preliminary efficacy of the therapeutic candidate • Coordinate various CROs to support the clinical trial the entire patient journey, including follow-up visits
Statement of Benefit to California (as written by the applicant)	The applicant organization is developing the candidate therapy under collaboration with major California medical center. The center will be the initial and lead center for the planned Phase 2 trial under the direction of the center's lead in the Advanced Heart Failure Treatment Program. The center will be a leader in gene therapy for heart failure, employing dozens of Californians to support research and clinical trials in this new fi eld.
Funds Requested	$5,808,735
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	3
Count	14
Votes for Tier 1	12
Votes for Tier 2	1
Votes for Tier 3	1

- 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.

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: 12 **No:** 1	• The only available treatment for Danon disease is cardiac transplant once patients reach a late stage of cardiomyopathy. Thus, there is an unmet medical need for treatment to slow the progression or reverse the cardiomyopathy. Without cardiac transplant, males with Danon disease die in the second to third decade of life. Affected females can also develop cardiomyopathy as adults and require cardiac transplant. Cardiac transplant can prolong life but is not curative, as it doesn't address the extracardiac manifestations of the disease. • Danon Disease is a uniformly fatal lysosomal storage disorder for which an AAV therapy is proposed. • Yes, as Danon Disease is highly fatal during the second and third decades of life. • This has the potential to make a major change to standard of care and provide a promising treatment alternative. • The candidate therapy appears to work in those patients already enrolled. • This is a novel AAV-based treatment for Danon Disease that has been tested in over ten patients to date and demonstrated potential benefit. Given the potential benefit, the FDA has provided approval for an open label single dose phase 2 study in more than ten male patients and an approximately 40 patient, 2 year natural history (NH) study, for which funding is sought. Several questions were raised in the prior review: lack of FDA correspondence, and thus, no indication of whether company was aligned with FDA assessment of therapy; results of the phase 1 study; whether recruitment could occur over time period indicated given long time required for fewer patient recruitment in phase 1; why not recruit females in phase 2; and whether 2 year duration was an adequate comparison for a NH study. • Sites will be in both the US and Europe. Only a quarter of subjects in the phase 2 are planned to be enrolled at the single CA site. • A reviewer questions that the study will be impacted significantly by CIRM's funding. It is ongoing, and nothing will be changed based upon feedback from CIRM (the resubmission was not changed at all). It is not clear why CIRM would be involved with, or needed for, this study.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• Clinical data from the phase 1 study of the candidate in evaluable adolescent and adult males with Danon disease provides encouraging evidence of the potential of this approach with improvement or stabilization at the molecular, organ, and functional levels with improvements in cardiac anatomical measures, biomarkers of heart failure, symptoms, and quality of life. These results support moving into this phase 2 study, which could potentially result in product approval for the male Danon population if efficacy is robust compared to the planned natural history cohort. This would be an accelerated approval based on 2-year data, but FDA apparently has indicated following these subjects for 5 years would provide the data set needed to convert it to a full approval. • The applicant responded in the resubmission to reviewers' request for data regarding the level of LAMP2B protein expression achieved by this gene therapy and whether this level is adequate for disease modifying activity in Danon disease patients. Although the minimum amount of LAMP2 required to improve the phenotype of a male Danon disease patient has not been precisely quantified, the applicant believes the phase 1 trial data indicates that modest levels of cardiac LAMP2B are highly likely to confer clinical stabilization or benefit through 36-54 months of follow-up. In the phase 1 trial, signals of consistent LAMP2 expression across cardiomyocytes in the biopsy area were observed in all subjects by 12 months post-treatment. • The rationale is sound. • At the latest submission, it appears some of the identified patients to be dosed in California may not be available due to their primary location in an area of active conflict. Beyond this, the investigators are trying to open sites in Europe. It is unclear if the European patients will be treated in the US or Europe. Taken together, the benefit to California is unclear.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 1	• The phase 2 study is a well written and designed open-label, single dose study in over ten male subjects with 5 years of follow-up. In addition, a concurrent, prospective natural history study is underway by the applicant to provide external comparator data for the phase 2. • The project is well planned, though there are certain aspects to the study design that could look different as outlined in the previous review. • The dosage is based on phase 1 safety and based upon agency feedback. The investigators have modified the trial per the FDA recommendations to include additional primary and secondary endpoints that increase the likelihood of finding good surrogates for success.

	• I don't believe the applicants demonstrated a feasible path forward to commercialization. The enrollment is challenging. FDA seldom accepts data from a single arm study for registration unless the natural course is very well understood, as in cancer. The applicant has pushed back on the request for a 5-year natural history study, for understandable reasons, but it will make it even harder with FDA.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The project is feasible. However, there is potential concern about the pace of enrollment, especially for patients to be treated in California. • Enrollment at California sites appears to be limited. • Enrollment appears to be much more challenging than their timelines would predict. • The timeline for completion of this study is extremely aggressive, and although multiple patients have been screened, the likelihood of meeting the 2024 deadline for 9 more patients is low. It is more likely that the timeline will be extended 6-18 months.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 1	• The applicant was responsive to concerns about DEI plans. • The primary clinical site in California was chosen for its prior experience in gene therapy, especially in cardiomyopathy, excellent facilities, and caring personnel. • The California site was chosen as a clinical study site due to the anticipated diverse patient population and commitment to DEI. The study will enroll a diverse population reflecting the overall US population. Applicants will have access to the sites community outreach programs that serves the rural area of the state and underserved areas in the host county. The small sample size may limit conclusions on disease progression or treatment response in ethnic minorities. • Given the limited Danon disease population worldwide, the degree to which DEI can be considered is unclear. The investigators are encouraged to make their trial information more broadly known in underserved communities to make every attempt to recruit therein. Concerns were raised in the prior review about how the applicants will ensure diversity in the trial. This critique was not addressed. The prior review said, “They do not propose sufficient action to ensure access to underserved populations." To the best of this reviewer's knowledge, they have not addressed this in any fashion. • The current phase 2 pivotal trial focuses on male DD patients, but the sponsor intends to investigate the treatment in female patients as well. • A reviewer disagreed with the approach to exclude women, especially given how hard it is to find patients with this disease and enroll. • The current trial focuses on males, the disease is highly fatal in males during the second and third decades of life. Danon disease is rare, with an unknown prevalence in the general population but reported in ethnic populations. Most genomic studies and disease understanding come from European ancestry, leading to limited knowledge of different ethnicities. Being a rare disease, it’s hard to gauge the impact to underserved communities. • The clinical trial's inclusion and exclusion criteria are based solely upon the medical condition of the candidate, determined by the PI and applicant team after examining medical records. • The applicants’ response to “The team is encouraged improve their cultural responsiveness through available DEI resources, it would be appropriate to have a baseline mandatory DEI training across the board for all team members” provided great details about internal company DEI culture. The initial suggestion was aimed at improving working with patients and the public.

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: 8.0

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 application presents a strong DEI plan. • Yes, the project upholds the principles of DEI.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-16156 #2
Title (as written by the applicant)	Selective, Off-the-Shelf Logic Gated CAR NK Cell Therapy Targeting CD33 and/or FLT3 Expressing Hematologic Malignancies
Therapeutic Candidate (as written by the applicant)	An allogeneic off-the-shelf chimeric antigen receptor (CAR) natural killer (NK) cellular therapy targeting CD33 and/or FLT3 malignancies.
Indication (as written by the applicant)	CD33 and/or FLT3 expressing hematologic malignancies, including acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).
Unmet Medical Need (as written by the applicant)	AML and MDS have a grim prognosis and a profound unmet medical need. The ideal therapeutic should target cancer cells and protect healthy ones. This product exhibits selective cytotoxicity against primary CD33 and/or FLT3 expressing AML/MDS patient-derived samples, while protecting primary HSCs.
Major Proposed Activities (as written by the applicant)	• GMP manufacturing and drug product release to supply the Ph1 clinical trial • Assess clinical safety, determine the recommended Ph2 dose, and evaluate preliminary efficacy
Statement of Benefit to California (as written by the applicant)	This product will benefit California patients with AML and MDS malignancies. In 2021, in California AML caused the death of 2 females and 3 males per 100,000 while MDS caused the death of 2 females and 2 males per 100,000. The incidence of AML and MDS are highest in the White population, but disparities impact survival in minority populations. We selected sites that have high percentages of Hispanic, Black, and Asian patients, such as Los Angeles (these comprise 58.4% of California's population).
Funds Requested	$8,000,000
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 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	1
Count	12
Votes for Tier 1	12
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.

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: 11 **No:** 0	• The current cost of treating relapsed/refractory AML is nearly $0.5M/patient, but cure rates for this patient population are less than 10%. Better and more cost-effective treatments are needed, an unmet need that could be addressed by this product. • This treatment will be given after standard chemotherapy for patients with relapsed/refractory AML, aligning the protocol with standard management of patients with AML. • A novel logic gate in the NK CAR could reduce on-target toxicity to normal hematopoietic progenitors, a problem with all therapies that target myeloid antigens expressed on leukemia blasts. The applicants provide appropriate data on the specificity of the NK CAR on AML cells with relative sparing of normal hematopoietic progenitors. • The study will enroll patients aged 20-74, a group comprising most patients with AML and MDS. • Applicants responded to all questions and concerns from the prior review point-by-point, and it is satisfactory. It makes it great application and deserves a fundable score. • The applicant addressed prior critiques.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 0	• The applicants responded to all concerns listed above. • The CAR includes a bispecific single-chain antibody that target myeloid antigens. The off switch is activated by binding to a protein present on normal hematopoietic progenitors and vascular endothelium in the bone marrow. The applicant has addressed previous concerns regarding the specificity and selectivity of the “on” and “off” switches. • Autocrine signaling of the product can sustain NK CAR survival in vivo. It is unclear why additional cohorts that receive a separate treatment are planned when the CAR product produces a tethered molecule generating autocrine signaling through a different receptor. • The pharmacokinetics of the product was done in mice that lack NK cells. The applicant has yet to determine how long they will persist in human patients who have their own NK cells (that persist after lymphodepleting chemotherapy) that may reject this product. • Clinical data from a related NK cell product tested in early-phase clinical trials in another country indicate 22%- 67% response rates, with responses lasting > 3 months. Dual targeting of antigens may allow control of bulk AML blasts and leukemia stem cells.
GWG Votes	**Is the project well planned and designed?**
Yes: 11 **No:** 0	• Several lots of the product will be used in clinical trial. • The release criteria include the expression of the intended CAR on a large percent of NK cells but also requires low percent of cells with undesirable expression profiles by flow cytometry. This mitigates the risk of on-target toxicity against normal hematopoietic stem cells. • The method of donor selection and a strategy to follow outcomes that may reflect donor heterogeneity during manufacturing are described. • If the product is given after induction therapy for relapsed/refractory AML, patients will likely require prolonged hospitalization, making administration in the outpatient setting impractical. The statement in the protocol “Patients will be enrolled from cancer centers with large patient populations adequate to meet enrollment goals. The clinical sites are renowned cancer centers, leaders in oncology research with established cell therapy centers” indicates that enrollment of patients at community hospitals is not planned. The FDA correspondence requires hospitalization for the first 21 days. • The dose for patients weighing less than 50 kg is 1/10 that for patients weighing 50 kg.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 0	• The dosing of patients enrolled in the phase 1 trial has begun, with a press release from the applicant indicating the “the majority of manufacturing costs associated with the trial have been pre-paid”. The applicant has sufficient employees with the requisite experience in clinical trial design, regulatory compliance, and trial execution to complete the planned study. • The contract organizations used for manufacturing, clinical trial execution, and data management are well-qualified. The manufacturing and release testing time frame includes a few weeks for manufacturing a GMP batch of the product from NK cells enriched from the blood of healthy donors, with testing and release requiring another few months and a few weeks for fill and finish and release/authorization. • The sponsor has de-risked protocol interruptions due to a lack of product by adopting a manufacturing plan with the manufacturer and supplier to manufacture multiple lots of the product before the clinical trial to ensure an adequate drug product supply. The planned

	manufacturing protocol also assumes a 15% manufacturing failure rate, so a sufficient product should be available. ● The clinical implementation of the protocol has been de-risked through an established process of coordination between the quality team staff at the applicant organization, the technical operations team, the staff at the contracted organization for the manufacturing, and the research organization responsible for fill and finish, and distribution of the product. ● More than 30 unique lots of CAR NK cells have been manufactured and tested in pre-clinical studies, supporting the feasibility of consistent manufacturing. ● The site for manufacturing has extensive experience with this product. Release criteria are standard to the industry and achievable in scale-up for the phase 1 clinical trial.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 11 **No:** 0	● Excellent DEI plan

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	3	● Meets all criteria across the board for DEI score. ● Strong DEI plan.
6-8: Responsive	1	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*