



Application #	CLIN2-17086
Title (as written by the applicant)	Optogenetic Gene Therapy for Treatment of Retinitis Pigmentosa
Therapeutic Candidate (as written by the applicant)	Optogenetic gene therapy for patients with Retinitis Pigmentosa
Indication (as written by the applicant)	Retinitis Pigmentosa
Unmet Medical Need (as written by the applicant)	[Redacted product name] will treat patients with advanced retinitis pigmentosa (RP) who currently have no other approved treatments.
Major Proposed Activities (as written by the applicant)	<ul style="list-style-type: none"> • CMC manufacturing • Phase 1 clinical trial • Assay development
Statement of Benefit to California (as written by the applicant)	Retinitis pigmentosa (RP) is a progressively debilitating disease which leads to blindness. Of the approximate 10,000 patients living with RP in California, many have advanced disease, to the point of total loss of visual acuity. Most of these patients need to receive healthcare benefits, special living assistance, and suffer from loss of financial independence. [redacted product name] represents a potential breakthrough treatment for a high unmet medical need for RP patients to improve their quality of life.
Funds Requested	\$7,975,224
GWG Recommendation	Tier 1: warrants funding
Process Vote	<p>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.”</p> <p>Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”</p>

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	<ul style="list-style-type: none"> • Retinitis pigmentosa (RP) continues to be associated with high morbidity and high unmet medical need due to progressive degeneration of retinal photoreceptors resulting



<p>No: 0</p>	<p>in vision loss and blindness. Loss of vision results in high impact on daily activities, ability to work, drive, interact socially, and other, as well as high caregiver burden.</p> <ul style="list-style-type: none"> • The applicants intend to use an optogenetic therapy approach to treat patients with RP. • There are no treatments available, outside of <1% of RP patients who carry biallelic retinal pigment epithelium-specific 65 kDa protein (RPE65) mutations that can be treated with Luxturna. • There is an unmet medical need here with no treatment options for advanced RP except for a small subset of patients with a specific mutation that can be treated with Luxturna. • If successful, this treatment would be a game changer for subjects with advanced RP. • Yes, this project holds necessary significance and potential for impact, if successful. • A gene/mutation agnostic approach, as the applicant proposes, could target broad patient population (many underlying mutations) and have great impact; potential also to extend this approach to other indications. If successful, this could have great impact (relative to mutation-specific approach which isn't feasible to use to address needs of all patients with varying mutations). • The project has medical value in an unmet need indication. • This is a repeat updated submission for a study currently in the clinic and enrolling successfully. The technology is likely to improve the visual function of patients with severe visual impairment with advanced RP and other photoreceptor degenerative diseases. This is an optogenetic gene that will transduce retinal ganglion cells to see "light". There is no therapy currently for this group of patients. The concept has already been proven by other companies, but there are still limitations which [redacted company name] hopes to address. This technology given it is mutation and gene agnostic for RP, offers a sufficient value proposition that supports its adoption by patients and/or health care providers. • Since the initial review, team has begun enrolling patients into clinical trial and has treated 3 patients at lowest dose with no reported adverse events. This is reassuring. In addition, the applicants have expanded their target population to include patients with another inherited eye condition, choroideremia – and have agreed with FDA. This reviewer agrees that there is a clear unmet need for better treatments for end stage retinal degeneration.
<p>GWG Votes</p> <p>Yes: 14</p> <p>No: 0</p>	<p>Is the rationale sound?</p> <ul style="list-style-type: none"> • Yes - the rationale is sound. The study is already enrolling, and applicants have committed staff, PI's, sites and patients. Applicant group have had numerous interactions with the FDA and are completing their milestones. This project deserves to continue, and the Phase 1 is ongoing. The team has a very well developed, regulatory supported program with timelines. Applicant is requesting funds for both the ongoing Phase 1 open label multiple ascending dose (MAD), clinical study. • While this reviewer is not an expert in the pre-clinical models it would appear that the rationale is sound. • Yes, the scientific rationale of the planned clinical trial and therapeutic approach is sound. • Applicant has a comprehensive nonclinical testing program, including multiple pharmacology studies in animal models of disease and multiple safety/tox studies in non-human primates. • Nonclinical data are compelling; applicant showed dose dependent response on several outcomes' measures. • From the prior review there was a question on how this technology is superior to others in development. In the response provided, preclinical comparisons claim superior light-sensitivity but this is only one parameter. For example, kinetics (inversely proportional to sensitivity) would also be important. Some inaccuracies are presented about one of the competitor's (Nanoscope's) product - it's transgene and target cell are different to what is compared here. Comparison is also provided about chrimson and ChR2 (channelrhodopsin) separately, not as one multi-channel opsin (MCO) (speculation that this is a combination of 3 different channel rhodopsins). However, since no reliable public information is available for this product, it is best to leave out from any current comparisons. • The applicants have developed extensive pre-clinical data that shows that this therapy can impact vision in rodent models. In some models the improvement was more dramatic than in others. • The prior review raised questions on whether this strategy will work in advanced degeneration (target population). The applicant provided a response but still unclear, they state the following - "All patients will undergo Spectral-Domain Optical Coherence



	<p>Tomography (SD-OCT) assessment at baseline (read by the reading center) to ensure the study eye has surviving retinal ganglion cells (target cell). This ensures that all treated eyes have the potential to respond efficaciously to the treatment." However, Rd1 and Rd10 mice have anatomically intact retinal ganglion cell layer for a long time after photoreceptors degenerate. But no convincing restored visual responses were demonstrated in these pre-clinical degeneration models.</p> <ul style="list-style-type: none"> • This reviewer appreciates the planned dose escalation and exploration in the clinic. • IVT route of administration has additional advantages (if it works). • CMC costs and costs at risk for enabling activities are reasonable. • This is a reasonable use of funds as they request for the clinical study and the CMC. Applicants' have had extensive regulatory and CMC input into the production of GMP materials. They are correct that these need to be started in parallel and at risk to deliver on their overall timelines. • Safety and toxicology studies have also been done in non-human primates. • There was a comment on overpromising in prior review. Applicant response now included not to overpromise. Applicant states that [redacted product name] may improve light sensitivity and potentially higher visual functions such as visual acuity, and mobility based on comprehensive animal <i>in-vivo</i> data. • Comment in prior review: "Transduction profile of [redacted product name] in large animal model is mostly limited to fovea". In response the applicant states "Our large animal model data shows that the [redacted product name] when intravitreally delivered results in high levels of biodistribution and expression to retinal ganglion cells across the surface of the retina at all doses tested (and is not limited to the fovea)" However, no evidence of product (channel protein) expression in large animal model retina is provided.
<p>GWG Votes</p>	<p>Is the project well planned and designed?</p>
<p>Yes: 14</p> <p>No: 0</p>	<ul style="list-style-type: none"> • Two cGMP lots of [redacted product name] have been produced, undergone QC and been released for clinical testing. These two clinical lots provide enough product for the Phase 1 trial and 36 months of stability testing. • Some questions were raised about the late stage enabling costs that represent risk expenses for CIRM in the event that the Phase 1 study does not warrant a subsequent study. • Yes, the project is well-designed and planned. • Appreciate the long-term planning for late-stage manufacturing (given long lead times for many activities); argument could be made that investment in some of these activities should be gated to proof-of-concept in the clinic (to de-risk further investment). • Timeline appears reasonable, albeit ambitious. Plans seem sufficiently mapped out and reasonable in attempt to meet timelines. • Extensive collaboration and partnership with FDA on CMC, nonclinical, and clinical development programs. • Applicant has made progress, including initiation of patient enrollment which mitigates some risk to program. • Applicants have expanded trial to choroideremia which FDA has accepted; no new funds for expansion of trial requested. • Proposal is efficient and sound approach to a potentially rapid approval if the product is successful in the clinic. • Considering the incorporation of novel endpoints and great discussions already initiated with the FDA, would like to see more details on plans to further develop these. • Participant fatigue has been addressed. Genetic testing and inclusion/exclusion still unclear: Independent of mutation, protocol will not wait for testing. For Choroideremia, patients will wait for genetic confirmation. • Prior review had a question whether Luxturna patients would qualify for this optogenetic treatment. Applicant says no, but this is not what's stated in the inclusion/exclusion criteria. Applicant states - 'The Luxturna label requires the presence of photoreceptors for treatment to be indicated. Patients enrolled in our study will have no demonstrable photoreceptors and would therefore not qualify for Luxturna treatment.' - This is not strictly true as Luxturna does not require presence of photoreceptors – but 'viable retinal cells as determined by the treating physician'. In this trial patients have visual acuity of 1.0-2.6 LogMar which indicates presence of photoreceptors, so not true that these patients will have 'no photoreceptors'. This is still OK but needs to be clearer and consistent and could be at the discretion of the treating physician and patient preference. • Yes - this is a repeat application. The company has resubmitted and updated its proposal and documentation, making changes as requested by the prior CIRM review.



	<p>The budget had been clarified and amended. IF CIRM wants to cut some of the budget, there are changes and edits that can be made around the patient and site education as well as the consultants and investigator meetings (IM). The CMC and clinical costs are necessary. Concern remains that for a small company, should this amount of funds be used to pay for Data Safety Monitoring Committee (DSMC) meetings, IM meetings and Scientific Advisory Board (SAB) members. Funds would be better put towards the mission critical issues like CMC and regulatory needs.</p> <ul style="list-style-type: none"> • Revised statistical plan, ad hoc as recommended, bio-statistician involvement and significant funds allocated, if anything these are over-allocated for the size of this Phase 1 trial. • Please scrutinize budget; appear to be a few extraneous costs particularly as related to consultants, advisors, executives etc. that may not be needed for the project.
GWG Votes	Is the project feasible?
<p>Yes: 14</p> <p>No: 0</p>	<ul style="list-style-type: none"> • While the timeline is tight the applicants have shown good progress since the last submission. • So far there have not been any issues with patient recruitment. • No issues are foreseen with manufacturing or the development of validated assays. The potency assay may take further time, but it is not needed until later in clinical development. • Yes, project is feasible. • The team appears good, and partners chosen by applicant are well-respected in community. • Note to ensure that funds allocated for clinical trial start-up haven't already been paid out, given the gap in submission of application and enrollment goals; to ensure CIRM funding goes towards needed activities. • Appreciate that risks outline significant timeline and cost risks associated with late-stage manufacturing, as well as the allocation of applicant's own funds of \$1.75mm to put towards potential mitigations. • Team has begun enrolling patients for clinical trial; nice to see progress here and no initial issues with patient recruitment, enrollment, etc. • Some late stage manufacturing activities are gated, most notably analytical development and validation; appreciate the change. • CMC aspects are feasible and well thought out, and experienced contract manufacturers are planned to be used. Collaborative relationship with FDA is a plus. • Yes - the timelines are reasonable. The team is already enrolling in the clinical study and has completed Cohort 1. The proposed team is appropriately qualified and staffed with access to all the necessary resources to conduct the proposed activities, including manufacturing. The applicants' have had close and numerous interactions with the FDA which strengthens the feasibility and de-risks. Applicant is also expanding into another patient population, also ultra rare, that could potentially benefit from this technology. • Revised timeline has been provided (page 52) including milestone review plans. Applicant states - 'The manufacturing itself is also gated on receipt of additional Phase 1 data and completion of 12 months follow-up of all patients; however, the milestone itself is not included in the Gantt chart and should be included in mid-2026. Funder might wish to see evidence of some form of efficacy as well as safety (note that short-term safety at low doses is to be expected).
GWG Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
<p>Yes: 14</p> <p>No: 0</p>	<ul style="list-style-type: none"> • The applicants have done a reasonable job at trying to include diverse populations in their study given RP does not show any strong racial or ethnic propensities. • DEI evaluation is positive. • Comment on DEI budget - The proposed DEI budget is for a 3-part training and to ensure the [redacted company name] team, Clinical CRO, as well as investigators and staff are DEI trained. The DEI budget is regardless of trial size and is a one-time cost. Funder to decide if this is appropriate. Defer to DEI experts. • There were some changes in the DEI plan that were not entirely clear.

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: 7.0

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	<i>none</i>
6-8: Responsive	7	<ul style="list-style-type: none"> • Appropriate demographic data understood and included. • The DEI proposal remains largely unchanged from the original submission. • Ray Therapeutics prioritizes patient support by implementing cultural sensitivity training, outreach pamphlets in multiple languages, and selecting sites with diverse patient populations, provide community outreach, work with advocacy groups to achieve their diversity, equity, and inclusion enrollment goals. • The trial population goal is based on the RP disease burden by race and ethnicity. • Trial sites have been strategically selected based on highly diverse population. • Plans to address barriers to trial participation include transportation, lodging, meal compensation. Information materials will also be available in Spanish as well as having a multilingual staff. • The study will provide cultural competence and DEI training by “Simply Patient” for staff, vendors, and partners. • A prior review concern was specifically the cost of the retained services. In their response, applicant explains that the proposed DEI budget is for a 3-part training. The 1st part is to “establish understanding, historical context, as well as FDA guidance and patient impact of DEI during clinical trials” at what appeared to be \$22,000 of \$58,000 in their 1st application. The revised application shows a new total cost allocation of \$36,000 for DEI. It would appear that applicants are still proceeding with part one, but CIRM is not paying for it since it’s not part of the cost summary? Applicants make no mention of a cost reduction and justify the revised spending while maintaining their three-part DEI training. Applicants have redacted a quote from “Simply Patient Statement of Work 1”. The problem is that the revised statement of cost and their proposed plans make things unclear as to what the applicant is doing, at what cost and who is paying for it. Due to this unclear conflicting information this reviewer’s original DEI score of 8 will unfortunately be reduced to a score of 7.
3-5: Not fully responsive	0	<i>none</i>
0-2: Not responsive	0	<i>none</i>