| Application # | CLIN1-16103 |
|---|---|
| **Title** (as written by the applicant) | Targeted DOK7 gene therapy for Congenital Myasthenic Syndromes |
| **Therapeutic Candidate** (as written by the applicant) | The therapeutic candidate to be studied under this proposal is a gene therapy product for the treatment of DOK7 Congenital Myasthenic Syndrome |
| **Indication** (as written by the applicant) | The target indication is DOK7 Congenital Myasthenic Syndrome (DOK7 CMS) |
| **Unmet Medical Need** (as written by the applicant) | There is no cure for DOK7 CMS. The proposed gene therapy will be the first treatment specifically designed for DOK7 CMS enabling a shift in clinical practice from chronic administration of drugs to alleviate symptoms to a one-off therapy allowing physicians to treat the entire affected population. |
| **Major Proposed Activities** (as written by the applicant) | • Manufacture the gene therapy product to support first clinical trial<br>• Potency assay development<br>• Biodistribution and shedding analysis |
| **Statement of Benefit to California** (as written by the applicant) | This proposal will allow to submit an IND for the first clinical trial in DOK7 CMS which will be held at [a California clinical site] in collaboration with a world-renowned expert on CMS from [another California institution]. The trial will benefit California resident suffering from DOK7 CMS, benefits will be particularly evident for the pediatric population, which will be spared lifelong limitations such as the need for tracheotomy or severe scoliosis. |
| **Funds Requested** | $2,894,305 |
| **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."<br><br>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.

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| **Highest** | 1 |
| **Lowest** | 1 |
| **Count** | 15 |
| **Votes for Tier 1** | 15 |
| **Votes for Tier 2** | 0 |
| **Votes for Tier 3** | 0 |

1. A score of "1" means that the application has exceptional merit and warrants funding.
2. 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.
3. 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 | • This application aims to treat a very rare genetic disease - Congenital Myasthenic Syndrome. There are only about 3,600 afflicted individuals worldwide. There is currently |

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| **No:**<br>0 | no curative treatment for this condition and therefore any new potentially curative therapy addresses an unmet medical need.<br>● This is a gene therapy proposal for a product that is intended to correct gene defects that lead to congenital myasthenia gravis; the defects are in the Dok7 protein. The gene vector will provide non-defective Dok7 protein to muscles.<br>● Highly significant trial and with potential high impact for patients with Congenital Myasthenic Syndromes.<br>● This will be a novel therapy. We know that there are only about 3600 cases worldwide. This technology may be the first of many therapies that could be spun off.<br>● The plan is to deliver a DOK7 plasmid driven by a muscle specific promoter to subjects in an open label phase 1/2 dose escalation study after a successful IND application.<br>● If successful, this product would be very beneficial and provide an improvement over the current standard of care because it aims to treat the cause of the disease.<br>● Team has put a lot of effort into addressing the potential for impact and meeting FDA requirements for clinical development. Their commercialization section is detailed, showing that they've done their homework in seeking investment from outside firms, including securing a term sheet from one of them.<br>● This is a rare and serious condition, and the submitters have taken our prior feedback seriously and made changes to the application. This application should be fundable at this point.<br>● There is significant value if the product is curative in affected individuals. There are quite a number of mutations giving rise to this condition as well as quite a lot of phenotypic variability in symptoms.<br>● The proposed therapy addresses a genetic disease without any curative therapies available. The genetic disease is an ultra-orphan disease.<br>● Rare disease and this treatment would be impactful. |
| **GWG Votes** | **Is the rationale sound?** |
| **Yes:**<br>12<br><br>**No:**<br>0 | ● There was a significant clarification of the phase 1/2 recruitment plan such that a disease specific expert at a named institution would identify patients who would subsequently be treated at the proposed clinical site and that several dozen potential subjects had been identified. There were further clarifications in the clinical protocol, which included the addition of this subject global impression of change. The applicants have had a new FDA meeting with good feedback and FDA indicated that the bridging mouse study previously proposed might not be necessary.<br>● Applicants also had a new publication on a preprint server showing additional efficacy in the mouse model and getting some clarification around the necessary doses.<br>● The main concern that was raised was that the preclinical testing plan might exceed the FDA requirements specifically for the shedding and biodistribution assays. It was mentioned that the shedding and ddPCR assays should need to be directed only to the highest dose delivered. Applicants have been responsive to questions related to the assays, and the rationale for ddPCR is explained. The minimum number of samples for toxicological analysis has been revised with a more efficient plan proposed.<br>● For assay development there will be a switch in contract research organizations (CROs). New quotes are obtained from a new CRO that may reduce project costs. Shedding analysis will be conducted at one time point only with additional time point samples retained for analysis if warranted. For mouse vector biodistribution and transgene expression, only the high-dose group will be initially tested, although this is slightly unclear as it is also stated that 40% of tissues from the low-dose group will be tested. The shedding analysis will initially be limited to two time points, with later time point samples retained for analysis if needed. For large animal biodistribution, both high and low-dose cohorts will be tested.<br>● Well explained and documented rationale for the proposed trial.<br>● The data presented in the grant proposal supports the scientific and clinical rationale. The transgenic DOK7 mouse model has demonstrated survival and restoration of normal muscle strength at achievable human dose levels.<br>● The applicants have generated convincing efficacy data in a rodent knockout model that suggest their approach has utility.<br>● Efficacy is dependent on dosage - at a lower dose there was no efficacy signal but at a higher dose there was a strong efficacy signal.<br>● While the mouse phenotype is severe, the early timing of dosing was also important with dosing at a later time point giving no survival.<br>● In this submission they added animal data that strengthened the application.<br>● They have been very responsive to previous critiques and the proposal is much improved. |

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| | • It is a pretty blunt tool for the problem of endplate assembly and maintenance, and it will be very interesting and important to understand the longer-term effects. Hopefully the planned biopsies will be instructive.<br>• It is still difficult to view Figure 6, showing labeling of the endplate in large animals that received the vector. |
| **GWG Votes** | **Is the project well planned and designed?** |
| **Yes:**<br>12<br><br>**No:**<br>0 | • The project plan appears to be appropriately planned to accomplish the goals for advancing the product through preparation of the IND.<br>• The applicants have now addressed concerns from other reviewers regarding definitive pre-clinical studies and the need for qualified assays. This has led to a decrease in budget.<br>• They are also switching CROs which will lead to a decrease in costs.<br>• They have now addressed in detail how they will respond to FDA advice. Importantly, the applicants have recently had very positive feedback from FDA with concurrence on most of their questions. This should lead to timely entrance into the clinic.<br>• The effort to hold an additional FDA meeting is appreciated. It sounds like the FDA is generally positive about the development program and on board with it progressing to the clinical stage.<br>• The FDA has provided more specific guidance, and the sponsor has modified its plans to be compliant with the FDA requests.<br>• It may be difficult to detect clear clinical effects due to the varied age and phenotype severity of the patients.<br>• Adequate trial design and proposed plans.<br>• The application has been extensively rewritten, and it now reads well.<br>• A longer follow up is recommended based upon experience with thymectomy that may take up to a year to demonstrate benefit. |
| **GWG Votes** | **Is the project feasible?** |
| **Yes:**<br>12<br><br>**No:**<br>0 | • The project plan appears to be feasible to accomplish the goals for advancing the product through preparation of the IND.<br>• The clinical design has improved considerably.<br>• The feasibility of the proposed trial is adequate, and the approach proposed is justified.<br>• From a manufacturing perspective, the Contract Development and Manufacturing Organization (CDMO) can produce drug substance and drug product and complete testing in a timely manner.<br>• Lead scientists/clinician are top notch and highly committed to the project.<br>• The applicant appears to rely on the deep expertise of [a named consulting group] to guide the preparation of the IND.<br>• The CDMO is well qualified to do the manufacturing work.<br>• Going forward, if they do complete a successful IND and enter the clinic, the applicants have also addressed questions about recruitment challenges.<br>• They plan to reserve a number of tissues for future analysis, but they don't mention if assays on these samples are needed how the costs will be covered.<br>• The potential for cardiotoxicity has been raised by the FDA and should be monitored closely.<br>• Dependence on successful clinical outcomes to help with financing is risky. If clinical data are necessary for successful funding, data may be delayed for a variety of reasons. Understanding the cash flow for the next 2 to 3 years could provide insight to the CIRM decision process.<br>• While the product is worth funding, there are concerns about the funding of the company to support the activities not covered by the grant. Small details, e.g., the copyright mark on the web page is 2023, should be updated to 2024.<br>• The intellectual property structure is not very robust. |
| **GWG Votes** | **Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?** |
| **Yes:**<br>12<br><br>**No:**<br>0 | • DEI breakdown: DOK7 at one clinical site: 10% Hispanic or Latino, 90% White. Trial will enroll equal males and females. Propose 50% <18 years of age, 50% >19-64 years of age.<br>• They estimate that there are approximately 350 subjects in the USA. Between 80 and 90% are white, non-Hispanic. It will be challenging to include diverse populations in their trials. They point out that there are probably more cases in the USA that are not reported because of one disparity or another. Given the small number of patients, if and when they enter the clinic, they are working with the right groups to enhance the chances of being inclusive in their trial.<br>• One of the proposed clinical sites has community partners with a center for vulnerable populations and office of Diversity and Outreach. |

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| | • Plan, documentation and efforts are adequate and well explained.<br>• The research team is already working collaboratively. The institutions involved understand the value of having a diverse workforce.<br>• The diversity of the target population will be guided by the genetics.<br>• The clinical program has yet to be fully defined. |

## 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 | • Excellent institutional track record with demonstrated success in patient access.<br>• Strong institutions with solid track record of commitment to DEI.<br>• Rare indication, but DEI proposal outstanding with a strong history. The DEI resources brought to the table include experienced staff, collaboration with other highly regarded institutions with access to a population of greater than 6 million people that represent a vast medically underserved community already exists and with DEI roots.<br>• Revised DEI improved with clearer data with more equitable distribution of trial participants.<br>• Responsive to prior review. |
| 3-5: Not fully responsive | 0 | *none* |
| 0-2: Not responsive | 0 | *none* |

| Application # | CLIN1-17165 |
|---|---|
| **Title** (as written by the applicant) | Advancing a novel antisense oligonucleotide for the treatment of spinocerebellar ataxia type 3 (SCA3), a devastating neurodegenerative disease |
| **Therapeutic Candidate** (as written by the applicant) | An antisense oligonucleotide that induces exon skipping of exon 10 of the ATXN3 gene |
| **Indication** (as written by the applicant) | Spinocerebellar Ataxia Type 3 (SCA3) |
| **Unmet Medical Need** (as written by the applicant) | SCA3 is a debilitating and life-threatening disease, with no available treatments for the cause of this disease. Currently, there are only 2 investigational products being studied in the clinic for SCA3. One of these clinical trials is not available to US citizens at this time. |
| **Therapeutic Mechanism** (as written by the applicant) | SCA3 is caused by a mutation in the ATXN3 gene leading to a CAG expansion repeat that is toxic. The antisense oligonucleotide has been shown to skip exon 10 of the mutated ATXN3 mRNA to produce the truncated yet functional protein. |
| **Project Objective** (as written by the applicant) | IND submission |
| **Statement of Benefit to California** (as written by the applicant) | Directly, there are hundreds of patients impacted by SCA3 who have no treatment options despite having a progressive disease. Thus, if successful, there may be direct benefit for CA residents. Secondly, we intend to hire our regulatory, scientific, and clinical leadership from CA which creates jobs for the state. Thirdly, the lessons learned from this development offer a potential framework for other rare drug development efforts. |
| **Funds Requested** | $5,692,538 |
| **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.”<br><br>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.

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|---|---|
| **Highest** | 1 |
| **Lowest** | 1 |
| **Count** | 14 |
| **Votes for Tier 1** | 14 |
| **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:** 12<br><br>**No:** 0 | • SCA3 is associated with significant morbidity and mortality with no effective treatments; following onset, disease progresses quickly; symptoms include gait issues, speech issues, vestibular and oculomotor disturbances, clumsiness, cranial nerve deficits, sleep disturbances, mild cognitive impairment, and other issues. SCA3 is fatal ~6-29 years from age of onset due to pulmonary complications and cachexia.<br>• Significant unmet medical need exists for new therapies; if successful, potential for this product to have impact.<br>• Per the applicant, there are a number of investigational therapies currently in clinical testing; unclear value proposition for this product versus those others.<br>• The proposed product is an ASO, and thus not a cell therapy or gene therapy by traditional definition.<br>• SCA3 is a rare disease with no available treatments for the underlying disease. The proposed ASO treatment could correct the ATXN3 defective protein and treat the underlying cause of disease and therefore have impact for patients.<br>• The sponsor is a non-profit biotechnology company with plans to take development through a phase 1 clinical study. After the completion of the phase 1, the applicant plans to license the therapeutic to a commercial biotech to finish clinical development. There is no detail regarding how this will be accomplished or if any potential partners have expressed interest. Without a clear path to further clinical development there is risk that the program will not progress beyond phase 1 trials. Business development discussions in parallel with clinical development should be part of the project plan to ensure a path beyond phase 1.<br>• The sponsor proposes a therapeutic to treat spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph Disease (MJD) without a currently approved therapy specifically for SCA3.<br>• Therapy development for SCA3, an ultrarare condition, addresses a significant unmet medical need. There is no effective disease-modifying therapy for SCA3.<br>• Current clinical trials for SCA3, also using oligos, have either failed or currently ongoing and unavailable to US patients – and the current proposal uses a different mechanism of action (exon skipping of exon 10 vs. downregulation of transcript).<br>• Oligo therapy, including delivery via IT, as is the case here, has a proven regulatory and therapeutic track record (including prolonged clinical application; Nusinersen in SMA). Therefore, if clinically effective, there should be a clear development pathway – with adoption by patients and health-care providers.<br>• Unmet medical need as there are no disease modifying therapies yet; two others are being developed with other approaches.<br>• Unmet medical need. |
| **GWG Votes** | **Is the rationale sound?** |
| **Yes:** 12<br><br>**No:** 0 | • The rationale appears sound and draws on recent experience described in scientific literature for other ASOs.<br>• FDA did not raise concerns on animal pharmacology data or preclinical proof-of-concept or scientific rationale. Thus, the applicant appears to have path to IND from a pharmacology regulatory perspective.<br>• Exon-skipping, while not specifically targeting the expanded transcript, seems to result in a truncated protein product that maintains known functions of ataxin-3. Also, exon-skipping is much less than 100% so there should still be enough full-length normal transcript / protein.<br>• A concern may be that exon-skipping – even in a controlled *in vitro* setting – seems to be <50% efficient (15-30%). Will this be enough when delivered IT? Functional improvement in the humanized mouse model suggests it might be.<br>• Pre-clinical data suggest that the current lead oligo (which is human-specific) affects exon-skipping in a dose-dependent manner, has few off-target effects in iPS-neurons, no overt toxicity in vitro and in a single non-GLP study with research grade oligo in rat, and with wide distribution in the humanized mouse model (including reduction in aggregates). It showed improved beamwalk phenotype >18 weeks, and equivalent exon-skipping in cortex and cerebellum.<br>• The applicant has conducted proof-of-concept studies in animals; data appear favorable, however, clinical meaningfulness of observed changes (e.g., beamwalk test) as compared to controls is unclear. |

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| | • The rationale appears sound. The designed ASO appears to remove the polyglutamine expansion in both cell and animal models. The behavioral improvement in the beam test did show an effect but there also appeared to be a mild effect from the scrambled ASO.<br>• The nonclinical data in humanized mouse support functional improvements.<br>• The chemistry used is the same as for exon-skipping drugs in DMD (MOE; phosphorothioate backbone) and have a known tolerability profile.<br>• The delivery method is based on proven delivery approaches.<br>• The preclinical data are supportive of the project. |
| **GWG Votes** | **Is the project well planned and designed?** |
| **Yes:**<br>12<br><br>**No:**<br>0 | • The project seems well designed, the CMC plan is straightforward and achievable. Good guidance was received from a pre-IND meeting and the sponsor has taken this guidance into account.<br>• The application would have been improved by including the drug product manufacturing scheme as well as final drug product release criteria in the body of the application. However, the DP manufacturing and release information in the pre-IND package alleviated concerns.<br>• The applicant conducted a successful preIND meeting and has a clear path to IND (assuming tox studies are favorable); comments from FDA appear to have been reasonably incorporated.<br>• The FDA has provided guidance that the Sponsor has considered in the proposed plan.<br>• FDA discussion for IND has set roadmap with robust pre-IND package.<br>• FDA response to pre-IND meeting was generally positive.<br>• The proposed plan (pre-IND workup: dose range finding in minipig, and GLP Tox in rat and minipig [IT]; and recommended mutagenicity testing and oligo sequencing) is consistent with FDA comments.<br>• Workup (including timing) is consistent with CLIN1 PA, ending with IND submission.<br>• The manufacturing plan seems adequate. The manufacturing partners are appropriately experienced. At the end of tox studies, more GMP material will manufactured in preparation for the phase 1 trial.<br>• The applicant should consider moving the DRF minipig study to after the rat study, as results from rat study may inform the range to test.<br>• It's not clear why only female mice are being used for tox-grade drug study in humanized mouse to confirm pharmacological effect.<br>• Since to oligo is human specific, there will not be splice-switching in rat and minipig. This means that any potential toxicity specific to truncated ataxin-3 / splice-switching will not be captured in the planned tox studies in rat / minipig. Of course, the humanized mouse could work for this.<br>• There is known tolerability for this chemistry.<br>• The oligo has a mismatch to rat and pig; tox effects of molecule on pig and rat transcriptome can be studied but exon skipping will not be detected due to lack of matching to those species due to human specificity.<br>• The 4-month cycle intrathecally potentially indefinitely seems challenging to sustain.<br>• The applicant states they'll plan on partnering the program for later stage development following the establishing of initial clinical proof-of-concept. Reviewers would rather see how they'll continue development if this partner does not emerge, as is quite possible especially in rare disease. The applicant is encouraged to build out long term plans beyond seeking a partner. |
| **GWG Votes** | **Is the project feasible?** |
| **Yes:**<br>12<br><br>**No:**<br>0 | • Yes, the project is feasible. The applicant should consider staggering the DRF minipig study for after the rat study, as results from rat study may inform the range to test.<br>• The CMC strategy seems sound and straightforward.<br>• The proposal outlines a reasonable plan for development of the product.<br>• The PI is a recognized clinical neurologist with expertise in hereditary ataxias.<br>• Regulatory lead, CSO, and clinical lead are TBD – which may add time to the project (although manufacturing and analysis could start fairly soon).<br>• The scientist that originated the tech and generated a lot of the pre-clinical data is an unpaid consultant (paid through some other agreement)<br>• The CRO is experienced and participated in the pre-IND meeting.<br>• Planned animal studies are standard, and the applicant has a working relationship with the CRO.<br>• The project management consultant will increase efficiency.<br>• Manufacturing will be provided by a commercial facility. |

| GWG Votes | Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)? |
|---|---|
| **Yes:**<br>12<br><br>**No:**<br>0 | • The DEI plan was fairly light and primarily relied on the expertise at the trial site.<br>• This proposal is for a rare, genetic disease and thus enrollment will be driven by eligibility.<br>• DEI is addressed via interaction with the patient community through a patient advocacy group.<br>• Some inadvertent skewing in recruitment may eventually occur due to the unequal geographical distribution of SCA3.<br>• SCA3 not uniformly distributed - recruitment will be dependent on disease prevalence which is very low. |

## 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 | *none* |
| 6-8: Responsive | 4 | • Due to lack of information on afflicted patient population the applicant does not go into how the success of the project will impact underserved communities but will strive for a lower cost therapy to ensure that vulnerable or disadvantaged patients are not precluded.<br>• Trial participants will be based on California's population rather than prevalence of the disease due to its rarity and the bulk of patients age range from 20-64, as the disease onset is typically during the third decade of life.<br>• The clinical trial will be conducted through a local academic medical center that has a good track record in regards to having resources to support diverse patients.<br>• The trial site provides resources for staff to learn about DEI under the categories of race, LGBTQ+, and disability status.<br>• A diversity oversight panel of approximately three members will be formed to oversee cultural sensitivity training and care delivery, including members of underrepresented communities relevant to SCA3 patient demographics in the US.<br>• Collaborations with experienced gene therapy sites and advocacy groups like the *[advocacy organization redacted]* aim to ensure a diverse clinical trial population for the phase 1 study.<br>• Outreach methods include alliances with community clinics, designating community liaisons through their partnerships, social network outreach, and distribution of printed and digital materials.<br>• To reduce the burden on clinical trial patients and caregivers, the trial will minimize critical visits and provide housing, transportation, and food stipends.<br>• Trial recruitment will target underrepresented and underserved communities by connecting with clinicians in vulnerable areas.<br>• Ultimately the trial will aim to enroll a diverse and representative population, but there are limited patient population and data availability.<br>• Concerns from the primary DEI reviewer about the overall commitment to this aspect of the project. It was mentioned that CIRM may require more robust efforts in this area, but my perspective is that this should be initiated by the study team, not CIRM. |

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| | | • Difficult to assess target population due to small pool. The trial site has strong track record for patient access. |
| 3-5: Not fully responsive | 0 | *none* |
| 0-2: Not responsive | 0 | *none* |

| Application # | CLIN2-14796 |
|---|---|
| **Title** (as written by the applicant) | The [REDACTED] Delayed Immunological Tolerance after Kidney Transplantation Program |
| **Therapeutic Candidate** (as written by the applicant) | CD34+ hematopoietic stem/progenitor cells (HSPC) and CD3+ cells |
| **Indication** (as written by the applicant) | Phase I/II trial evaluating the safety/efficacy of infusion of donor CD34+ HSPCs and CD3+ T cells into recipients with HLA-identical kidney allograft. |
| **Unmet Medical Need** (as written by the applicant) | The standard of care post-transplant remains triple-therapy immunosuppression, which predisposes patients to short- and long-term complications, including nephrotoxicity and re-transplantation. This study can free patients from immunosuppression and prolong the lifespan of the patient and allograft. |
| **Major Proposed Activities** (as written by the applicant) | • This project will enroll 10 recipients and 10 donors over the course of the study. Patients will be followed for a total of 48 months.<br>• The project will manufacture CD34+ HSPC and CD3+ cells for the recipient infusions according to the manufacturing plan outlined in the protocol.<br>• The project will evaluate immune monitoring assays as risk assessment tools and test how mixed chimerism impacts donor and recipient immune cells. |
| **Statement of Benefit to California** (as written by the applicant) | The waiting time in the US is over 5 years, with California hard hit with much longer average waiting times compared to residents in other parts of the US. By avoiding allograft loss through tolerance this would reduce the need for re-transplantation, helping both the patient and other transplant candidates who are in need of a kidney and would have less competition, resulting in improved transplantation rates, a component of the 2019 executive order on advancing American kidney health. |
| **Funds Requested** | $7,343,925 |
| **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.”<br><br>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:** 12<br><br>**No:** 0 | • If successful, the approach will offer a significant advantage over current standard of care. Kidney transplant recipients typical losing organ in 10-15 years and suffer multiple side effects of life-long immunosuppression therapy. This tolerance induction approach offers one-in-a-lifetime transplant with withdrawal of standard immunosuppression.<br>• The proposed technology is aimed at addressing unmet medical need in solid organ transplantation, namely, multiple harmful effects of standard immunosuppression protocols to prevent organ rejection.<br>• There is an unmet medical need.<br>• Tolerance induction could save big spending on immunosuppression, dialysis or re-transplant.<br>• Tolerance induction is the ultimate desire for long term graft survival with minimization of unwanted side effects of immunosuppression.<br>• Improved outcomes would benefit not only the individual patients but also decrease costs (including additional kidney donations) to the healthcare system.<br>• The ability to reduce or eliminate the need for immunosuppressive drugs after renal transplant is a major goal for the patients and healthcare community.<br>• The potential impact of this proposal is the main score driver, with the potential for future impact beyond the HLA matched setting.<br>• In this resubmission, the applicant emphasizes that this phase 1 study of inducing delayed immunological tolerance in HLA-matched kidney transplant patients could be the first step towards applying this approach to patients with HLA-mismatched kidney donors as well as recipients of liver, lung, and heart transplantation who are recovering in the ICU and thus not suitable candidates for the immediate conditioning (i.e., radiation) required for simultaneous tolerance. Delayed tolerance using this approach could allow these patients to recover from surgery before undergoing the conditioning regimen months later. This group at [REDACTED] has already initiated protocols to perform delayed immunological tolerance in recipients of liver transplants.<br>• Even though, the applicants describe the path to widen technology use through commercialization (academic patent was licensed out to company), it is still not convincing that the technology is commercializable. Previous attempts to commercialize these types of technologies have failed. It is not clear what intellectual property could be protected in the product-candidate. CD34+ selection procedure is in wide clinical use by hospitals worldwide. The CD34+ selection process, described in the proposal is not novel, but standard. One of the potential paths forward for this technology is non-commercial multi center licensure and approval of CliniMACS Plus/Prodigy for selection of CD34+ cells for tolerance induction in organ transplant. |
| **GWG Votes** | **Is the rationale sound?** |
| **Yes:** 12<br><br>**No:** 0 | • The rationale is sound. It is based on long-term stable mixed donor chimerism. It was demonstrated in several clinical trials previously. Therefore, the applicant does not refer to any animal studies.<br>• The rationale is sound.<br>• The applicants significantly revised mechanistic studies, including kidney biopsy.<br>• All previous concerns have been addressed with key changes.<br>• The applicant has responded to previous concerns with data from non-clinical and human studies.<br>• Further development is warranted, based on the results of multiple clinical studies, utilizing similar manufacturing technology (CD34+ selection, using CliniMACS Plus instrument).<br>• The ongoing phase 1 study has treated a 4th patient 11 months after kidney transplantation and they display engraftment with 35% donor cell chimerism. These data further support the potential for inducing tolerance in patients who have previously received an HLA-identical kidney transplant with the possibility of reducing reliance on immunosuppressant drugs, increasing the duration of graft viability, and reducing the need for repeat transplantation. |

| GWG Votes | Is the project well planned and designed? |
|---|---|
| **Yes:** 12<br><br>**No:** 0 | • The project is well planned. The trial is ongoing. The applicant is asking CIRM to support further clinical activity and immuno-monitoring.<br>• The manufacturing plan is simple here since CD34+ selection by CliniMACS Plus is a standard FDA-approved procedure for AML (Acute myeloid leukemia).<br>• The applicant added information about the manufacturing strategy in the revised proposal. Specifically, the purity of CD34+, the dose of CD34+ and CD3+, and one or two collections.<br>• Yes, this project has been modified in response to prior reviews and is now very well designed. This is a meritorious project that will have an impact on outcomes.<br>• The sponsor has proposed a well-constructed clinical development plan.<br>• The regulatory correspondence is adequate, meeting the current requirements. The clinical trial design could be improved if additional clinical benefit or mechanistic data could be obtained.<br>• The most recent changes to the protocol following prior (2nd) review include:-<br>  • A kidney biopsy obtained 1-4 weeks before the start of the conditioning regimen has been added to provide a baseline comparator for the Month 15 biopsy.<br>  • A prospective untreated external control group has been added for the QoL (Quality of life) data.<br>  • The study stopping rules for grade 3 or higher GvHD (Graft vs host disease) have been clarified.<br>• Of note, the prospective external control group (comprised of patients not eligible for the study) is not being evaluated for other study endpoints such as graft rejection, graft failure, hospitalization, mortality, GvHD, graft function or any of the other clinical endpoints. The utility of this prospective control group would be enhanced by assessing clinically important endpoints.<br>• The proposal also mentions a historical control group based on the applicant's repository of HLA-matched donor-recipient pairs on standard triple therapy immunosuppression, however this has not been added to the protocol. This control is also intended only for the QoL data.<br>• Introduction of company added some confusion as to their role. |
| **GWG Votes** | **Is the project feasible?** |
| **Yes:** 12<br><br>**No:** 0 | • The project looks feasible.<br>• The team is most qualified to conduct a delayed tolerance induction clinical trial.<br>• This project is definitely feasible. In fact, the protocol has already been started. Funding of the project should be done in order to obtain statistically significant outcomes of this approach.<br>• Feasibility is demonstrated by 4 subjects treated.<br>• In response to concerns regarding whether this approach could be commercialized, a C-corporation, [REDACTED] has been established and holds the patent to this method of inducing delayed tolerance. Apparently, a business plan has been submitted to CIRM. It appears that the business model would be based on collecting and cryopreserving donor stem cells to offer future patients the potential of immunosuppression withdrawal. Applicant also plans to create a training program for other transplant centers and "facilitate the establishment of an independent FDA-approved tolerance program". It's not clear what such a program would entail.<br>• The study remains approximately 1 year behind the planned timeline for enrollment according to the enrollment projection graph (dated Nov 2023). A revised enrollment timeline has not been provided with either of the resubmissions.<br>• It is recommended that the financial sustainability of the company be considered. The current investment environment has been difficult. |
| **GWG Votes** | **Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?** |
| **Yes:** 12<br><br>**No:** 0 | • 50% minority participants is substantively higher than what is currently done nationwide which is admirable.<br>• The principles of DEI are included in this application.<br>• The sponsor addressed some of the concerns from the last CIRM review. |

# 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 | 7 | • Good demographic data, strong institution for accessing broad range of patients, well-considered elements to overcome barriers.<br>• Clarification of ethnicity in these 4 delayed participant/proof of concept trial were now described as one middle east person, one Latino/a, and 2 White.<br>  • Updated comments on revision document clarified that the inaugural proof of concept trial in fact had 2 participant of minority status, one middle east and one Latino for a 50% diverse group (out of 4 recipients)<br>  • On the question of how the 4 participants were chosen to participate in the proof-of-concept trial, the applicant discussion was still vague. The applicant just comments again that 50% of the participants were minorities. |
| 3-5: Not fully responsive | 0 | *none* |
| 0-2: Not responsive | 0 | *none* |

| Application # | CLIN2-17083 |
|---|---|
| **Title** (as written by the applicant) | Phase 1b Study of [redacted] in Adults with PKP2 Mutation-associated Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) |
| **Therapeutic Candidate** (as written by the applicant) | The therapeutic is an adeno-associated virus (AAV)-based gene therapy designed to deliver a functional PKP2 gene in adults with ARVC due to PKP2 gene mutation |
| **Indication** (as written by the applicant) | Arrhythmogenic right ventricular cardiomyopathy (ARVC) due to variants in the Plakophilin-2 (PKP2) gene |
| **Unmet Medical Need** (as written by the applicant) | U.S. prevalence of PKP2-associated ARVC is estimated at 70,000 though the condition is frequently undiagnosed; in nearly one in four cases, sudden cardiac death is the first sign of disease. Current treatments do not address the underlying genetic cause of disease or hinder ARVC's progression. |
| **Therapeutic Mechanism** (as written by the applicant) | PKP2 mutations result in loss of key proteins required to maintain structural integrity and signaling of heart cells. Without these proteins, heart cells are replaced by fibrofatty tissue; electrical pulses in the heart become unstable, resulting in adverse remodeling, irregular heart beats and heart failure. This gene therapy is intended to deliver a functional copy of the human PKP2 gene to replace the missing proteins, restore proper structure and function and slowing or reversing disease progression. |
| **Project Objective** (as written by the applicant) | Phase 1b study completed |
| **Statement of Benefit to California** (as written by the applicant) | Heart disease is leading cause of death among California citizens. ARVC (a type of heart disease) is often underdiagnosed. The proposed clinical research evaluates a potential treatment for patients with ARVC. Part of the research will be conducted by staff at UCSF and include outreach to identify eligible patients. Medical testing offered as part of this research increases engagement of patients with healthcare workers. This work supports California jobs at UCSF and the sponsor organzation. |
| **Funds Requested** | $8,000,000 |
| **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."<br><br>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:** 13<br><br>**No:** 0 | • Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a rare disease with no treatment for the underlying cause targeted by this therapy, mutation in the PKP2 gene. The development of a gene therapy for ARVC would meet an unmet medical need.<br>• ARVC due to PKP2 mutations is an autosomal dominant disease affecting ~70,000 in the US and characterized by the progressive loss of muscle cells in the right ventricle (RV) which are replaced with fibrosis and fatty deposits. This AAV9 gene therapy [redacted] is intended to replace the defective gene in myocytes to restore the structure and function of desmosomes and gap junctions.<br>• This disease is diagnosed at a mean age of 36 years and thus has a major impact on the lives of younger adults. The current standard of care (SOC) for PKP2-ARVC includes restriction in physical exercise, beta blockers, implantable ICDs, anti-arrhythmic drugs and occasionally radiofrequency catheter ablation and cardiac transplantation. There are no approved treatments to address the underlying cause of ARVC. [Redacted] offers the potential for a disease-modifying approach that may slow or reverse disease progression. This would be a major improvement over the current SOC and address the major unmet medical need in this population at risk for sudden cardiac death due to arrhythmia.<br>• This would be a one and done treatment that would be very helpful to patients.<br>• AAV-PKP2 gene therapy is designed to treat patients with Plakophilin-2 (PKP2) associated arrhythmogenic right ventricular cardiomyopathy (PKP2-ARVC).<br>• There are no curative products approved at this time, symptoms are imperfectly controlled with current medications and implants. There is a risk of sudden cardiac death.<br>• This is an important disease population for whom to develop a potentially curative gene therapy.<br>• Yes, AVRC is a rare disease that sometimes first presents as sudden cardiac arrest. The need for better treatment is clear.<br>• If successful, the treatment will be a profound improvement and warrants adoption.<br>• The proposal describes a first in human (FIH) trial of a cardiac-selective transgene cassette for AAV-PKP2 for genetic cardiomyopathy. There's a clear clinical need for the approach. Patients have no current therapy to be offered and have significant cardiac disease progression due to the clinical pathology associated with the genetic cardiomyopathy.<br>• Improvement in the SOC can be expected.<br>• AAV therapies are likely expensive, but these are one time treatments with long term correction/improvement for patients. Thus, the value proposition is clear.<br>• The project addresses an unmet medical need.<br>• If [redacted] is safe and effective in slowing or reversing the progression of myocardial dysfunction and arrhythmias it would be adopted by HCPs and patients, particularly if IVDs were no longer needed and the risk of sudden cardiac death was reduced. As with all gene therapies, cost would likely be the limiting factor. |
| **GWG Votes** | **Is the rationale sound?** |
| **Yes:** 13<br><br>**No:** 0 | • This FIH study is supported by toxicology and preclinical efficacy data in mice and a second relevant preclinical model which supports moving into a FIH study. In a series of studies, [redacted] or the mouse ortholog were shown to prevent or reverse ARVC phenotypes in the PKP2-cKO mouse model with a near maximal efficacious dose.<br>• The rationale appears sound, and pre-clinical animal model data are supportive. CMC activities to support a Phase 1b trial are complete & therefore de-risked.<br>• The nonclinical data support the clinical development, and the applicant has an active IND with clinical sites initiated. UK clearance for their clinical trial application (CTA) has been obtained.<br>• The rationale is clear.<br>• Enrollment in the phase 1 is limited to severely affected adults with the pathogenic PKP2 mutation who already have an ICD implanted and ongoing ventricular electrical instability. The applicant's goal is to establish safety and efficacy in this population before moving |

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| | into patients regardless of ICD status. The risk/benefit in this initial population appears acceptable.<br>● The applicant presents a clear rationale and approach to deliver the wild type version of the gene to correct the haploinsufficiency.<br>● The target product profile looks good. The clinical trial protocol appears solid and well-justified. The starting dose is the estimated efficacy dose, and the dose then escalates to double this. In the preclinical studies specific for this study, the investigator's brochure data supports that the human dose range is appropriate.<br>● IV infusion of the AAV vector appears to be one of the best vector delivery options.<br>● Yes, the rationale seems sound. |
| **GWG Votes** | **Is the project well planned and designed?** |
| **Yes:**<br>13<br><br>**No:**<br>0 | ● The project is well planned and designed. The activities requesting support are clinical activities. The trial has both FDA & UK MHRA clearance to proceed. Support is requested for clinical site management, patient engagement activities regarding genotyping, patient screening & data management, all of which seem reasonable.<br>● Clear design and credible timelines are proposed for this FIH study. It is designed well and applicable. The data safety and monitoring board (DSMB) is established and the first patient is dosed.<br>● The project seems quite well designed and resourced. Key investigators have been allotted adequate time and seem well-prepared for their responsibilities.<br>● A well designed study with FDA clearance.<br>● Well written.<br>● The applicant has released a clinical lot, and a first patient has been dosed.<br>● The phase 1 protocol is a well written, open-label, dose finding clinical trial to evaluate the safety, tolerability, and pharmacodynamics of the gene therapy in adult patients with symptomatic PKP2 mutation-associated ARVC. The trial will consist of 2 dose cohorts.<br>● Although this phase 1 study has no control group, the applicant has initiated a "phase 0" non-interventional (observational) study in patients age 14-65 with PKP2-ARVC to better characterize ARVC disease history, patient demographics, and serostatus of ARVC patients (level of AAV neutralizing antibodies). This will provide a characterized cohort of patients from which to select appropriate matched controls for the treatment arm of interventional trials, including the phase 1. It will also provide a well characterized pool of patients who may be eligible for subsequent interventional trials.<br>● The letter from CDRH authorizing use of the neutralizing antibody assay with conditions limits its use to a specific number of institutions and subjects. It's not clear how many of the US clinical sites in the phase 1 study will be conducting this assay. Currently, the protocol allows up to a maximum subject number greater than that noted in the above authorization.<br>● The sponsor doesn't appear to have submitted an orphan drug designation request. The rationale for this is not clear. |
| **GWG Votes** | **Is the project feasible?** |
| **Yes:**<br>13<br><br>**No:**<br>0 | ● The phase 1 study appears feasible, assuming sufficient patients can be enrolled at the planned US sites, with additional sites being considered in the UK. Per the enrollment projections, over ten subjects would be enrolled by Q3 2026.<br>● The project appears feasible. The main identified risks are delay in patient enrollment, which seems well addressed by the phase 0 trial and engagement activities.<br>● This project can be conducted.<br>● The sponsor has started the clinical trial. The proposal is to obtain CIRM funding to complete the clinical trial with analysis of the data.<br>● Strong feasibility and timeline, number of sites are planned.<br>● The study is already open.<br>● Given the resources and the prestigious partners, this seems quite feasible.<br>● The applicant will need to address the CDRH requirements to expand the use of the neutralizing antibody assay beyond the delineated number of sites and participants for which it is conditionally approved. |
| **GWG Votes** | **Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?** |
| **Yes:**<br>13<br><br>**No:**<br>0 | ● Their strategy for reducing barriers is quite robust; it includes reimbursement and stipends, home and electronic health visits, dispersed sites, bilingual materials and no-cost genetic testing.<br>● The cultural sensitivity and awareness activities undertaken by the applicant seem very useful and creative including "Why we do what we do" sessions that feature client |

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| | feedback. They also attest to the DEI awareness and activities of the various partner sites.<br>● The sponsor's plans to address DEI include the inclusion of 7 geographically diverse clinical sites in US, a “hub-&-spoke” referral network model linking community physicians to study investigators, no-cost genetic testing and counseling services, engagement with patient advocacy groups, multilingual information materials, reimbursement and stipends (including a proposal to compensate study subjects for loss of income, which could be very costly), and the option of some home healthcare or phone visits.<br>● The DEI plan appears reasonable.<br>● The sponsor provided a plan with considerations for implementing the principles of DEI, although white men will be the predominant treated group.<br>● There was discussion of the limited diversity of individuals with this condition; however, that is not the fault of the investigators.<br>● Yes, strong DEI attributes.<br>● Yes, the authors spent some time wrestling with the difficulties of upholding DEI principles with a rare disease that seems genetically most to affect White males. The used analogous data from sudden cardiac death to broaden the field, but still the enrollment targets reflect the problem they faced.<br>● Their goals still have them reaching an 87-90% white population with the remaining bit mostly Latino and Black. Age choice is well explained for not including those under 18, and they will aim at slightly more male than female participation.<br>● The table of trial participation goals by race, ethnicity etc. includes the observational "phase 0" study but not the phase 1 study. Phase 1 enrollment goals should be established. |

## 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 | 3 | ● Good outreach plans and choice of clinical sites.<br>● The project does a good job of exploring potential gaps in ethnic data through their choice of project sites which include various premier institutions in very diverse areas of the country. They also are quite generous with the use of supports and stipends to make sure their sample is as economically diverse as possible.<br>● Their use of the spoke and hub methodology gives them the chance of recruiting and treating in rural and underserved areas as well.<br>● Yes, this project attempts to handle the issues of DEI in what is a very challenging situation. The global data on AVRC (incomplete though it well may be) show it to be a genetic condition that is 65% male and 99% white. Using analogous data for sudden cardiac death (of which this is a subtype) does provide some degree of possible ethnic diversity. They don not exclude minorities, but doubt that they will find many with the qualifying diagnoses. |
| 3-5: Not fully responsive | 0 | *none* |
| 0-2: Not responsive | 0 | *none* |

| Application # | CLIN2-17091 |
|---|---|
| **Title** (as written by the applicant) | Phase 3 (Pivotal) Clinical Trial for SPG50 |
| **Therapeutic Candidate** (as written by the applicant) | A recombinant serotype 9 adeno-associated virus (AAV9) encoding a codon-optimized human AP4M1 transgene |
| **Indication** (as written by the applicant) | Spastic Paraplegia Type 50 caused by the AP4M1 gene |
| **Unmet Medical Need** (as written by the applicant) | Today there is no treatment of any kind beyond supportive care for SPG50/AP4M1 |
| **Therapeutic Mechanism** (as written by the applicant) | The introduced cDNA should exist primarily as an episome following transfer of the product and express a normal version of functional human AP4M1 protein continuously, which is expected to prevent or slow the onset of SPG50 if treated pre-symptomatically, or slow/halt or reverse the progression of SPG50 if treated after symptom onset. |
| **Project Objective** (as written by the applicant) | Phase 3 Trial With BLA Approval |
| **Statement of Benefit to California** (as written by the applicant) | The gene therapy for AP4M1/SPG50 offers significant benefits to California. It improves the lives of those with this rare condition, reduces healthcare burden, and positions the state as a leader in medical innovation, attracting talent and investment. It also contributes to job creation and technology advancement. |
| **Funds Requested** | $14,908,859 |
| **GWG Recommendation** | **Tier 3: sufficiently flawed, cannot be resubmitted for 6 months** |
| **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.”<br><br>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: 3

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** | 3 |
| **Lowest** | 3 |
| **Count** | 14 |
| **Votes for Tier 1** | 0 |
| **Votes for Tier 2** | 0 |
| **Votes for Tier 3** | 14 |

- 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:** 9<br><br>**No:** 4 | • The proposed gene therapy is intended for the genetic treatment of Spastic Paraplegia Type 50, caused by bi-allelic mutations in the AP4M1 gene. SPG50 is an ultra-rare (1:3M), progressive neurodegenerative disorder that affects the legs first and is characterized by initial hypotonia, progressively worsening spasticity, epilepsy, and can eventually lead to severe paralysis. Essentially all patients experience spasticity and motor delay. There is no curative treatment.<br>• The project aligns well with CIRM's mission and goals. If further developed, the project has the potential to make a substantial impact.<br>• If this project was successful, it could significantly impact outcomes in this patient population thereby impacting not only the patients but their families.<br>• The defective protein interferes with protein trafficking in the cell, a common theme in neurodegeneration.<br>• Some individuals with AP-4-HSP have reached their early twenties or older, but the long-term life expectancy for this condition remains unclear, as it was first recognized in 2011. However, many children with hereditary spastic paraplegias generally have a life expectancy into their 20s, and it is usually not considered a fatal condition. If severe motor disabilities occur, they are typically present by ages 6 to 8. The disease is heterogenous in its expression.<br>• This is a rare childhood disease that has no real treatment, making the possibility of this treatment impactful.<br>• Ultra rare disease with unmet medical need.<br>• Major strengths of the project: The vector has been developed and tested in preclinical models. The project team is supported by world leaders in SPG50, including physicians, researchers, and family foundations.<br>• Although the project is based on sound scientific rationale, seeking to replace the defective gene with a corrected gene, this updated application is less compelling than the prior one. At this point they have treated a number of patients, however, outside of a vague statement about “potential improvements” they do not provide data which proves efficacy. It is therefore difficult to picture this phase 3 study providing meaningful data which would lead to product approval.<br>• If the treatment is successful, it could be very important, although it's not clear how the availability of the product could be sustained over time for this and other AP4 diseases that might be potentially treatable.<br>• The product is designed to potentially cure a genetic neurological disease with no curative therapy at this time. The lifespan for individuals with this condition appears to be limited, however there are no long-term data yet available given the genetic cause was identified approximately 15 years ago.<br>• The strength is that there are no other available therapies, and this proposal addresses the need. The concerns are that the impact appears to be modest at best. It also appears that all available patients that are eligible for treatment will be treated in the clinical study.<br>• Worldwide, there have been several patients treated but anecdotal information was only provided for one patient which makes it difficult to analyze the potential impact of this proposal.<br>• If this treatment is successful it would definitely be adopted by both patients and health care providers as a treatment for this disease. However, if the efficacy is sub-optimal it is not only unclear how many patients/families would agree to this treatment, there is also a potential that due to the nature of the treatment and the immunosuppression following treatment that the patient's future treatment options could be altered in a way that isn't in their best interest.<br>• The major concerns are:<br>  ◦ SPG50 is clinically heterogeneous without a well-established natural history. The recent report of n =1 clinical trial for this product indicates some improvement in cognitive and communication functions. However, there is no information on the efficacy measures for other existing trials. It remains too early to approve the proposed phase 3 (Pivotal) clinical trial.<br>  ◦ The preclinical data in large animals regarding the AAV9-AP4M1 remain preliminary (given the n = 1 for each animal for each dose).<br>  ◦ The applicant cited the work: "the GAN trial demonstrates widespread CNS distribution with AAV9 vectors (Bharucha-Goebel et al, 2024). Despite using a dose approximately 30-fold lower than our SPG50 trial, intrathecal administration resulted in detectable transgene levels in multiple CNS regions, with significant |

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| | clinical improvements in patients. These outcomes challenge the notion that near-complete transduction is necessary for efficacy, suggesting that partial correction of CNS neurons can lead to observable clinical benefits, supporting continued development of AAV9/AP4M1." However, the GAN trial supplements a different gene using a different promoter. Given the distinct role between GAN and AP4M1, and their possible differential expression profiling in the CNS, the dose and outcomes from the GAN trial do not necessarily support the argument in this proposal.<br>● Insufficient clinical data is provided to justify a pivotal trial given that several subjects have been treated.<br>● Insufficient data to support the use of this particular vector.<br>● Unfortunately, from the data presented it does not appear that this project will be/is successful. |
| **GWG Votes** | **Is the rationale sound?** |
| **Yes:**<br>7<br><br>**No:**<br>6 | ● The proposed project is based on sound scientific and clinical rationale as it seeks to literally replace the defective gene (which is causative for the disorder) with a corrected gene.<br>● SPG50 is an ultra-rare disorder caused by an autosomal recessive mutation of AP4M1. The coding size of the AP4M1 gene fits nicely with a single AAV vector. This proposed project uses AAV-AP4M1 as a gene supplementing strategy and has a sound rationale.<br>● The project included preclinical data to document safety and efficacy.<br>● Preclinical studies established the correction of ATG9A trafficking in transfected patient fibroblasts. In mice, AP4M1 knockout mRNA expression was detected in multiple regions in a dose-dependent manner. Maze test behavior improved with both early and delayed administration in male mice, but only with early treatment in female mice.<br>● The theoretical scientific rationale is sound. As with other gene therapies with AAV9 vector, the concern for significant adverse effects is significant.<br>● The stated approach is reasonable, and the rationale should therefore be sound. Unfortunately, it appears that a significant number of cells are not modified in a manner to allow for correction of the disorder.<br>● The rationale for providing the missing gene is sound. However, the ability of the chosen vector and route of administration to generate sufficient transgene expression/protein production to change the disease course is not clear. The preclinical data is modest at best with only about 10% of neuronal cells being transduced.<br>● The applicant's response to the primary critique (not enough cells will be corrected) points to presumed errors in the evaluation of the reviewers but does not provide data showing that detecting AP4M1 vector DNA in multiple brain regions with the quantification shown is sufficient to provide meaningful responses in these patients. Absent the ability to re-dose these patients, this approach does not seem viable.<br>● A prior critique was that insufficient cells in the CNS would be corrected to have a clinical effect. The applicants responded that this was due to a misinterpretation of an RNAscope figure and that approximately 10% of neurons should be transfected. From biodistribution data, the applicants argue for [redacted] vg/dg (vector genomes per diploid genomes). Still, this seems quite low.<br>● The proposed dose, extrapolated from preclinical studies, has been approved by Health Canada and the FDA, but it is high. No dose finding is proposed.<br>● Adverse events have been consistently reported as neutropenia, vomiting, upper respiratory infection, weight loss, and anemia.<br>● The project included toxicity data in patients. However, the clinical data is limited, possibly related to the small number of subjects available for treatment. It would be interesting to know the clinical efficacy outcomes (or indications of outcomes) in the patients treated in the phase 1/phase 2 study because although those studies weren't designed to prove efficacy, the potential for benefit in those studies did exist. Absent inclusion of this information, reviewers are left to speculate that outcomes were not good.<br>● There is a wide choice of subjects with variable presentations which makes it very difficult to understand effect; narrowing the scope for greater uniformity in either age or presentation would be helpful. |
| **GWG Votes** | **Is the project well planned and designed?** |
| **Yes:**<br>2 | ● The funds are requested for plasmid manufacturing, vector manufacturing and a phase 3 clinical trial. |

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| **No:**<br>11 | • Letters of support from leading experts are beneficial. One clinical collaborator led a study on giant axonal neuropathy was the first IT AAV gene therapy and a substantive phase 1 study involving about a dozen patients initiated in 2015, reported in March 2024 (NEJM). The study includes several dozen items for motor function measurement and quantitative nerve conduction. There is also a letter from another clinical collaborator who has compiled the most important SPG50 disease registry.<br>• In theory, the project is well planned and well designed. Unfortunately, it doesn't seem that the approach will be successful.<br>• The trial is designed as phase 3, involving children, matched by age and highest level of motor function at baseline, with consideration of the presence of seizures. While serum and CSF biomarkers are proposed, no data has been provided. It is an open-label trial, and it is unclear how blinding can be implemented. The matching is not very convincing, as it includes other forms of spastic paraplegia.<br>• The potential to achieve a definite phase 3 answer will be difficult to obtain with the small number of patients and proposed number of age-matched controls. The pivotal study for Zolgesma had 21 patients with a rapidly developing disease and hard endpoints (survival) with a comparison group of 34 in a natural history study.<br>• In a single case, now reported, the largest feasible dose was administered. Multi-drug immune suppression was used.<br>• The ability of these patient numbers and the research design to serve as a pivotal trial is not at all convincing. It seems premature in this program development to conduct a pivotal trial.<br>• The reasons for changing the enrollment age are unclear, as is the three-year endpoint.<br>• The study is designed to meet its stated objectives. The use of a clinically meaningful endpoint makes the results interpretable. There are some questions about the natural history control group, less around the fact that they are different SPG variants, and more around the fact that they do not seem to be on a clear protocol.<br>• The randomization controls are not truly "matched."<br>• The clinical trial design does not appear to lead to a registrational approval.<br>• There are ethical concerns with this submission as beyond "failing to work." There is a high likelihood of worsening or accelerating bad outcomes for the recipients AND it may preclude them from receiving other more efficacious products in the future.<br>• Proposed phase 3 design raises questions.<br>• There is no individualized outcome data or individual toxicity data.<br>• Outcomes by disease severity and symptoms is needed.<br>• A statistical analysis plan for the clinical data is proposed. However, in some sections, it is stated that a change in total points of the proposed scoring method will be used to analyze the primary endpoint, while in other sections, the percentage from baseline is referenced. The minimal clinically important difference for SPG50 is not clear, and the standard deviation used in the planned power analysis is considerably lower than pivotal studies in other diseases that use the same outcome measure such as cerebral palsy. |
| **GWG Votes** | **Is the project feasible?** |
| **Yes:**<br>5<br><br>**No:**<br>7 | • I think the team is well qualified and have the necessary resources to conduct the proposed activities, including manufacturing.<br>• The team has demonstrated enrollment of previous subjects.<br>• The team is well-qualified.<br>• Enrollment in the trial appears generally feasible. There is a very thorough clinical protocol. The number of subjects who will consent from those available is unclear, although several have already been treated.<br>• It is unclear that this revised protocol is feasible. The patient population is small, the control group is not truly matched, and the number of cells modified is likely inadequate to lead to modifications in disease outcome. As previously stated, there are ethical concerns with allowing this project to move forward as the outcomes may be worse rather than better for these patients. With these factors, this project should not be funded.<br>• There are barely enough patients in the world to enroll the study when you consider that some of them will not be willing or eligible. There is a significant concern regarding the ability of the sponsor to enroll the study. If the sponsor is successful in completing the study, there are additional concerns about the expertise and ability to move the file through the BLA process. |

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| | • The FDA regulatory correspondence mentioned nonclinical and clinical deficiencies in the discussion on the phase 3 clinical trial. The sponsor's response was not clear, and the FDA's conclusions were not presented.<br>• Concerns about the efficacy and targeting of the vector.<br>• Unclear if they can recruit enough control patients. |
| **GWG Votes** | **Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?** |
| **Yes:**<br>11<br><br>**No:**<br>2 | • The principles of DEI are upheld in this application.<br>• The available population is specifically limited to the very small group of children who have the disease. The worldwide natural history study has shown a diverse incidence, including Middle Eastern and North African individuals.<br>• The disease affects many ethnicities and seems to qualify.<br>• This is a rare condition; they did the best they could given the incidence.<br>• The DEI proposal could be improved. |

## 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 | *none* |
| 6-8: Responsive | 6 | • Good demographic information.<br>• Better data on what has happened on current activities rather than future would be helpful.<br>• Small numbers preclude optimum diversity. |
| 3-5: Not fully responsive | 0 | *none* |
| 0-2: Not responsive | 0 | *none* |