Application #	CLIN1-14874 #2
Title (as written by the applicant)	Extracellular Vesicles for Ventricular Tachycardia
Therapeutic Candidate (as written by the applicant)	Extracellular vesicles derived from cardiosphere derived cells
Indication (as written by the applicant)	Patients afflicted with recurrent fast and irregular heart beating (a.k.a. ventricular tachycardia).
Unmet Medical Need (as written by the applicant)	Ventricular tachycardia (VT) is a rapid heart rhythm from the ventricles. Current therapies lack effectiveness, have side effects, and lack consensus. Non-destructive fibrosis-reducing therapy can improve outcomes in some patients with recurrent VT.
Major Proposed Activities (as written by the applicant)	• Manufacture product for the proposed study • Completion of preclinical safety studies • Completion of preclinical efficacy studies
Statement of Benefit to California (as written by the applicant)	A non-invasive cell-derived therapy for ventricular tachycardia offers significant benefits to California. It provides a safer alternative to invasive procedures, reducing risks and complications. This enhances healthcare by lowering costs, improving quality of life, and promoting accessible and effective treatment. California fosters a healthier population, ensuring a brighter future for residents.
Funds Requested	$5,999,441
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	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.

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 **No:** 0	• Cardiomyopathies remain a significant public health burden; the proposed product has the potential for significant impact. • The product has the potential to treat ventricular tachycardia. Extracellular vesicles (EV) are potentially easier to administer than cells. Safety studies in pigs have been shown out to 12 months. • The use of EVs is early in development, similar to monoclonal antibodies in the 1980s. One of the reasons I support this application is that developing EVs as a category of therapeutics will need experience. • The applicant does a good job describing why the current therapies are not sufficient and proposes that targeted coronary intravenous delivery of cardiosphere-derived EV would both be safe and compare favorably with regard to cardiac function, scar volume and electrical stability. The preliminary data presented with a similar product or its precursor show improvement that if recapitulated with the clinical product would be a viable therapeutic strategy. • In response to prior critiques the investigators appear to have removed microvascular disease as an exclusion criterion for enrollment in their clinical study obviating the concern about excluding women. • The investigators have presented preclinical data and reinforced that the proposed route of administration is likely to lead to localized and thus good delivery. What is still unclear about the delivery is how the investigators will choose the multiple sites in a given patient or animal and if/how the distribution may affect outcome. • In reply to the reviewers the now proposed pig efficacy studies will include a > 6-month subset with multiple sites of administration as utilized with patients. Again, how they choose multiple sites is unclear. The safety studies will now occur for a later time point in response to prior reviewer's request for > 6 months.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 1	• The preclinical data support the rationale for the product. • The applicants have performed additional experiments to demonstrate the efficacy of the proposed route for delivering the product. • Extensive preclinical and clinical data exist for the use of cardiospheres - the parent product of the cardiosphere-derived EVs. New preclinical data were presented demonstrating the efficacy of research grade research grade EVs delivered via coronary sinus/venous infusion. • Investigators have significantly extended study endpoint monitoring of arrhythmias, post infusion. They have included comprehensive investigations and questionnaires for patients to complete. • The clinical application mentions quantifying biomarkers if patients consent; these are still not listed in the clinical protocol or in the proposal. The discordances in the clinical protocol and proposal otherwise appear to have been cleaned up. • The removal of the prior catheter from the market is likely one reason for the new delivery method. The investigators propose catheter delivery if the preclinical data do not demonstrate better efficacy. No new information was presented about their new catheter which was to be prototyped by June 2023. • Given the number of various experiments using extracellular vesicles in a large number of different indications, I'm not convinced this will work. The proposal may address some of these concerns, but overall, I lack enthusiasm for this product.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 1	• Additional data presented support the efficacy and safety of the coronary venous delivery technique. Two weeks after therapy, areas of isolated late potentials, previously identifiable within the arrhythmogenic substrate, were markedly reduced in EV-treated animals compared to controls. • The current team has had two studies with cardiosphere-derived cells demonstrating improved outcomes, in part because of careful choice of clinical endpoints; first post infarction with improved ejection fraction and scar size; second in Duchenne's muscular dystrophy with cardiac and skeletal muscle "function." The current trial design is similar; very carefully chosen endpoints that are likely to be impacted by the interventions. If true, that EVs mediate this, EV would appear to provide the benefit of cells with better stability, shipping potential, and delivery profiles than their parent cells. • In response to the prior critiques, the investigators have proposed preclinical studies with the GMP-grade EVs lasting more than six months as well as acute and chronic toxicity studies in rats at multiple doses.

	• The applicant addressed the nonclinical issues by extending the duration of the safety study. • The most compelling change in this project is the extension of the pig study duration. This extension allows for a more comprehensive assessment of the safety and efficacy of coronary venous delivery of the EVs. It also provides initial data on the durability and potential therapeutic benefits of this treatment approach. • Their response justifying single injections was one of their weaker responses. It was based on effects observed in previous studies with allogeneic cardiospheres in myocardial infarction models. There was no work proposed to study repeat dosing, but the potential of this approach might be seen in the expanded preclinical work. • Manufacturing concerns were not well addressed.
GWG Votes	**Is the project feasible?**

Yes:
13
No:
0
	• With the state of purification and analytic technologies at this point, the program is feasible.
	• The team assembled for this program have a successful track record in conducting clinical trials in cardiomyopathies.
	• As the researchers are transferring a lab protocol to manufacturing, it would be prudent to budget in activities to further optimize the manufacturing process since the lab protocol likely will be inefficient in providing larger volume of EVs from phase 1 and 2 trials. Some of the areas of improvement are listed below:
	  ◦ How long can the cardiospheres be passaged before senescence?
	  ◦ How will the quality of the EVs be changed when making EVs over a few days vs. over two weeks in the prior publication?
	  ◦ Explore switching to a suspension culture method to make EVs would be more amenable for translation into bioreactors.
	  ◦ What is the alternative method to size exclusion chromatography for larger volume processing?
	  ◦ Can the production process be reduced to be completed in one continuous run without two freeze thaw cycles?
	  ◦ High dose injections should cover up to a dozen infusion points to increase area of treatment, rather than injecting a larger dose in the same smaller number of points.
	• It is still unclear if a single batch of product will be sufficient for the preclinical or clinical study; likewise, the batch-to-batch variability is still unclear; no new data were presented regarding this. Previously it appeared that a single lot of product may not be sufficient for this study. Currently it is unclear if functional comparisons across lots have occurred previously given that one lot appears able to supply over a dozen pigs and most studies are small. This comparison will be key for interpreting any clinical results.
	• The FDA correspondence strongly encourages development of a potency assay. At one place in the proposal the investigators mention a qPCR potency assay, but no description is available. The qPCR identity assay of five proteins is shown but it is unclear how these relate to potency. Admittedly, potency is not needed at this stage, but development will need to occur.

GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• Working together with the Health Equity Office, investigators are assessing additional centers at different locations to increase recruitment of Black/African American populations. • DEI additions regarding outreach to African Americans strengthen the plan. • A product such as exosomes may allow for a broader reach to communities that are underserved with significant prevalence of cardiomyopathies. • Overall, there were no real changes or improvements to the DEI (Diversity, Equity, and Inclusion) section.

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	6	• Good discussion of impact to different demographic groups. • When ready to move into clinical patient study, good discussion on accessing from many diverse population centers to meet the noted impact on these communities. Like that zip codes will be used to access socio-economic challenged patients. • Though regional in nature, strong discussion on utilizing the Alpha Clinic sites in California for accessing patients. Plans not well defined but intention is strong. • Good demographics, ability to access Alpha Clinic network. Could have better outreach analysis. • Adequate description of DEI efforts.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*