Application #	CLIN2-14302
Title (as written by the applicant)	Phase 3 Trial and Related Activities to Support Clinical Development of Genetically Modified Human Umbilical Cord-Derived Vascular (Endothelial) Cells
Therapeutic Candidate (as written by the applicant)	Our proposed therapy is an intravenously infused medicine containing genetically modified, umbilical cord-derived human vascular (endothelial) cells intended to repair damaged tissue
Indication (as written by the applicant)	Treatment to reduce/prevent severe multi-organ complications from curative high-intensity cancer treatments involving stem cell transplantation
Unmet Medical Need (as written by the applicant)	Aggressive cancers can be cured with high-dose chemotherapy, radiation, and stem cell transplantation. However, highly effective cancer treatments also tend to damage healthy tissues, making patients gravely ill and prolong hospitalization. Our proposed endothelial cell therapy is intended to address this serious unmet need.
Major Proposed Activities (as written by the applicant)	• Conduct and complete late-stage (Phase 3) trial • Conduct manufacturing and quality control activities related to the Phase 3 trial • Conduct laboratory testing (non-clinical) activities related to the Phase 3 trial
Funds Requested	$15,000,000
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 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	10
Votes for Tier 2	3
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: 12	• Yes, the product is being developed for severe regimen-related toxicities (SRRT) which are serious, and at times, life-threatening morbidities that greatly impact the quality of life

	of patients post hematopoietic stem cell transplant (HSCT). There are no available therapies for SSRT; thus, the proposed product addresses an unmet medical need. ● The proposed therapy is human umbilical vein endothelial cells transduced with the pro-survival adenoviral E4ORF1 gene. The therapy will be administered to lymphoma patients undergoing high dose chemotherapy/radiation and HSCT. ● The viral transduction results in a stable and potent engineered cell therapy that can supplement or even replace the function of endogenous vascular niche endothelial cells that have been injured from regimens used prior to transplantation. ● The proposed therapeutic directly addresses the underlying cause of SRRT by repairing the injured stem cell niche. ● It may allow the administration of fully effective doses of chemotherapy in more frail patients without causing SRRT, which would address a significant unmet medical need. ● Importantly, the US FDA has recognized SRRT as a serious unmet medical by conferring two 'special status' designations to the therapeutic proposed in the current project: the Orphan Drug (OD) and the Regenerative Medicine Advanced Therapy (RMAT). ● High SRRT rates occur even in US oncologic transplant centers employing state-of-the-art prophylaxis regimens. This agent could be the first to address SRRT, by restoring the organ vascular stem cell niches and their function in multiple organs. ● The occurrence of SRRT dramatically increase costs and burden to the healthcare system. ● The success of this project would result in the first FDA marketing authorization for a human engineered endothelial cell therapy.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	● Yes, the rationale is sound, and the proof of concept has been demonstrated in both non-clinical and phase 1/2 clinical studies. ● Yes; extensive preclinical data and clinical data support the project. ● In animal models, transplant of healthy endothelial cells can supplement or even replace the function of endogenous vascular endothelial cells that have been injured from radiation, aging, and chemical injury. ● Clinical translation of endothelial cell transplant has been limited by donor cell availability and instability/senescence of endothelial cells in large scale culture. The core technology accompanying the proposed therapy takes advantage of the inherent neonatal nature of human umbilical vein endothelial cells (HUVECs) and enhances and stabilizes them by transduction with the pro-survival adenoviral E4ORF1 gene. The result is a stable and potent engineered cell therapy product that can be scaled in automated bioreactors for clinical studies and commercialization. This product is the first iteration of the core platform.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 11	● Yes: Clinical feasibility and practicality of distribution, site preparation, and treatment is currently supported by the experience of the successfully completed phase 1b/2 study and expected to be further supported by the experience through the phase 3 study involving up to 30 clinical sites, all of which represent high volume HCCT centers in the US. Many serve diverse populations. ● The proposal includes extremely detailed study start up, initiation and conduct activities and detailed budget justification; no concerns. ● The timeline is well-described. ● Well designed. The applicant has done a good job answering FDA questions. ● Trying to do stratified randomization with four factors is not practical with this number of sites and the sample size. You will end up with many empty cells and very few with n>15. I would reduce to one or two factors and then model the rest at the analysis stage. ● It would be useful to give the DMC a futility boundary; otherwise, it's unclear how they would establish a recommendation to stop the trial. ● For the 100-day endpoint I would consider a time to first toxicity analysis - timing of the toxicity is surely important. ● Excellent Data Sharing plan.
No: 1	● The FDA repeatedly asked for the following supplemental data as part of the BLA submission:

	● FDA would like to see at least one other bioactivity assay and measurement of at least two other angiocrine factors. "The MOA of your product is complex and it is not clear if measuring G-CSF secretion alone is sufficient to account for the potency of your product. Please consider evaluating additional potency assays before initiating efficacy studies." The applicant proposes an animal study is to develop in vivo data for the supplemental assay. While FDA has accepted the current G-CSF based potency assay for phase 3 and BLA submission, it is unclear what the animal study will measure or how the animal study will actually enable the development of additional measurement of angiocrine factors. ● FDA also mentioned that a "[p]otency assay for the retroviral vector would need to be qualified before initiation of the proposed efficacy study. Expression of the E4ORF1 transgene is not an acceptable potency assay at late stage of development as it does not reflect the activity of the vector." However, the applicant doesn't seem to directly address the development of a biological assay for the retroviral vector. It seems imperative that the sponsor develop a biological activity assay for the retrovirus vector.
GWG Votes	**Is the project feasible?**
Yes: 12	● Yes. However, the need for CIRM funds is not clear as the trial has already begun enrolling. ● The project is feasible and has demonstrated clinical proof of concept. ● **Yes:** the applicant has developed a plan for the regulatory path to licensure in the US. ● The trial has received a RMAT designation by the FDA, and a "safe to proceed" designation was provided in October 2021. ● Budget is appropriate: appropriate amount of effort for major players; requested funds for consultant contracts. ● The proposal includes a detailed team description including clinical, medical and quality management, DEI, CRO, data collection and handling, central and specialty labs, etc. ● The proposal includes detailed manufacturing/CMC plan; have already shown ability to scale up in phase 1,2 trials including development of animal potency markers, biomarker assays. ● Overall, the manufacturing procedures for both vector and DP are well described and have received FDA approval, as have the release testing criteria. ● The applicants have satisfactorily responded to a variety of CMC requests from the FDA and received a "safe to proceed" designation. There are some recommendations that the FDA has made relating to potency and stability but apparently the applicants responded to these. ● The manufacturing plan has been approved by the FDA. The retroviral vector manufacturing is well described at an excellent level of detail. The drug product preparation is also detailed and has received FDA approval. ● Details of release testing are provided together with the acceptance criteria. ● As would be expected for a phase 3 trial, the manufacturing plan is detailed and well presented. All of the manufacturing and testing information has been approved by the FDA. ● Overall, yes. However, the path to the BLA from a CMC perspective, seems incomplete and has ample room for enhancement with regard to ensuring a successful submission. ● Major risks identified are DP contamination (mitigated by use of a closed system and rigorous release testing) and problems during transportation (mitigated by use of a cold chain transport company). The applicant has agreed to cover the costs of these risks should they occur. ● Supply chain security has been addressed by procuring large amounts of the required reagents and materials.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	● Very strong approach to DEI. ● Yes. Severe regimen-related toxicities (SRRT) are pervasive, affecting all patients, with no known association with the patient's race, ethnicity, sex or gender, but more prevalent in patients > age 40 and with comorbidities. Thus, recruitment is specifically focused on patients >40 undergoing hematopoietic stem cell transplant (HSCT) (as recommended by FDA) with no upper age limit.

	• The applicant's phase 1b/2 trial population reflected the diversity of the broader population of the area surrounding the trial sites. • The applicant discusses the large Hispanic and Latino populations in California. • The applicant discusses their goal for the phase 3 study: To recruit patients from each ethnic/racial group to reflect burden of disease, with adjustments to reflect the relative percentage of patients from each ethnic/racial group that receive HSCT. • The applicant has plans to obtain the perspective of trial participants as the trial progresses, and use this perspective further reduce barriers to participation. • The CRO will make phone call and discussion scripts for site staff, with language and culturally appropriate considerations, translate all materials into other languages as needed at the trial sites, and provide live translators to assist with the informed consent process. • Clinical staff will be required to complete all six modules of the training program "Equity by Design in Clinical Research: A Six Part Course."
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	1	• The mortality rate for lymphoma is essentially the same for different ethnicities and races. The trial goal for phase 3 is to recruit patients from each ethnic/racial group to achieve average ratio between the lymphoma population of California and US, with modifications. • The five trial sites in California reflect the diversity potential for clinical trial participants, all ensuring a diversity of clinical trial participants which they found in their phase 1b/2 study drawing patients from diverse populations. • Well-described DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*