Application #	CLIN1-14789 #2
Title (as written by the applicant)	IND-enabling program for the secretome from polarized stem cell-derived RPE cells, for the treatment of dry-age related macular degeneration
Therapeutic Candidate (as written by the applicant)	Polarized Retinal Pigment Epithelium-Secreted Factors
Indication (as written by the applicant)	Advanced Dry Age-Related Macular Degeneration (Geographic Atrophy)
Unmet Medical Need (as written by the applicant)	Provides a treatment option for millions of patients with geographic atrophy to preserve vision.
Major Proposed Activities (as written by the applicant)	• Pre-clinical testing of therapeutic candidate • Manufacturing the therapeutic candidate for clinical trials • Develop clinical trial protocol for the therapeutic candidate
Statement of Benefit to California (as written by the applicant)	AMD is one of the most common causes of blindness in those 50 or older with an estimated 400,000 Californians projected to suffer from AMD. With a $3 billion economic burden annually in California, AMD is a debilitating disease that results in loss of independence and productivity, increased injury and dramatic decline in quality of life. This product is being developed in California and creating additional jobs in California.
Funds Requested	$5,993,562
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	8
Votes for Tier 2	6
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: 12 **No:** 1	• There is a large unmet medical need for the treatment of dry Age-Related Macular Degeneration (AMD) which can progress to Geographic Atrophy (GA) with consequent decline in sight or legal blindness which can affect many aspects of normal life leading to a decreased quality of life and productivity. • The therapy proposed in this application may slow the progression of age-related macular degeneration leading to geographic atrophy, a disease with limited approved therapies. • Large unmet need for Geographic Atrophy, dry AMD, that can impact vision and result in blindness across various populations and ethnicities groups. There are no good therapies for this indication. The currently approved complement inhibitors have fallen short given they do not improve vision, and they have a risk of converting to wet AMD. There is a large health care burden in CA as well as globally. Large unmet need. • While there are two approved products on the market that target the complement cascade there is a need for additional products as the complement pathway inhibitors slow the progression of GA, but they do not slow decline of or improve best corrected visual acuity (BCVA). • The project targets drug age related macular degeneration with a goal of improving BCVA (best corrected visual acuity). This is an unmet need and could significantly improve the quality of life of individuals 50 years of age and older. • This application has the potential to have a significant impact on patients with dry age-related macular degeneration. • Large impact. • The aspiration to improve vision with this therapy has yet to be proven; would be a significant improvement in treatment of the disease. • This product complements another product which the applicants are developing for a similar indication, and which is in clinical trials currently. The concept of using the secretome from RPE cells to treat GA is conceptually simpler than a cell therapy on a membrane. The product is likely to be simpler to produce and less costly than the RPE cell therapy already in clinical trials by the same group. • This product is worth further investigation in the clinic. • The use and production of a secretome-based therapy may provide a proof-of-concept for treating other indications. It may also lead to a more cost-effective treatment than the cell therapy currently in clinical trials for AMD/GA.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 2	• The in vitro, non-clinical and clinical data presented, especially the data provided in the resubmission, support the decision to fund the application. • The applicants have both in vitro and in vivo data supporting the use of an RPE secretome to treat GA. The data look compelling; the project plan is supported by the data the applicants have generated. • The animal data do support the continued development of the treatment. • Neuroprotection is a proven strategy in animal work. • The use of secretome is interesting... better than a cell therapy. • The scientific rationale as provided by both in vivo and in vitro data seems sound. While there was significant discussion of the animal model selected for the in vivo work it is not clear that there is a better model or that the model selected isn't adequate for the evaluations. The rationale for the project is sound. • The approach is based on scientific and developmental data, though the animal model could be more relevant to the disease. • Translatable, although the animal model is questionable. Would benefit from more preclinical work to increase the confidence that there is benefit and a potential for visual acuity/visual function improvement.
GWG Votes	**Is the project well planned and designed?**
Yes: 11 **No:** 2	• My main criticism in the previous review was that the applicants had not really given any details on how they would address FDA concerns particularly as it pertained to CMC. They have now addressed FDA concerns point by point and they understand what needs to be done. • Significant work has already been done in the planning/design of the project. Much of this has already been seen and reviewed by the FDA. Concerns raised by the FDA were addressed in this submission. • The PI has a long history of successfully translating therapies into the clinic and through an IND. The proposal is based on in vitro and in vivo data that they have generated. The proposal incorporates and takes into account necessary CMC studies with stability, assays, tech transfer needs and necessary steps to get a cGMP batch.

	• The shift in the therapeutic paradigm from a cell therapy to a mixture of compounds secreted by these same cells is well designed. • There are still many unanswered questions that may impact the timeline and budget. In particular, variability from batch to batch and scaling of the concentration process (which might lead to variability) will need to be addressed. As the applicants point out, concentration methods for small scale manufacturing cannot really be used when one manufactures at scale. • Characterization of the product may be challenging as the program progresses to a Biologic License Application. • More pre-clinical data needed with a second animal model and better secretome profiling in in vivo work. • Concern that there is no clinical protocol.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The project is feasible. The move to a secretome is seen as a strength as it circumvents the limitations of other cell-based approaches like cell viability. • The applicants addressed FDA concerns in this application point by point. • The final objective is to deliver an IND within the timelines and budget is doable. • The plan seems feasible. • The proposed project is feasible, and the sponsor has a record of success in conducting clinical trials. • The experience of the team with the cellular substrate and the disease indication supports the feasibility of the program. • The timeline and budget are appropriate. The PI and the team have the knowledge and experience to de-risk the project and move into clinic. However, the regulatory risks may not have been fully addressed. • A concern is no clinical protocol given. We need to see the clinical protocol to make it a tier 1.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• The DEI plan is good. This group has quite a bit of experience with DEI because of their previous CIRM grants and they are building on those DEI activities in this application. • The patient population is well described. Plans to increase diversity are well thought out. • For the stage of development, the program appears to be sufficient for upholding the principles of DEI. • Satisfactory DEI principles. • DEI adequate.

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	5	• Strong DEI plan. Sensitive to access and affordability concerns. Alpha Clinic resources will be utilized to improve enrollment. Addresses rural and metro access regarding site selection. • Excellent institution based on on-going DEI evaluations. Draws from a strong catchment area of southern California. Thoughtful considerations for other proposed clinical sites. • Strong goal of an affordable therapy. • Good data supporting make-up of underlying population including rural / specific urban groups. Good assessment of clinical trial

		population based on overall data, their own experiences with current Phase 2b trial and data from two other FDA approved treatments in the general space. ● Ability to draw upon Alpha Clinic resources related to recruitment and retention along with institutional race & equity resources. ● Good consideration to overcome barriers to participation. ● Plan to follow FDA draft guidance on patient diversity.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*