Application #	CLIN1-14602
Title (as written by the applicant)	Clinical Translation of Autologous Regenerative Pluripotent Stem Cell Therapy for Blindness
Therapeutic Candidate (as written by the applicant)	The therapeutic candidate is a patient specific (autologous) induced pluripotent stem cell derived retinal pigment epithelium (AiPSC-RPE) product.
Indication (as written by the applicant)	AiPSC-RPE cell product will be indicated for the treatment of maculopathies related to retinal pigment epithelium (RPE) atrophy.
Unmet Medical Need (as written by the applicant)	Several degenerative diseases of the eye cause permanent vision loss due to RPE cell dysfunction. There are no available treatments for these diseases. The proposed AiPSC-RPE cell product may rescue vision, providing the potential to address one of the world's major unmet medical needs.
Major Proposed Activities (as written by the applicant)	• Manufacture six AiPSC-RPE cell products for potential use in a Phase 1 clinical trial. Conduct AiPSC-RPE final product manufacturing runs. • Assess safety by conducting IND enabling non-clinical GLP safety/toxicology/biodistribution studies. • Generate materials and conduct regulatory review of AiPSC-RPE cell products to support an IND submission to the FDA.
Funds Requested	$6,000,000
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	15
Votes for Tier 1	13
Votes for Tier 2	2
Votes for Tier 3	0

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

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

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

Yes: 13	• The proposed approach offers advantages over the current standard of care. There is currently no curative therapy for macular degeneration with retinal pigment epithelium (RPE) and photoreceptor atrophy. • There remains a major unmet need for treatments that could restore vision. The proposed treatment could have a significant impact for patients. • Yes. This approach would be accepted by healthcare providers and patients if it even slightly improves visual function. • There is a high unmet need in degenerative retinal diseases that lead to blindness. • The proposed product has potential for addressing blindness in this condition. • Yes. The proposed cell therapy fulfills an unmet need. • The project is high risk and potentially high gain.
No: 1	• The clinical value proposition is limited as this does not appear to be a vision restoring treatment. Thus, I don't think this approach significantly addresses an unmet need. • Autologous transplantation is not commercially viable for the indication.
GWG Votes	**Is the rationale sound?**
Yes: 13	• The applicant team has strengthened their proposal, completed due diligence with the FDA and various consultants, and has addressed the concerns from the previous GWG review of this application. The new proposal better supports their translational approach for preclinical work, IND enabling studies, and CMC and better positions their program for success. • Overall, yes, though the efficacy data in rodents may not fully support potential translatable efficacy. However the FDA feels that this efficacy data is confirmatory and that all four cell lines are comparable. Thus, the applicant has tried to derisk the program and has addressed our prior concerns. • While there is not a lot of data suggesting functional improvement in vision, the preclinical studies suggest that the AiPSC-RPE cells migrate and integrate into the appropriate structures. • Overall, yes, but the transplanted cells may not persist past 8 weeks per one preliminary study. Instead these cells may provide additional support for residual host cells and mitigate apoptosis. • The applicant has a sound rationale that is based on available evidence.
No: 1	• Autologous transplant may be the wrong approach because the patient's own cells may retain the defects that originated the problem. • Despite many years of effort, RPE transplants have not shown clinical benefit.
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• Yes; the project is appropriately planned. The non GLP stepwise approach is better planned to address dose volume and dose ranging that will inform the GLP IND toxicity studies. The likelihood of an FDA clinical hold is reduced by the currently proposed IND enabling work. • The redesigned studies more adequately address unresolved regulatory issues. That is, two new studies are proposed to definitively determine the maximum feasible number of cells and the maximum feasible volume that can be administered subretinally in the rat model. These studies will inform the pivotal safety study and ensure that FDA requests are met regarding the cell dose and volume. • The new experiments proposed in the project plan are essential for translation to the clinic and create value that advances CIRM's mission. • Good, responsive resubmission. The GWG appreciated the applicant's effort on the plans for toxicity studies. • The clinical protocol is reasonable with a DSMB, stopping criteria, dose escalation and numerous exploratory functional and structural endpoints that will have clinical relevance. • Overall, yes, but the quotes from their CRO are astronomical and an alternative vendor should be used. • The CMC controls and assays are now better positioned to deliver a drug product for the Phase 1 trial. These revisions seems to address prior GWG concerns. • The CMC plan is well designed and responsive to all previous comments. • The applicant has been very responsive to previous GWG concerns. • The timelines and budget are reasonable.
No: 1	• This is an excellent team with excellent expertise.

	• I am concerned about including patients who are on anticoagulation. If the planned trial is very small, why expose this unique population to risk before more data are available? I would recommend excluding this population. • Is there a way to select the worse eye for the injection?
GWG Votes	**Is the project feasible?**
Yes: 14	• Yes. The intended six objectives are reasonable and the proposed timeline is appropriate. • The team is very well qualified. They have well known consultants and CROs helping them - some of the best in our field. The retinal experts are all well trained and excellent surgeons who have experience with clinical trials. • The team has a limited contingency plan to manage risks. • An excellent group is assembled to execute the proposed program. • Yes, the team has consulted extensively with their CRO and other experts to ensure the critical issues regarding the animals studies are being addressed. • The project appears feasible and the applicant provided additional details and made appropriate changes based on the previous grant review feedback. • Based on the applicant's responses to the issues raised by the FDA, I believe that the manufacturing section is now acceptable provided they generate the remaining data requested by the Agency. • This is a seasoned team, a feasible injection, and an established cell process. • One is concern is the potential viability of the injected cells - can viability be tested prior to injection? • Overall, yes, though it's unclear how long-term manufacturing will support a commercially viable product.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• The applicant has a well thought out DEI plan and approach. Macular pathology affects all ages, all races, all genders, and all societal and educational levels. • The institution is supportive and DEI-oriented.
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	4	• By working with inner city universities in the conduct of clinical trials, the applicant will capture an expansive group of patients across various educations, ages, genders, social levels, and races. • The proposed FIH trial will be small (N=12) and may not be able to mirror the demographics provided for AMD. However, the applicants indicate that they will focus on outreach to ensure as diverse of a patient population as possible. • The applicant states up front that the trial will not directly mirror demographics for the target disease indications; they will however ensure broad representation of a geographic area to include as much diversity as possible.

		• The institution provides access to broad and inclusive patient populations. Each of the partner sites serves diverse patient populations. • The trial site is an Alpha Clinic; AC's have a system to support community outreach as well as DEI tenants. • The applicant plans to draw from partner organizations across California. Engagement and outreach efforts include alliances with community clinics; patient concierge services (navigators), designating community liaisons, social media network outreach; and distribution of printed materials. • The applicant demonstrates an understanding of the potential barriers to participation in the clinical trial. • The applicant acknowledges barriers to trial participation and will leverage Alpha Clinics resources and partnerships with CBOs, service providers, and local health systems. • The applicant emphasizes relationship building can inform strategies to ensure the dignity of the subjects and enhance knowledgeable decision making about participation in the trial. • The applicant team comprises people with diverse socio-economic, educational and cultural backgrounds. • The proposal includes robust DEI efforts and community engagement. • The proposal includes a plan to address potential barriers to participation. • The team and institution are committed to DEI.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN1-14764
Title (as written by the applicant)	Treatment of the temporomandibular joint (TMJ) disc complex.
Therapeutic Candidate (as written by the applicant)	Tissue implant engineered using expanded, allogeneic chondroprogenitor cells
Indication (as written by the applicant)	Defects of the temporomandibular joint disc (TMJ) complex
Unmet Medical Need (as written by the applicant)	Current TMJ treatments are inadequate. Non-surgical treatments provide temporary relief. Invasive treatments include removal of the TMJ disc complex and total joint replacement. Unmet medical needs exist in the treatment gap between palliative non-surgical and end-stage surgical approaches.
Major Proposed Activities (as written by the applicant)	• To develop GMP manufacturing for the product and test shipping and stability • To complete the IND-enabling preclinical studies • To submit the IND and initiate clinical start-up activities
Funds Requested	$6,000,000
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	1
Count	15
Votes for Tier 1	15
Votes for Tier 2	0
Votes for Tier 3	0

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

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14	• The proposed treatment is a biomechanically functional tissue-engineered implant with the potential to fill the gap between palliative non-surgical approaches and the need for invasive surgical intervention including the need for successive surgeries of the TMJ disc complex. • The use of allogeneic cells allows for a readily available implant, eliminating the morbidity and the added time for manufacture associated with autologous approaches.

	• Acute injury and chronic degeneration of the TMJ disc complex are significant unmet medical needs with no current curative treatments. • Current treatments focus on treating symptoms and are not curative. The preclinical data are impressive but focus on the acute model, where injury is more significant than inflammation and chronic degeneration. The applicant realizes this - it is a shortcoming of the animal model. • TMJ is a VERY common problem. The ultimate source of TMJ issues is the disc (similar to the cervical spine). Treatment has been historically supportive rather than curative. The applicant takes the field a step forward by starting to address the source of the pathology in the TMJ. Current solutions include arthroplasty (which is similar to what is happening in the orthopaedic world). • The aim of this project is to establish a new approach that can repair/regenerate the TMJ disc complex prior to joint replacement. It is likely to improve the current treatment strategy, which will benefit a large number of patients with TMJ and disc displacement. Overall, this is a strong application with high significance. • The value to this product comes from the ability to actually treat the condition rather than the symptoms. • This has important impact.
No: 0	*none*
GWG Votes	**Is the rationale sound?**

Yes:
14
	• The proposed product is the culmination of 30 years of research by members of the team to address defects in the TMJ disc complex.
	• Clinical feasibility has been demonstrated in an animal model using the analogous animal product construct, although this model is for a slightly different indication.
	• The applicants have conducted three studies in the animal model. As mentioned above the model is an acute injury model and thus only represents a subset of subjects with TMJ disc complex issues.
	• With that caveat (that the applicants are well aware of) the data are very supportive of moving into the clinic after definitive pre-clinical studies and phase appropriate GMP manufacturing.
	• The team has already engaged extensively with the FDA. They have a step wise progression to take from manufacturing through human implantation.
	• The team has completed extensive, compelling preliminary studies including material design, in vitro cell culture, pilot preclinical test on large animals with a related defect. The results are promising.
	• However, some information is missing:
	  • 1. It is not clear what age group will most benefit since there was no age information on the animals used in the preliminary studies. Age does matter for the treatment effects of TMJ disorders. The young and old animals may have different reactions to the surgery and/or implants.
	  • 2. TMJ surgery can affect the normal growth of condyle and mandible, causing ankylosis and mandible deviation. Since there was no information about the age of the animals, it is not clear whether this would be a concern. If the studies were done on young animals, the mandible growth pattern should be analyzed.
	  • 3. The team shows some histology images from the animal studies, but they show an enlarged area with no comparison to the normal disc. The TMJ disc cartilage has dense fibers so that it can bear loads. Analysis of fiber distribution and density of the regenerated disc will be helpful to confirm its healthy and functional condition compared to the native normal cartilage.
	  • 4. In preliminary studies 1 and 2, the applicant only shows the comparison of mechanical properties between repaired disc and non-treated trauma disc. It is necessary to compare with normal native tissue.

No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The applicants have benefited from a productive pre-IND meeting with FDA and have incorporated the Agency's suggestions into their Project Plan. As a result the project is well planned and should lead to productive CMC activities, definitive pre-clinical studies and production of data and phase appropriate GMP product for the conduct of first in human studies. • The applicant has benefited from a successful pre-IND meeting which has provided a very clear roadmap for translation to the clinic.

	• The project is well planned and designed. There was some concern around relying on the one animal model. However, the goal of the animal model is proof of concept - the implant used in the model won't be identical to the implant used in humans.
	• The applicant proposes extensive experimentation on safety of the proposed product, but no detailed plan on evaluating the function of the repaired TMJ complex after surgery.
	  • The maximal incisor opening was not enough to determine the joint function.
	  • The jaw-tracking and mandible symmetry need to be studied.
	  • Heterotopic ossification should be determined by CT and histologically.
	• The timeline is appropriate - aggressive, but strikes a balance between the urgency of developing a new product for an unmet medical need and the reality of product development.
	• The budget is extremely unreasonable.
	• Housing and care costs are exorbitant for the location.
	• The applicant needs to better assess the budget; the GWG had concerns about item costs.
	• The CRO quotes are astronomical and an alternative should be sought.
	• Costs seem excessive.
	• The applicant was responsive to pre-review questions from the GWG.
	• This application is very well written and was a pleasure to read!

No: 0	*none*
GWG Votes	**Is the project feasible?**

Yes:
14
	• The proposed activities are well defined with an appropriate team and resources to execute.
	• The team is really well qualified and have taken into account valuable input from FDA. The timelines are achievable - while there might be some delays, I don't think these would stall the project.
	• The contingency plans are reasonable and I think the applicants will be on course to submit an IND in a timely manner.
	• There is tremendous pre-clinical work that suggests that this project may succeed.
	• The project will likely be finished within the proposed timeline.
	• The team has extensive published expertise in material development, in vivo and in vitro studies, and genomic analysis.
	• The applicant team has extensive expertise; they have been working on this project for several years.
	• The manufacturing aspects are well described in the proposal.
	  • There does not appear to be testing for specified viruses on the MCB or WCB which would normally be expected. Adventitious agent testing is mentioned and may be sufficient since the trial aims to recruit <30 patients. If this is the case then it is not clear that adventitious testing would also need to be performed on the final product.
	  • The FDA has provided written responses to the application for RMAT status. In response to these the applicants have
	  • 1) eliminated antibiotics from their medium,
	  • 2) agreed to conduct mycoplasma testing on the cell banks and DP,
	  • 3) development of potency assays (by Cartilage).
	  • They have not provided responses to all of the points raised by the FDA in their CIRM proposal, but I have confidence that they should be able to do so, since the issues raised are not extraordinary in nature.
	  • In their risk mitigation strategy section the applicants confirm that they will respond to all the issues raised by the FDA (stability testing, shipping procedures etc.) and will source materials from different vendors to avoid supply chain issues.
	  • The applicant states that they have not had a lot failure to date, and that a potential failure can be addressed by producing additional WCBs the cost of which would be borne internally.
	  • Based upon the information provided and the applicant's apparent commitment to respond to the remaining issues raised by the FDA, the manufacturing plan is acceptable.
	  • The release testing is extensive and would appear to meet the requirements.

No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**

Yes: 14	• The applicant will take advantage of infrastructural support to help achieve diverse clinical enrollment. • TMJ disorders occur less frequently in racial minorities and the trial is small. Thus, the applicant provides population goals for the series of clinical trials. • The principles of DEI are considered in the clinical development plan. • The DEI section is well written and thoughtful. • The proposal includes a plan to increase cultural sensitivity on the team.
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: 8.0

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 applicant makes a robust DEI presentation. • The proposal includes good data analysis related to a variety of demographics, including description of a TMJ disorder gender paradox and assessment of economic stratification. • The applicant's DEI plan includes good outreach considerations, a solid DEI focus at the initial trial site and very strong track record at future trial sites the applicant is considering. • The planned activities to increase cultural sensitivity on the team match the needs of the project.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-14315 #2
Title (as written by the applicant)	Reduced intensity conditioning with [candidate product] prior to TCRαβ+ T-cell/CD19+ B-cell depleted hematopoietic stem cell transplant for Fanconi Anemia patients
Therapeutic Candidate (as written by the applicant)	αβdepleted-hematopoietic stem cell (HSC) grafts and a reduced-intensity preparative conditioning regimen containing the candidate product
Indication (as written by the applicant)	Treatment of patients with all genetic forms of Fanconi Anemia (FA) with evidence of cytopenia
Unmet Medical Need (as written by the applicant)	Current conditioning regimens for hematopoietic stem cell transplantation (HSCT) are toxic for FA patients. FA patients are also very susceptible to graft versus host disease (GvHD) post-HSCT. HSCT approaches that diminish pre-transplant toxicity and post-transplant GvHD could improve outcomes for FA patients and become a new global standard of care.
Major Proposed Activities (as written by the applicant)	• Manufacture αβdepleted-HSC graft product for proposed trial • Clinical testing of reduced intensity [candidate product]-based conditioning before αβdepleted-HSC graft transplant in FA patients • Complete evaluation of primary, secondary and correlative objectives
Funds Requested	$11,813,964
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	3
Count	15
Votes for Tier 1	10
Votes for Tier 2	3
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, 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
	• FA is a bone marrow failure syndrome caused by inherited mutations that result in DNA repair defects. FA patients also have a propensity to develop acute leukemias and other solid organ neoplasms. An allogeneic hematopoetic stem cell transplant (HSCT) is the only way to treat the bone marrow failure and prevent the development of acute leukemias, but it does not address the development of other solid organ malignancies. The use of alkylators such as busulfan and cyclophosphamide and radiation in the form of total body irradiation (TBI) during an HSCT may in fact exacerbate the development of secondary malignancies. In this proposal, the investigators sought to replace the use of these approaches with a combinatorial conditioning regimen containing the candidate product prior to HSCT. This new combination has not been used broadly in FA patients. This proposal generates excitement about the prospect of using a non-genotoxic conditioning regimen in a non-malignant condition, and the proposal is interesting as it progresses that paradigm with the potential for extension to other non-malignant conditions.
	• The proposed strategy has the potential to enhance donor hematopoietic and immune reconstitution while decreasing GvHD and enhancing engraftment.
	• The proposed treatment and approach appear to address a significant unmet need for this rare disease population, with the potential to provide better long-term outcomes.
	• FA related bone marrow failure can be treated with bone marrow transplant; this approach reduces regimen related toxicity long term (in 20 years). This is especially important in children whose whole life is ahead of them.
	• As a result of this proposal, controlled data for the pediatric participants will be available in a population that usually has little opportunity for rigorous data collection, especially with long-term follow-up.
	• There is an opportunity to decrease morbidity and mortality of transplantation in children with the proposed shorter term safety and efficacy endpoints.
	• The program will advance the transplant treatment for FA because it elucidates early efficacy of the regimen.
	• Two key concerns are that it will be difficult to detect long term efficacy (i.e. decrease in malignancy) and there is still the need for cyclosphosphamide.
	  ◦ However, the protocol does include a long-term follow-up plan, which is standard in gene-modified therapies.
	• Although this protocol may be accepted widely if it meets the short-term objectives, the real underlying issue of reducing the incidence of malignancies long term is pending adjudication, which leads to questions about the appropriateness of funding this proposal.
	  ◦ However, the investigators claim that the primary goal is to improve short-term outcomes.
	• The protocol is not long enough in duration to detect regimen related toxicities.
	• It is difficult to detect decreases in regimen related toxicities; FA patients are likely to develop cancer even without transplantation, so it may be difficult to detect reductions in regiment related cancers versus de novo malignancies.

No: 3	• Given that the new product proposed for use in the combinatorial conditioning regimen is already under investigation for other indications, this seems like the kind of investigation that could be done in a post-approval setting if the product is successful. There is no apparent evidence that it might be more successful, or show better efficacy, in this particular indication. • Based on the current trial design, it will be difficult to determine whether this product adds a benefit on engraftment.
GWG Votes	**Is the rationale sound?**
Yes: 13	• Yes, as mentioned in the proposal, TCR-ab depleted HSCT has been performed in patients with FA with remarkable success, and this product has been used and demonstrated to be useful in other disease cohorts. So there is sufficient background data to support the use of this combinatorial strategy and regimen in the FA population. • There is novelty in the use of this product to remove the damaged FA cells. • The proposed strategy has proven useful for GvHD prevention using T cell depletion. • The CMC plans are sound, and several patients have been treated to date, and show improved short-term outcomes relative to historical controls. • The planned continued use of cyclophosphamide can still induce regimen related toxicity, so the study may not achieve the objective of reduced regimen related toxicity.

No: 2	• From the perspective of finding a treatment plan without TBI or busulfan for patients with FA, the rationale is sound. TBI and busulfan will likely have a side effect profile that is presumably more severe than this product. However, this is not the planned primary endpoint. Rather, this proposal is focused on engraftment, which is not a problem with current treatments performed around the world. Further, the Curitiba transplant program has already demonstrated that engraftment can be achieved after cyclophosphamide and campath, without TBI and busulfan. Yet cancer risk remains high, which in part undermines the rationale for the current study.
GWG Votes	**Is the project well planned and designed?**

Yes:
13
	• The clinical trial is well designed to address the short term safety objectives.
	• From a CMC perspective, the manufacturing and testing proposed are appropriately designed, and have proven successful to date.
	  ◦ The manufacturing process begins with the use of unrelated donors for obtaining apheresis materials, which then undergo a depletion process to yield αβ-depleted HSCs. This process is established and has been successfully utilized for previous clinical patient treatments.
	  ◦ The manufacturing and testing sites are qualified for GMP up through phase 1/2. In addition, the FDA has approved the current CMC plans. In addition to the cell therapy, full patient treatment also involves the use of this product. The product is manufactured and released for use by the applicant organization. The product is provided in vials ready for infusion, and no additional manipulation is required. As such, the CMC plan is sound.
	• Restrictive entry criteria should be considered for transplant.

No: 2	• The proposal is not designed to differentiate the contribution of high cell dose from the proposed product in terms of facilitating engraftment. To be definitive, either a different primary endpoint should be considered or the investigators should consider an alternative strategy for demonstrating the engraftment benefit of the product. The applicants did not address this criticism after the first review. • Eligibility for this experimental protocol needs to be more restrictive. The indications for transplant in this protocol will potentially include patients who do not need transplant in the near term, if ever. For example, the TPP states that patients with blood counts less than the lower limit of normal would be eligible. Lower limit of normal in one lineage is not an accepted indication for transplant. In the clinical trial section, there is more definition, but still these criteria would be atypical even for standard of care protocols, and much less so for an experimental therapy. • The TPP says that >50% chimerism in all lineages would be the base target. This is problematic as it means that it would be acceptable to have 51% chimerism in the myeloid compartment, which has potential risks. • To know whether the product replaces TBI or BU, the current trial design will not provide data to distinguish the effect of the product vs the TCRab depleted graft with high CD34 cell numbers. This means that it will be difficult to determine if the product can replace TBI or BU. • Stopping rules for toxicity are presented in various ways throughout the proposal. In one place the proposal indicates that one stopping rule is >50% stage 2 acute GvHD or chronic GvHD. While not likely based on prior data, this seems too high. • Donor inclusion of up to 65 years of age and donor weight >10kg may not be optimal due to (1) risk of clonal hematopoiesis in those older than age 60 and (2) apheresis risks in children slightly over the weight threshold (due to central line placement, blood transfusions, etc.).
GWG Votes	**Is the project feasible?**
Yes: 14	• Several patients have been treated to date, supporting feasibility. • The trial is already underway and is feasible. • Following the IND submission, the FDA requested additional information. Responses were provided and accepted in a formal amendment. • The graft manipulation process has been widely used and presents no concerns. • The release and additional testing are all appropriate. The risk mitigation factors (supply chain issues) are identified and appropriately addressed. • The source of funding for replacing outdated unused commercially available kits needed in this proposal is not indicated. • This proposed study has a very high cost for enrolling a relatively small number of additional patients, given that patients in prior trials had complete or partial insurance coverage. As the study is already open and enrolling patients, much of the work has

	already been done to get regulatory approval. Cost recovery is allowable for TCR ab depletion and the product has already been provided to the applicant. ● For the proposed number of patients, the costs are very high.
No: 1	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	● The investigators have made a genuine effort address the principles of DEI. ● The revised application includes a focused effort towards enhancing/expanding patient support through a dedicated "Access Facilitator" role. The goal is to "...ensure seamless passage for trial participants." One of the Access Facilitator's primary responsibilities includes proactively supporting the recruitment of patients from underserved demographic populations to this trial from California. ● The proposal describes outstanding plans to increase cultural sensitivity of team members.
No: 1	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

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

DEI Score: 9

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

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

9-10: Outstanding response	4	• There is a strong track record at the applicants' institution related to patient recruitment. The applicants have added an access facilitator role, presented a good plan for patient material development, and justify their catchment area.
		• The plan to increase cultural sensitivity in the team by way of specific training and activities is outstanding. For example:
		  ● A patient-intake survey to determine the preferred healthcare language.
		  ● Justice, Equity, Diversity, and Inclusion (JEDI), teaching and training.
		  ● Training forums to address mistrust that is based on historically unacceptable medical interventions.
		  ● Developing 5th-grade level reading materials in multiple languages.

6-8: Responsive	1	• The applicants provided a strong JEDI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-14516
Title (as written by the applicant)	Phase 2b Clinical Study of a Topical Ophthalmic Human Mesenchymal Stem Cell Secretome for the Treatment of Persistent Corneal Epithelial Defect
Therapeutic Candidate (as written by the applicant)	The candidate product is a human bone marrow mesenchymal stem cell secretome formulated as a topical ophthalmic therapeutic
Indication (as written by the applicant)	Treatment of persistent corneal epithelial defect (PCED), a cornea defect refractory to conventional treatments that can lead to blindness
Unmet Medical Need (as written by the applicant)	No effective PCED therapies exist that address all etiologies, as they do not target the multiple dysregulated pathways in persistent wounds. With its ability to target multiple healing pathways, the candidate product has the potential to heal PCEDs, thereby helping to protect vision and reduce pain.
Major Proposed Activities (as written by the applicant)	• Complete a Phase 2b clinical study to demonstrate safety and efficacy of the therapeutic candidate • Conduct product and process characterization studies to support product development • Evaluate and develop additional analytical methods for product comparability studies
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	14
Votes for Tier 1	10
Votes for Tier 2	4
Votes for Tier 3	0

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

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the members of the GWG were asked to indicate whether the application addressed the key question and provide brief comments assessing the application in the context of each key question. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: **13**	• There are no FDA approved products for the treatment of PCED. In 2017, the FDA approved Oxervate™ (cenegermin-bkbj ophthalmic solution). Oxervate is the first and only drug to date approved for the treatment of neurotrophic keratitis, which is the primary etiology for approximately one-third of PCED cases. Oxervate contains a single growth factor, nerve growth factor, and has been demonstrated to be effective in only the subgroup of PCED cases whose underlying etiology is neurotrophic disease. Oxervate also imposes a significant compliance burden on patients. It is administered 6 times per day at 2-hour intervals for 8 weeks, with each administration requiring the use of a vial containing the drug product, a vial adapter, a single-use pipette and disinfectant wipes. • PCED is a rare condition (~100,000 cases in the USA) with few treatment options. The sole approved product, Oxervate, contains a single growth factor and is effective in treating only about one third of PCED cases. Therefore, there is an unmet medical need for PCED which the applicants intend to address with their drug product. • There is a significant unmet medical need. Conventional therapies, which may include bandage contact lenses, autologous serum, punctal plugs, and surgery, are often not effective in addressing the multifactorial processes that result in impaired healing associated with PCED. • PCED is a rare condition of the cornea with no FDA approved drug treatment; there is unmet need because it can progress to blindness. • This product has the possibility for improved treatment of PCED. • This proposal fulfills a major unmet need. • Pre-clinical data as well as limited data in several patients showed that the product is safe and remarkably effective. If these results are borne out in the larger clinical trial proposed in this application, it will provide a vast improvement over the current standard of care. • While this treatment is likely to be expensive, it may still offer a sufficient value proposition given the current lack of treatment options for PCED.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The product is a human bone-marrow derived allogenic mesenchymal stem cell (MSC) secretome (MSC-S) composed of biologically active components secreted from the MSCs, including growth factors, protease inhibitors, extracellular matrix (ECM) proteins, and neurotrophic factors targeting many of the pathways involved in corneal healing including ECM remodeling, corneal epithelial cell growth and migration, and regeneration and maintenance of neurons. Each of three principal functional molecular categories are represented by a critical quality attribute protein. These three proteins are used to monitor product manufacturing, and depletion of these components blocked the product's ability to enhance corneal wound healing in vivo. Nonclinical studies of the product support its capability to promote corneal wound healing. The phase 1/2 studies were single-arm, prospective, open-label trials conducted at two ophthalmology specialty hospitals. A small number of healthy volunteers were treated in a lead-in safety cohort, and several PCED patients were treated in an efficacy cohort. The treated patients experienced a good outcome. In sum, the scientific rationale sounds appealing and the mechanism makes sense. • The product is composed of a secretome from bone marrow derived MSCs. The secretome contains over 900 proteins as well as other biologically active moieties like exosomes. The applicants theorize that a subset of components is critically involved in the biological activity of the product. Depletion of some of these components from the secretome leads to a decrease in corneal healing in an animal model. However, the significance of this cannot be gleaned from the data in the application as there are no error bars on the graph depicting the decrease. It is therefore not clear if this experiment has only been conducted once or multiple times. Regardless, the decrease is not down to baseline, suggesting that other factors are involved in the healing process. • Given the body of pre-clinical data, the limited set of clinical data, and the known activities of some of the molecules in this product in promoting corneal healing, the proposal is sound and merits further testing in humans. • This proposal is supported by well designed preclinical studies and encouraging phase I data. • Although the study was not controlled, the clinical data collected to date are promising. • The proposed mechanism is supported by multiple preclinical studies, as well as one small scale human study. However, the secretome is complex and the active components

	are not completely known. The applicants propose to characterize the product using three control proteins, but this may be insufficient. ● The applicants performed animal toxicology studies and dose response to determine suitable dosage. The data from these studies support the rationale for the phase 1/2 study. ● The applicants have scaled up Drug Substance manufacturing to a scale sufficient to support product requirements for the phase 2b clinical study, which is also the scale required to support a future BLA submission and early commercialization.
No: 1	● The prior study, which was conducted outside the US, showed efficacy signals. ● The allogeneic human MSC secretome is not well characterized. ● It is unclear if it is sufficient to base the manufacturing process and quality control on three proteins, and the limited characterization of the components of the secretome is concerning.
GWG Votes	**Is the project well planned and designed?**
Yes: 8	● The project is well designed to identify an optimal dose to take into phase 3 studies. ● The target dosing is industry standard for this type of treatment and a reasonable burden to patients. The dose tested in the completed phase 1/2 clinical trial yielded a good outcome. If the phase 2 study will pin down the best dose, that will serve the purpose for the phase 3 larger scale study to further evaluate this drug for the treatment of PCED. ● The timeline seems fine with regard to patient enrollment and treatment. The applicants have also planned contingency budgets and timelines due to enrollment delay or manufacturing delay. ● The applicants are working with a well qualified multi-product GMP facility that works with bone marrow and MSCs as well as other products. ● The manufacturing plan is well thought out, the CDMOs used are all well versed in GMP manufacture and sterile fill and finish. No issues are foreseen in the manufacture of the Drug Substance or the Drug Product. ● The applicants should perform multiple manufacturing runs of the product (ideally at least five) to see if they see the same biological activity in each run. Product from each run should be tested in an animal model. There will very likely be variability in each manufacturing run, and it will be important to test if that variability impacts the biological activity. ● The applicant should expand product characterization assays (not necessarily as release assays) to be better able to interpret clinical data if clinical responses are variable and to better define final critical quality attributes. ● While not needed for this phase 2 study, there is a considerable challenge in developing a potency assay. This will be needed for registration trials. The applicants have done a reasonable job in defining critical quality attributes of the Drug Substance but much more needs to be done. ● The development of a potency assay will be complex and time consuming so work should begin on these aspects immediately. ● The applicants need better characterization of the final product to create a useful potency assay. ● The reproducibility of product manufacturing is concerning.
No: 5	● The likely complex mechanism of action brings concerning challenges for the development of relevant potency assays for product characterization. The applicants should add more biological, mechanistically relevant product measurements that could eventually lead to a relevant potency assay(s). ● Emphasis on product characterization and potency testing methodologies should be incorporated in the proposal. ● Confirmation of efficacy in a controlled trial is an important goal for this product, and an audit of the results of the current trial is recommended. ● The applicants are planning enrollment at too many centers. ● Although the applicants cite the ease of use of the final product, it is not clear how they will ensure compliance. ● In their prior trial, the placebo has an effect which may impact detectable differences. ● This is a very expensive effort for a condition that is not life threatening. ● The applicants should expand the scope, as MSCs likely have therapeutic value beyond their secretome.

GWG Votes	Is the project feasible?
Yes: 12	• The applicants will be able to prosecute the phase 2b clinical trial in a timely manner. • The team is highly qualified, but may benefit from expertise in product characterization as discussed above. • The contingency plans are reasonable. • The clinical trial is possible to achieve within the proposed timeline. However, the proposed timeline for exosome assay and characterization assay may not provide sufficient time to achieve such goals. • The consistency of drug product manufacturing will need to be monitored. • The largest concern/challenge is to ensure a consistent product and criticality of defining critical quality attributes. • It is concerning whether the applicants can produce detailed characterization of the drug product and develop a potency assay, especially in response to FDA feedback. • The development of a potency assay, the further understanding of the critical quality attributes of the drug product, and characterization of other potentially bioactive components of the drug product like exosomes will be critical to the successful development of a commercial product. Understanding batch to batch variability and how it relates to biopotency will also be critical. • The FDA's review of the manufacturing process, especially for the master cell bank generation, is open for further evaluation at phase 3/BLA and other significant issues may need to be addressed at that time.
No: 1	• Potency testing and product consistency are concerning, especially since there is limited characterization for product release criteria. • It is concerning whether the product can be consistent across multiple sites. • The proposed timeline to develop a potency assay is very short. The applicants should consider broadening the development of this assay in multiple aspects, including RNAs, chemokines, additional growth factors, angiogenesis, ECM components, or lipids. There is a large focus on the three proteins tested so far. Regarding these proteins, what is the result if only these components are provided? What is the rationale for manufacturing the secretome if only these proteins provide the effect? It will be important to characterize additional factors that contribute to efficacy. • It is not clear why multiple doses per day are needed; this suggests that there is something very short acting in the secretome. How can this/these short acting component(s) be identified?
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**

Yes: 13	• The applicants present a highly sophisticated DEI plan.
	• The staff assigned to oversee DEI indicate that the applicants are assigning high priority to this aspect of the study.
	• The applicants demonstrate a very good understanding of the race, ethnicity, sex, and age-based health disparities associated with the target indication.
	  ◦ From a biological and scientific point of view, this condition has no sex predilection and enrolling 50-50 male and female should be appropriate.
	  ◦ The applicant presented an appropriate rationale for the proposed trial study population that is based on current knowledge of the demographic groups at risk for the target indication, including underserved populations.
	  ◦ Some of the PCED risk factors such as diabetes, exposure to farming activities, or severe dry eye affect certain groups more than others. And treatment of PCED frequently requires money and time that underserved population do not have. As such, the application proposes to pay for transportation, childcare, pet care etc to allow the disadvantaged population to be enrolled and treated in the study.
	  ◦ The applicant developed goals to achieve an inclusive distribution of subjects by race, ethnicity, sex, and age. Their target enrollment percentage of race and ethnicity is proportional to the actual population markup of California. Data to inform population goals for nonbinary participants and certain ethnicities within racial groups are not currently available.
	  ◦ The applicant provided adequate justification for the proposed exclusion of any group(s) at risk for the target indication. In terms of age, adults are the target population, which is appropriate as PCED is much more prevalent among adults. Pregnant people are excluded and negative pregnancy tests are required for the duration of the study for participants who can potentially get pregnant. This is acceptable, as the teratogenic effect of this drug is not known.

	• Given that PCED is a rare disease, the applicants will have many trial sites. The sites range from private practice clinics to large academic centers, which is helpful to capture racial and ethnic diversity, as well as other types of diversity such as patients of different socioeconomic backgrounds. Geographically, they are targeting locations where causative diseases such as diabetes, ocular surgery, severe dry eye, and infectious keratitis are more prevalent. Sites in California are selected due to the large number of farmworkers that reside in those areas. Having sites in large urban areas is helpful. • The applicants propose to inform surrounding providers to establish a referral network. They will present these programs to community and patient advocacy groups, and identify community clinics and organizations connected to underserved populations and provide initial outreach. Patient education materials will be provided, and patient recruitment and outreach will be multi-lingual and use several social media avenues. • The selected DEI vendors are not only competent, but are also diverse and culturally aware. One vendor will provide diversity and cultural sensitivity training to investigators, study coordinators, and site staff. This will include holding periodic presentations to help investigators further understand the diverse participant population and enhance the understanding of multi-cultural/ethnic differences. The applicants will also engage with organizations serving diverse populations. These engagement activities are feasible for the proposed timeframe. • The application clearly describes how the success of this project would lead to a therapy that positively impacts underserved or disproportionately affected communities. • The applicants should consider whether paying for participation is taking advantage of underserved populations.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

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

DEI Score: 9

Up to 7 patient advocate and nurse members of the GWG score each application. The final score for an application is the median of the individual member scores. Additional parameters related to the score are shown below.

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	4	• This applicant has done an outstanding job of addressing DEI. PCED is a rare condition with a number of etiologies. The applicant has reported the race, gender, age, ethnicity and socioeconomic issues related to each of these causal factors for PCED. The reasons for excluding children make sense for this trial. The recruitment goals make sense for both the demographics of California and issues of the disease itself. • The outreach and engagement plan is very impressive and is led by a credible researcher with a strong track record. The effort to outreach to farm workers who are at high risk for a variety of reasons will be impactful. Recognizing the importance of retention and anticipating potential issues, the project has budgeted a significant amount for client transportation, stipends, childcare and many other suggested supports. • The applicants are planning to enroll at many geographically diverse sites both in California and nationally to ensure proper recruitment demographics are achieved. They will also do outreach to outpatient clinics within 75 miles of the sites. To further aid them, they will employ an outreach firm with great expertise. • Their cultural sensitivity plans are quite adequate.

		• The applicants present a well described effort to reach underserved high risk populations. • The proposal strongly embraces DEI values. • The applicants will use unique outreach tactics and partner with the appropriate organizations. • Activities are well matched to the needs of the project.
6-8: Responsive	1	• There is an excellent data analysis regarding 13+ etiologies and determination of demographics for primary focus areas of several demographics that inform setting the target patient population. The application benefits from information from their phase 1 trial in a rural area. The partnership with a patient recruitment agency will aid in patient access.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*