Application #	CLIN1-17090
Title (as written by the applicant)	Development of a novel intravitreal AAV gene therapy for the rare disease blue cone monochromacy.
Therapeutic Candidate (as written by the applicant)	[Redacted product name] AAV.7m8-Lopsin retinal gene therapy administered by a single intravitreal (IVT) injection.
Indication (as written by the applicant)	Blue Cone Monochromacy (BCM), a rare inherited retinal disease (IRD)
Unmet Medical Need (as written by the applicant)	There are no available treatments for BCM. [Redacted product name] is the only known program in development. [Redacted company name] product will provide a single intravitreal injection in an in-office setting that can restore visual function and improve quality of life in patients with BCM.
Major Proposed Activities (as written by the applicant)	• Test and release of [redacted product name] Product lots, Diluent Lot, as well as run tests on the Drug Substance lot. • Complete documents for submission to regulatory authorities: IRB's and FDA to obtain an approved IND prior to Phase I/II study initiation. • Establish clinical startup activities and specialty labs for Phase I/II study.
Statement of Benefit to California (as written by the applicant)	[Redacted company name] is a California non-profit organization that employs the majority of its staff in California. Significant efforts will be made to reach out to underserved communities in California to provide access to free genetic testing for the proper diagnosis of BCM, inclusion into the BCM global community and to learn more about the clinical trial planned to be conducted in California.
Funds Requested	$4,691,936
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	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.

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
 	
No: 0
	• The proposed project includes CLIN1 activities ahead of first-in-human gene therapy trial for patients with Blue Cone Monochromacy (BCM) – X-linked inherited disease. The condition is ultra rare 1/100, 000. It is estimated that there are 3000 patients in the US. The comments from our initial review have been well addressed and this reviewer was impressed by the level of engagement with KOLs (key opinion leaders) and patient advocacy groups in formulation of the responses. So, credit to the applicants on how they have addressed over-expression, risk-benefit ratio and budget/timeline adequately. Some key points -
	  ◦ There were some reservations about the severity of symptoms and progression, given the risks of current gene therapy treatments in development are not negligible and almost all are for much more severe disease states. However, adequate evidence is now provided that the disease state is sufficiently disabling to the affected individuals in terms of quality of life – irrespective of the visual acuity. The studies quoted refer to all patients with IRDs (inherited retinal diseases) and low vision, but the evidence from their patient advocacy group highlights the need for color vision improvement and reduction in photophobia which impact daily life and employment.
	  ◦ The applicants acknowledge that there might be a degree of amblyopia, i.e. developmental impairment in vision, but the applicants provide evidence that this is less than in achromatopsia, hence potential for better improvements with treatment than seen with achromatopsia gene therapy trials.
	  ◦ The applicants have acknowledged the risks- benefit ratio and have agreed that the first cohort of patients will include those that are more severely affected.
	  ◦ Applicants provided evidence from pre-clinical data that over-expression in S-cones has not been a concern and dismiss the hypothesis of dominant negative effect. Applicants feel that gene replacement with L-opsin alone will be enough to improve symptoms.
	  ◦ Ultimately it will be up to patients consent, but the applicants need to ensure that the patient information sheet explicitly states these potential risks and the possibility of making their vision and photophobia worse.
	  ◦ Overall, the rebuttal process has been very detailed and thorough and the answers provided will help with IND submission and clinical trial design. Will there be a beneficial effect after treatment remains to be answered by the first in human trial. Will the therapy be commercially viable is a question for later stages of development.
	• Yes, the proposed therapy is for an ultra-rare retinal genetic disorder that could be treated with a gene therapy. AAV will deliver vector optimized for cone-specific expression of human L-opsin. Currently no treatment, can be progressive and visually debilitating and is X linked. This is also attractive as it is IVT (intravitreal) injection and does not require subretinal injections.
	• The resubmission adds significantly more information about the potential impact.
	• Applicant provided an expanded discussion regarding the severity of BCM and impact on quality of life, employment, and loss of visual acuity, as well as overall socioeconomic and psychological impact. (e.g., income disparities, mobility and independent, other)
	• Applicant provided additional information on long-term collaboration with patient community (as well as financial support of patient community on R&D in the field), which appears to be indicative of general support of the proposed approach.
	• There is a clear need for this research given lack of any current therapies.
	• This re-submission is extremely important and valuable due to it targeting a very rare and X-linked orphan disease and therapies are not available today. The experimental therapy has received the FDA orphan drug and rare pediatric disease designations which are strong benefits.
	• The group went to extensive lengths for reaching out to patients and KOLs to validate their approach and need. Applicants have confirmed the need and acceptance.
	• There might be some limitations from the commercial viability viewpoint due to the small patient population linked to this rare disease.

GWG Votes	**Is the rationale sound?**
Yes: 13 No: 1	• Concerns have been adequately answered from prior review. • Project is appropriately built on prior preliminary data. • The resubmitted application provides strong preclinical evidence (i.e., 6 rodents + 4 large animal model) of cone transduction and safety. The FDA Pre-IND consultation is positive toward a favorable clinical and regulatory development pathway. The use of an AAV platform safety profile is well established for retinal indications. Mutation-agnostic provides the greatest applicability.

	• The IND is open, and the approach validated. • Applicant is leveraging the use of an AAV that has been used already in clinical studies. • It is surprising the applicants aren't taking genotype into account since different mutations affect the density of cones at the fovea. • It is unclear what cones are left at the fovea in blue cone monochromacy. Figure 4 in proposal does not show improvement of ERG (electroretinography) responses. • It is the opinion of this reviewer that a limited discussion is provided in this resubmission relative to the vector spread efficiency.
GWG Votes	**Is the project well planned and designed?**
Yes: 14 No: 0	• The proposed project includes CLIN1 activities ahead of the phase 1 clinical trial. The updated timeline and activities are improved including CMC activities, IND filing and clinical operations. • Additional detail regarding timeline and milestones has been added. Significant details added about rigorous approaches for community engagement, patient centered research, and training of study personnel. • Defined milestones (i.e., drug release, biocompatibility testing, IND filing) are clearly explained. Updated gantt chart and vendor reports show improved control. FDA concordant efficacy metrics (15 early treatment diabetic retinopathy letters is clinically meaningful) were also clear. • The applicant responded to this reviewer's concern satisfactorily. Specifications for drug product are now listed in the table. • The applicants have addressed the reviewers' prior comments. • The applicant has dropped the plan for a Type C meeting, which is supported by this reviewer. • The rationale is sound and the CMC/CTM (chemistry, manufacturing and control/clinical trial manufacturing) is available. It is supported by the body of evidence. However, it is unclear if the therapy's risk is worth the benefit and if it would change the prognosis and reverse vision loss and improve symptoms with only 1 injection in children and young adults. • There is very little description of CMC and quality activities in this resubmission. • It is surprising that genotype isn't being considered since genotype affects the density of cones at the fovea.
GWG Votes	**Is the project feasible?**
Yes: 14 No: 0	• The CTM is ready to go, and the team has had interactions with the FDA as [redacted company name]. The PIs are experts in the field and the team has drug development expertise. • The proposed timeline is improved and feasible. Team is excellent and 2 planned clinical sites are excellent. Dr. [redacted] has a combined pediatric and adult IRD gene therapy practice at [redacted hospital name]. Second site is [redacted hospital name]. Experts will care for adult and pediatric population. • There is a robust IND-enabling package that is completed. The clinical-grade drug supply is secured. The clearly experienced study team with prior gene therapy development success is a strong component. • Revised activities, milestones and budget yielded "savings"/decreased budget by ~$2.5M. • Changes in CRO (contract research organization), as well as other changes, allowed for a significant budget reduction. • Overall supportive and changes appear reasonable and more in line with efficient drug development; applicant appears to have sought additional quotes for key activities and was able to lower cost significantly for a few key activities. • In the original proposal the CEO was collecting a salary that was 50% of the budgeted total salary. The PIs and PM/CSO were not receiving such high salaries, and this is a budget for a medical clinical trial. The CEO has taken down his salary and the budget has been decreased considerably from $7M to $4.7M with changing from a CRO that is notorious for overcharging. Unusual that a CEO has such a committed role to clinical operations and start up especially with a CRO and medical team. • Some remaining concern with allocated budget for salaries; recommend CIRM look at this closely prior to awarding grant (e.g., CEO salary for clinical start-up at 85% effort); similarly unclear if appropriate to have in budget overhead costs for certified public accountant (CPA), legal administration, and general and administrative (G&A) expenses. • Per prior comment, a detailed timeline was provided. • The FDA did provide feedback that they would not necessarily accept a change in best corrected visual acuity (BCVA) unless it was clinically meaningful and this is still

	questionable. Also, the FDA was not 100% in agreement with allowing the applicants to go into a pivotal study. ● One concern is the eventual commercialization of the project. In such an ultra-rare disease will the applicants have patients to actually sell the product to. ● Concern: The AAV manufacturing scalability risks is simplified in this resubmission.