Application #	CLIN1-12880
Title (as written by the applicant)	A novel stem cell-based implant for articular cartilage restoration
Therapeutic Candidate (as written by the applicant)	The implant consists of pluripotent stem cell-derived chondrocytes, seeded onto a scaffold; it is intended to treat damaged cartilage in the knee joint.
Indication (as written by the applicant)	The implant is intended to be surgically implanted in the knee and regenerate injured cartilage - relieving pain and improving function of the joint.
Unmet Medical Need (as written by the applicant)	FDA approved treatments for articular cartilage injury are costly, involve complex logistics, and often do not restore functional hyaline cartilage. This implant aims to address this need by providing an inexpensive, off-the-shelf therapy with the capacity to regenerate functional hyaline cartilage.
Major Proposed Activities (as written by the applicant)	• Manufacture pluripotent stem cell (PSC)-derived cartilage implants compliant with the GLP release criteria for tumorigenicity studies • Assess the potential toxicity, biodistribution and tumorigenicity of the implant in an immunocompromised nude rat • Manufacture of two fully GMP grade compliant lots of the implant prior to IND filing and subsequent Phase 1 clinical trial
Funds Requested	$5,999,782
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 proposal have the necessary significance and potential for impact?
Yes: 13	• This application addresses articular cartilage lesions which, after progression, lead to osteoarthritis. Currently there are no robust treatments for these lesions, so this proposal

	has a significant potential for impact in this indication. • An off-the shelf product to repair articular cartilage with the potential to reduce issues down the road, such as osteoarthritis, is an unmet need. • The novelty of this pluripotent stem cell/scaffold and the strength of preclinical data may allow for a less expensive and potentially routinely applicable therapy, where no relatively simple options currently exist. • Approach is innovative and thoroughly researched. • If successful, this treatment would provide an improvement over current standard of care. • The current strategy should provide an improvement to the current standard of care. The treatment offers the potential increased benefit of a longer-term engraftment with consequent cellular and paracrine signaling to affect cartilage repair. • While the clinical trial aims to treat a subset of subjects with lesions, success in this subset should allow expansion to other groups. • An additional value proposition is an improved shelf life and an anticipated reduced cost.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The applicants have very promising pre-clinical data which is a major strength. • Novel pluripotent allogenic cell source in combination with established surgical criteria. • The preliminary data, importantly in weight bearing animals, support better formation of native hyaline cartilage compared to other modalities. • Animal work is in a good weight bearing model. However, the FDA seems to be asking for additional data from the pig studies, such as mechanical studies, clinical parameters (body weight, movement etc) and inflammation assessment. Hopefully this data exists, so the study can move forward. • A good Pre-IND meeting led to FDA giving very constructive feedback. Most of FDA's issues have been addressed but there are still some areas of concern. • FDA has asked for the cell product to be fully characterized including identification of off-target cell types. This is a gap in the application and needs to be addressed. Once that has been done applicants will also need to demonstrate whether the off-target cell types are the same and in similar quantities for repeat manufacturing runs (preferably at least 3).
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• The proposal is well planned. • Challenge of patient recruitment addressed by community/school based Certified Athletic Trainer network. This could address both the entry of a broader socio-economic and disadvantage patient population (e.g., un- and under insured) as well as increase the number of patients eligible for screening for inclusion and exclusion criteria. • The project has benefited from a successful Pre-IND meeting which clearly outlined the additional expectations of FDA. • Several pigs will have received high dose of cells seeded onto membrane and a few the low dose. It will be important that these studies address the specific endpoints outlined in the Pre-IND meeting, as this detail was not provided in the proposal. • While there is no specific requirement to have a placebo-controlled trial it was recommended by the FDA. There needs to be a better discussion regarding the rationale for not including a placebo control for the first in human study. • Would be helpful to consider a placebo control as part of the clinical trial design. • The various knee outcome scores are hard to interpret without a control group. The proposed MRI study could add objective measures to measure cartilage health. This is another good reason to fund the study and disseminate this information to future studies. • The timelines are tight and require everything to go according to the plan. Something like a karyotypic abnormality in the master or working cell bank would set them back in terms of timing.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• The project appears feasible as designed. • The internal staff and external consultants are experienced to carry out all required activities. • Yes, the project is feasible. The major challenge is managing the timeline and making sure the applicants address all points raised by FDA.

	• Concern about the large number of research grade reagents used for manufacturing that will need to be qualified for clinical production use (especially the cell selection materials). Need to include a risk assessment and explain how this will be addressed. • An identified issue is a lack of GMP grade antibodies for the selection step - this can be resolved by FDA discussions and interaction with the contracted manufacturer. This will also apply to other supplements and growth factors. • Need to present actual manufacturing results to date, including scale of runs, cell selection efficiency and recovery of target cells, etc. • Manufacturing approach is logical and release criteria are appropriate. Relevant potency assays can be further developed during clinical trials. • Not clear if the product is designed or intended to treat more complex and common forms of cartilage injury disease. Refinement of the inclusion criteria in the clinical protocol is recommended to distinguish between different types of cartilage lesions.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 10	• Potential lower cost, more universally available product to treat a principal cause of osteoarthritis. • Given the location of the institution and the use of athletic trainers I believe they will adequately serve the needs of underserved communities. • There will be active social media recruitment to underrepresented athletic communities. • Recruitment resources will be available in multiple languages including providing interpretation as needed. • The investigators will take advantage of the institution's patient education and community outreach center for reaching underrepresented communities. • The potential is there but hard to assess at this point from what has been written.
No: 3	• Outreach primarily focuses on athletes rather than ethnic groups - but the institution is in a very ethnically diverse location. DEI is rather weak.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate 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 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 Votes	Has the applicant sufficiently addressed how they have or will incorporate perspectives from individuals with diverse experience and from underserved groups in the implementation of the proposed project?
9-10: Outstanding response	1	*none*
6-8: Responsive	2	• The applicant institution draws upon a very diverse and underserved population and has a strong history related to DEI considerations. The application could have been better developed.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*