Application #	CLIN1-14945 #2
Title (as written by the applicant)	Pre-Clinical to Clinical Gene Therapy Development for CMT4J
Therapeutic Candidate (as written by the applicant)	AAV9 Gene Therapy for An Ultra-Rare Disease Called CMT4J
Indication (as written by the applicant)	CMT4J or the FIG4 Gene
Unmet Medical Need (as written by the applicant)	CMT4J is an ultra-rare disorder that presently lacks any available treatment options and represents an underserved orphan population.
Major Proposed Activities (as written by the applicant)	• Produce the therapeutic agent to support the proposed preclinical research activities. • Evaluate the safety profile of the therapeutic in an animal model. • Assemble the preclinical data to submit an Investigational New Drug (IND) application.
Funds Requested	$3,930,964
GWG Recommendation	Tier 1: warrants funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

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

- A score of "1" means that the application has exceptional merit and warrants funding.
- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement.
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding.

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14 **No:** 0	• Charcot Marie Tooth type 4J (CMT4J) is an ultra-rare neurological disease identified in an approximate ratio of 1:1,000,000 children. CMT4J is a rare, severe peripheral neuropathy resulting from recessive inheritance of loss-of-function FIG4 alleles, characterized by motor developmental delay, slow nerve conduction velocities, and progressive motor weakness. Quadriplegia, respiratory compromise, respiratory failure leading to ventilatory

	dependence, and premature death can occur with disease progression. Patients present with a range of severity of phenotypes. ● There are no current treatments available to date to halt or reverse disease progression. The standard of care is limited to symptom management and supportive care, including physical and occupational therapy, assistive devices, and pain management. Although these interventions may help improve daily functioning and quality of life, they do not address the underlying genetic cause of the disease, allowing disease progression to continue. Based on nonclinical proof-of-concept studies, the approach is likely to provide an improvement over the standard of care. ● Yes, the proposed product and therapeutic approach offers, if successful, a positive value proposition and improvement over standard of care for the intended patient population. ● Applicants have provided a substantive response to a prior review. Given that the condition is not treatable, the proposed gene therapy may be an improvement over standard of care. ● Yes, there is an unmet medical need for CMT4J and data from the preclinical mouse model studies using the AAV approach appear promising. The ultra-rare nature of the disease makes enrollment a challenge, however the demonstrated enrollment of 20 subjects previously for a natural history study makes the target number of trial participants appear achievable. ● There is limited information on the history of disease or population kinetics. A natural history study is planned as part of the CIRM grant application that will help to inform on patient demographics and possible correlations with disease severity. The timing of therapeutic delivery appears to be a critical element in determining effectiveness and good prognostic outcomes. Given there are no alternative therapeutics to halt or reverse symptoms, and the safe adoption of AAV9 therapies has been demonstrated for other neurological disorders, this is very likely going to be supported by patients and health care providers. The main caveat is the extremely rare and potentially diverse patient population to be treated versus the cost of development which is likely to make the therapeutic cost-prohibitive to most, even administered as a single dose.
GWG Votes	**Is the rationale sound?**
Yes: 14 **No:** 0	● Yes, the rationale for the proposed project is sound. The suitability of the proposed route of administration to efficiently transduce the target cells has been established by the applicant and others in scientific literature. The applicant has also already completed compelling proof-of-concept / pharmacology studies in mouse model of disease, which demonstrated improved grip strength, improved peripheral motor nerve conduction, and dramatically increased survival following administration of the product. ● The applicant(s) have considered the potential use of AAV9/FIG4 treatment for CMT4J patients based on nonclinical and clinical administration of AAV9 in other complex genetic neuro pathological disorders. As such, the proof of concept and preliminary toxicology studies were conducted with the intended route of administration, challenging mice with high doses of AAV9-FIG4 to determine gene transduction in a FIG4-/- dominant mouse model and in wild type mice. High levels of AAV9/FIG 4 were demonstrated in neuronal target tissues. The maximum feasible dose levels informed on human equivalent dose and demonstrated rescue from the severe FIG4-/- phenotype depending on the timing to dose administration in post-natal mice. ● The nonclinical data presented to FDA was well-received and the tox plan was tentatively agreed-upon based on providing adequate comparisons of animal phenotype relative to humans. There are no animal models that completely recapitulate the variability of human phenotypes, but the FIG4-/- phenotype was considered as worst-case loss of function phenotype in humans, hence the potential for a clinical therapeutic effect appears to be feasible with a sound scientific rationale. ● The applicant took into consideration appropriate dose levels that could be safe and effective clinically, whilst designing a future toxicology study in wild type rats to evaluate safety in 3 dose groups, taking into account the intended clinical dose, dosing regimen and route of administration using GMP grade material. FDA agreed to the proposed toxicology plan. Depending on the outcome of the planned toxicology and biodistribution studies, the data will inform on the plan for clinical development. The clinical target is peripheral neurons which regenerate slowly, offering the potential to reverse symptoms based on prolonged/permanent vector expression in neurons. ● Existing pharmacology data appear sufficient to satisfy regulatory requirements for initiating human clinical testing (pending acceptable results from animal toxicology study), which significantly increases probability of success of successful IND.

	• Applicants have updated IND toxicology endpoints to include 90 and 180 Days post-treatment. • Applicants provided additional information regarding DRG toxicity observed with AAV9. Across many studies it is not clear that the observed effects are pathogenic. • Applicants indicate that liver toxicity risks are reduced by the proposed method of delivery. • Applicants have further emphasized findings from the 2021 study that showed improved neuronal survival in DRG, spinal cord, and cortex. The report indicated that transgene expression was higher in neurons (80% in ChaT) as compared to Schwann cells (7%). • The applicant's response detailing their plan for two additional full scale GMP batches with appropriate release specifications has addressed prior concerns. The more detailed CMC plan appears reasonable. • It is important to note that early postnatal correction occurred with P1 and P4 vector delivery, but effects were negligible at P11. This is clearly important in gauging the prospect for efficacy. • The caveat to consider is patient selection. Nonclinical studies indicate that early administration correlates positively with good prognosis and survival in fatal phenotypes. • Some additional discussion may be warranted regarding the rationale and need of the planned prospective natural history study to meet project goals.
GWG Votes	**Is the project well planned and designed?**
Yes: 14 **No:** 0	• Yes, the project is well designed and planned. There were some concerns raised by a few reviewers regarding the proposed timepoints in the rat toxicology study, specifically that single planned scheduled sacrifice may not be sufficient to identify potential toxicities; the applicant has revised the scheduled sacrifices to include a day 90 time point. This could be interpreted as overly conservative but is more than sufficient to meet any concerns regarding whether an appropriately comprehensive preclinical evaluation for potential axonal or neuronal degeneration was being planned. • In the meeting minutes FDA tentatively agreed to enabling an IND within 28 days. However, it is likely that a clinical hold would ensue until more safety data were available. The 28-day time point of the toxicology study would not be sufficient to fully evaluate safety and thus enable an IND. The FDA agreed to a single dose rat toxicology study with an IND-enabling endpoint of 28 days. However, a more informative study would include evaluations at both 3 and 6 months for the assessment of toxicities such as dorsal root ganglion neuropathy and potential liver toxicity which are time-dependent and progressive. The applicant has changed the nonclinical toxicology study from 28 days to 90 and (180 days) to provide a more robust assessment of nonclinical safety. • The applicant has addressed concerns regarding preclinical testing; no new issues. • Responsive to prior review. • The CMC plan is sound and appears well planned and designed. • Applicants clarify that they intend to produce 2 non-GMP batches of drug product at 2L and 50L non-clinical scales. Subsequently, they plan 500L GMP batches for clinical studies, with all four studies using the GMP plasmid. • Applicants indicate that their IND will include characterization and analysis of 4 batches/runs of drug product. • Applicants now propose a 20-participant natural history study with 5 year follow-up. Natural history studies are subject to more problems with follow-up and data collection than clinical trials. Applicants are exploring outcome measures. • Applicants have added considerable material related to outcome measures and biomarkers that may be useful in CMT4J, such as the 6-minute walk test (CMTPPedS), timed up-and-go test, and hand grip strength. • NCS and EMG methods are not specified, muscle MRI for fat proportion as an index of atrophy, disease-specific disability scales, QOL, and serum neurofilament. However, the literature for this variant (4J) mainly consists of case reports with a very severe pediatric-onset disease, and a milder adult-onset variant. Thus, the role of these outcome measures is undefined, which suggests that they need to be assessed and validated going forward. • Applicant obtained license to AAV9/FIG4 in August 2023.
GWG Votes	**Is the project feasible?**
Yes: 14 **No:** 0	• Yes, the project appears feasible. • Based on the requirement for regulatory feedback on important nonclinical study designs, the timelines are likely to be impacted and possibly costs if FDA requires additional dose groups and assessments in juvenile animals.

	• The application is missing a number of key details relating to testing and are relying on CRL expertise for study planning. This represents an omission in the team and an understanding of the models and requirements for pediatric testing. • The feasibility of the project would be enabled with specific FDA feedback in light of a possible requirement for juvenile toxicology studies based on the patient demographics.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14 **No:** 0	• The clinical study will require the support of national rare disease family foundations for which the applicant has existing collaborations and relationships with, to help recruit additional participants who meet eligibility. Subjects will be recruited through referrals from investigators and treating neurologists with whom care has been established, and thus all patients with the phenotype who meet inclusion criteria will be recruited. The application specifically states that there are no plans to specifically exclude any sex/gender, racial, or ethnic group. • Due to the small patient population, it is highly challenging to establish specific targets for diversity within the trial population. • Applicant intends to engage in a natural history study to identify specific patients and patient groups worldwide by understanding patient demographics and distribution. • Proposal appears sufficient to uphold principles of DEI. • Yes, the DEI approach is sound.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

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

DEI Score: 9

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	4	• I thought the DEI response was quite good given the rarity of the disease and the other reviewers concurred. This remains my view. • Strong plans.
6-8: Responsive	3	• Strong DEI though compromised by the small patient population. • Limited information related to rare disease status.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN1-15060
Title (as written by the applicant)	A 1XX-enhanced and fully non-viral BCMA chimeric antigen receptor (CAR) T cell therapy for Relapsed and Refractory Multiple Myeloma
Therapeutic Candidate (as written by the applicant)	Cryopreserved autologous TRAC locus 1XX BCMA-CAR T cells
Indication (as written by the applicant)	Relapsed and Refractory Multiple Myeloma
Unmet Medical Need (as written by the applicant)	No durable treatments are available for relapsed and refractory multiple myeloma (RRMM) and only ~30% of patients can access current BCMA CAR therapies. This product can improve product safety, potency, and persistence, and enable treatment for patients without access to FDA-approved CAR-T therapies.
Major Proposed Activities (as written by the applicant)	• Manufacturing process development and validation • Completion of pre-clinical pharmacology and toxicology studies • IND submission
Funds Requested	$4,585,501
GWG Recommendation	Tier 1: warrants funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

Highest	1
Lowest	2
Count	14
Votes for Tier 1	11
Votes for Tier 2	3
Votes for Tier 3	0

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• This approach could provide a significant advance in CAR-T technology and improved safety for patients. The approach is likely to be welcomed by existing and future patients as it is no more of a burden to the patients than current CAR-T approaches.

	• This project has a significant potential impact on patients with relapsed and refractory multiple myeloma (RRMM). The novel approach negates the requirement for viral vectors and offers an opportunity to more rapidly develop a therapeutic with significant impact, even though other products have been marketed for this disease. • There are many BCMA targeting strategies that have already been approved or are in development for multiple myeloma. These include two approved CAR-T cell products currently in use that produce high response rates in patients with relapsed and refractory disease. However, it is not clear that these are curative, as the relapse curves do not appear to be plateauing. The proposed product may improve the long-term efficacy of these agents by enhancing the activity and persistence of the CAR-T cells. Furthermore, the approach may enhance the manufacturing capacity of CAR-T cells in general. • Developing yet another therapeutic targeting BCMA in RRMM may be necessary, but is weakly justified in the application. The applicant acknowledges great clinical results after the treatment of commercially available anti-BCMA CAR-T products and outlined all limitations. It is not clear, however, if all these limitations (earlier line of therapy, manufacturing constraints) could be solved with already approved therapies or warrant the development of a brand-new "same target" CAR-T product. For example, moving the approved therapies from 5th line to 1-2-3 line of therapy and solving the manufacturing capacity issue in the next 3-5 years could be faster and more beneficial than developing any new CAR-T with unknown efficacy/durability (which could take 10 years to reach the market). Moving approved CAR-Ts from 5th line to 1-2-3 line of therapy may solve/improve current issues with relapses. • The potential significance of developing this type of CAR-T cell therapy at point-of-care manufacturing, specifically for California, is interesting but too remote at this point. • The technological impact of this application is significant because it will allow the creation of a platform technology that could be utilized for the development of multiple CAR-T products. • The proposal for enhanced durability of targeted T-cells would help overcome weaknesses in the two approved products with the same target in multiple myeloma. • The platform represents a clear advance over current manufacturing methods and could be used for several other indications as well.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• There is major unmet medical need for multiple myeloma, especially for access to new and significant therapies available to patients in underserved communities. • This technology has the potential to completely change the therapy of choice in this indication and in ALL populations! • The major strength lies in the CRISPR method rather than use of viral vectors. This is likely to have many other applications as the methods are worked out. • Proof-of-concept studies in mouse models indicate that this non-viral CAR-T can effectively target BCMA using CRISPR CAS9 technology and eliminate myeloma xenograft cells. The technology appears to be advanced and effective. • Several innovations in the design of the product may lead to overall improvements in product characteristics. • Preliminary data are provide proof of concept (i.e., potential benefits of the new CAR-T architecture) and support continued development. • All technological advantages proposed by the applicants are well-taken. • The existing data support the claims that non-viral manufacturing is feasible. The applicant points to preliminary data demonstrating that HDR templates can be designed to overcome lower knock-in efficiencies and yields that have been seen with non-viral approaches in the past. • The scientific and clinical rationale is sound. • The manufacturing process has been established at a clinical scale. • The BCMA target has been validated with two approved CAR-T cellular products. • Yes, but, additional development data to support the consistency of the proposed product over multiple product development lots or campaigns to demonstrate the potential to provide consistency over rLV-based treatment approaches would be helpful. • Yes, but, by the time this product is ready for commercialization, other products will have been approved. The clinical development plan for market approval will need to consider control groups and economic feasibility.
No: 1	• It is not clear that this project solves the problem of relapses in patients on BCMA; the 1XX technology alone is probably not the solution.

	• To help patients there must be a clear commercial path. It appears the the CAR used is owned by another entity and may not be available for licensing. The applicant would also likely need licenses to use CAS9 and the 1XX technology.
GWG Votes	**Is the project well planned and designed?**

Yes:
13
	• Overall, the path to the clinic is clear. However, it's not clear why a mouse PDX tumor model is needed when the applicant has already tested the product in other xenograft models. The application also refers to both traditional models and PDX models in the study plan. The PDX work does not appear necessary for IND-enabling work since the other models are sufficient for demonstrating the mechanism of action (MOA).
	• The nonclinical testing strategy is well-considered, and the applicant has sought nonclinical testing advice from FDA in a robust pre-IND package. An ongoing study in mice, funded by the applicant, is currently underway to determine the maximum feasible and, importantly, safe doses to inform the GLP toxicology study design.
	• The activities are logical and align with the CLIN1 requirements.
	• The manufacturing objectives are well-planned and designed.
	• What is the IP/licensing position for the product?
	• There are a few concerns about the future clinical trial design (listed below). No questions about any studies proposed under this CLIN1 award. They are very well-planned and designed.
	  ◦ It is not clear why the authors would not include patients eligible for currently approved BCMA-CAR therapies that do not have a manufacturing slot. The prognosis for these patients is very poor.
	  ◦ It is not clear why the authors would not include a cohort of patients who relapsed after treatment with currently approved BCMA-CAR. One of the points the applicant makes is that their product candidate could be the best for durability of response and prevention of relapses. So, why not prove it in the trial in comparison to commercially available CAR-Ts?
	  ◦ It is not clear how the applicant can justify the enrollment of patients after failing 3 lines of treatment if all of these patients are supposed to get the standard 4th line and then standard CAR-Ts (5th line)?

No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 12	• Overall the plan is feasible. However, it's not clear why developing immune monitoring assays runs the entire length of the provided Gantt chart timeline. The applicant states these are previously established assays at the applicant institution, with no expected delays. • The project appears feasible from nonclinical, CMC and clinical perspectives, with a clear plan in place. There are patients lining up for the current standard of care, with inadequate resources to treat all of them. • The studies are feasible based on the expertise of the team and the preliminary data. • The proposed studies are feasible and realistic in a 15-month period. • The applicant institution is poised to successfully develop this improvement in CAR-T technology. • The team is great and qualified. • All risks and mitigation strategies are described for manufacturing.
No: 1	• The technology exists and data support the proposal. However, the duration of clinical trials needed for marketing approval may be impacted by other products approved and in development.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• The application includes extensive and detailed review of the benefits of this therapy/technology to the institution's patient catchment region (and beyond). The institution captures about ⅓ of the California population. • The trial population is well researched and summarized. The recruitment targets appear realistic. • This was very well considered and appropriate. • Yes. The applicant is relying heavily on DEI infrastructure at the their institution. • Excellent and thorough work. • This is an easy proposal to get excited about!
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

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

DEI Score: 9.0

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	3	• The applicant conveys an excellent understanding of the patient community. • The applicant has made improvements to the CAR-T technology, mapped out the underserved populations within their catchment, and made plans for how they will serve currently underserved patients. Their plans incorporate inclusivity not only in clinical trials but also in delivery of the future approved product. • The applicant institution has a truly exceptional DEI track record. They make world class, truly game changing cancer therapy available to medically underserved populations. • This is a big YES for FUNDING!
6-8: Responsive	1	• The applicant has a strong DEI plan that reflects a good understanding of the patient population.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-15085
Title (as written by the applicant)	Personalized antisense oligonucleotide therapy for rare pediatric genetic disease: SCN2A
Therapeutic Candidate (as written by the applicant)	Investigational personalized antisense oligonucleotide drug (nL-SCN2A-002)
Indication (as written by the applicant)	SCN2a-associated genetic disorder
Unmet Medical Need (as written by the applicant)	There is currently no available targeted therapy for SCN2A related genetic disorder. There is significant genotype-phenotype heterogeneity in SCN2A related genetic disease. The study patient has a rare variant of SCN2A for whom commercial drug development is not feasible.
Major Proposed Activities (as written by the applicant)	• Assessment of safety, tolerability, and efficacy of personalized ASO nL-SCN2A-002 in first in-human n=1 trial per FDA-approved schedule of activities. • Identification of additional children with the same variant or ASO-targeted polymorphism who may derive potential benefit from the study drug. • Scientific data sharing and publication of trial outcomes to support development and delivery of therapeutics for other nano-rare genetic diseases.
Funds Requested	$985,713
GWG Recommendation	Tier 1: warrants funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

Highest	1
Lowest	2
Count	14
Votes for Tier 1	8
Votes for Tier 2	6
Votes for Tier 3	0

- A score of "1" means that the application has exceptional merit and warrants funding.
- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement.
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding.

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12 **No:** 1	• Yes, the proposal addresses an unmet medical need. The proposal is for a single patient, investigator-initiated study. The patient is a child with severe neurodevelopmental disorder presenting with intractable epilepsy and severe neurodevelopmental delay due to a rare pathogenic de novo p.R853Q gain of function SCN2A variant for which there are currently no effective or targeted therapies. If the patient benefits, this will likely provide evidence for other patients who can benefit from precision therapy. • Antisense oligonucleotides (ASOs) are already in use for various genetic disorders such nusinersen for spinal muscular atrophy. The study patient has one of many severe early onset epileptic encephalopathies for which treatment is mainly for intractable seizures. Standard antiseizure medications are often palliative and standard epilepsy surgical procedures are not used. Thus, there is an unmet need for these types of ASO therapies. • Since the study is in one patient, the outcome is difficult to predict, though it is possible this patient would benefit with low risk. While this genetic disorder is uncommon, patients usually would require costly lifelong care that would disrupt family life. It could improve lifespan as well. • The project has far-reaching implications with regard to precision ASO therapy in SCN2A mediated epilepsy. The safety and efficacy data is likely to pave way for future therapies in this devastating disease. Understanding is required with regard to seizure and EEG scoring and the monitoring protocol as clinical efficacy may be limited considering the duration of epilepsy and developmental impairment noted in the proband. • This is a proof-of-concept study in a single patient using an antisense oligonucleotide to establish gain-of-function for the treatment of a rare form of epilepsy. • Significant unmet need. • Drug delivery by the method proposed would require a commitment by the parents that is not trivial. If ASO therapy is successful, other patients and those with other disorders could benefit from this precision medicine. • This N of 1 study may limit its broad application but is still worthwhile. • Very limited number of patients, i.e., 1.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 1	• The rationale is sound. This is a precision medicine therapy with a personalized antisense oligonucleotide (ASO) drug. There are numerous disease-modifying FDA approved ASO therapies for rare neurological disorders, and many more ASOs are currently being tested in safety and efficacy trials for numerous rare and common diseases. The personalized ASO, nL-SCN2A-002, has been developed by a foundation and tested against iPSC derived cells obtained through skin biopsy fibroblast culture from the study participant. The foundation works with expert research physicians in personalized medicine centers to treat participants under investigator-initiated INDs. Their activities are governed by and consistent with the draft guidance documents of the FDA developed for individualized ASO drug products for extremely rare patients. • The approach to establish gain of function in the affected patient may be used to develop a therapeutic in other patients, given that the gene mutation has been clearly established. • Rationale is sound and based on previous ASO experience. • ASO research is a potentially rewarding area of research for treatment of well understood genetic disorders. Available data for the specific gene disorder in the study case would be very limited though. • The patient is over ten years old, nonverbal and nonambulatory. Because of the damage already done, it may be irreversible. Ideally, the patient for this study should be enrolled as early as possible in life. The investigators mention that only 9 cases with this specific genetic disorder have ever been identified and I imagine most were older by the time whole genome or whole exome sequencing was performed in most. • The proposed justification of dose levels is at least supportive of the initial dose level. It will be important to monitor subject carefully to support increasing dose in addition to staying below supporting toxicity data. • Sound rationale as this is a developmental and epileptic encephalopathy with significant phenotype genotype heterogeneity. Clarification required on how the dose planned was finalized. • Life-long repeat therapeutics seem problematic.
GWG Votes	**Is the project well planned and designed?**

Yes: 12 **No:** 1	• This study is for an N of 1, so limited data would be generated but if it meets the study objectives, it will provide supportive evidence to continue development for others with the same rare disorder (however this is extremely rare with <10 known worldwide). Manufacturing is appropriately designed and budgeted. Storage for extended duration of time appears feasible. • I believe the project is well planned. • The project design is simple and feasible. Some concerns were raised as to the feasibility of treating the patient for life based on potential lack of drug availability. The nonclinical strategy appears to have been robust. • Seizure outcomes are based on parental observation. I would suggest long term EEG studies (inpatient, outpatient ambulatory, or prolonged in EEG lab) be considered at various time points, not just an EEG at 12 months. Many disabled children have frequent subtle or subclinical seizures. Parents and physicians may not recognize certain behaviors as ictal, while stereotypies or other ictal-like events are not true epileptic events. • Methodology well planned with a robust monitoring protocol in place. Kindly streamline the seizure score and developmental assessment protocol as the benefits will be limited given the age of the subject. • Would recommend more assessments pre- and post-treatment, as determining effectiveness will be challenging in such a severely affected patient. • Collect more EEG data. • Concerns from reviews need to be taken into account and discussed by applicant.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• Yes, the intended objectives are likely to be achieved within the proposed timeline, protocol well developed, product manufacturing feasible, patient identified, and team appears well qualified. • The study is feasible since the ASO is already developed and the child has been identified. The team seems qualified and prepared. • The project is feasible in the short term. However, drug manufacturing could be problematic unless it is adopted by a pharma company. • Assurance for continued provision of the drug in setting that the therapy works is needed. • Plans for long-term care of the patient are recommended. • A revised EEG plan is recommended.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 1	• This is a single patient investigational study so DEI may not be applicable/practical. Unfortunately, patients with nano-rare variants such as the study participant are extremely rare (< 10 known cases worldwide), are particularly underserved by lack of industry effort by default and are adversely affected even within the already underserved population with diagnosed rare genetic variants. • This aspect of the application was strongly addressed. • Since the one case has already been identified, the DEI plan will not be utilized. However, the plan seems sufficient for the State of California's purposes. If the study expands to enroll additional cases, the main issue is that poor and/or minority patients often lack the best diagnostic workup such as genetic testing. Hopefully, that will change, but for now, the poor, underinsured patients have less access to quality care. • This is planned in a single proband at an advanced stage of disease and the results will probably be applicable to a wider group of children across the world with this genotype. It is also likely to pave way for further ASO development with other pathogenic genotypes. Issues that need to be verified include a) Computational modelling and structural and functional validation of the predicted effect of the variant, b) Partial gain and loss of function effects as a consequence of the ASO treatment need to be predicted using the above techniques, c) How the dose planned was finalized needs to be mentioned with evidence, d) Seizure scoring protocol, seizure type and EEG monitoring protocol need to be detailed.

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: 8.5

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	3	• While an n=1 trial is contemplated, the overall DEI assessment in the application is comprehensive. The applicant institution is very well-known for their strong DEI track record which includes significant language support among multiple other considerations such as ability to draw upon a broad demographic catchment area. This is amplified by the fact that the applicant is the only Level IV epilepsy-type center in the area. • There is a good definition with respect to outreach via public relations and strong connections to local epilepsy foundations. • While this specific application is beyond exceedingly rare, the proposed address of variants of SCN2 may address up to 90 other disease conditions.
6-8: Responsive	3	• Strong institutional DEI support. Given the N of 1 approach, there is no other basis on which to measure DEI. • N of 1 limits diversity despite good diversity discussion.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-15115 #2
Title (as written by the applicant)	The CuRe Trial: Cellular Therapy for In Utero Repair of Myelomeningocele
Therapeutic Candidate (as written by the applicant)	Allogeneic Placenta-derived Mesenchymal Stem Cells Seeded on Cook Biodesign® Dural Graft Extracellular Matrix (PMSC-ECM)
Indication (as written by the applicant)	Myelomeningocele (MMC) -or Spina Bifida- diagnosed prenatally
Unmet Medical Need (as written by the applicant)	The current standard of care in utero surgery, while promising, still leaves 58% of patients unable to walk independently. There is an extraordinary need for a therapy that prevents or lessens the severity of the devastating and costly lifelong disabilities associated with the disease.
Major Proposed Activities (as written by the applicant)	• Enrollment of 29 patients to demonstrate safety and preliminary efficacy of PMSC-ECM product
Funds Requested	$8,996,477
GWG Recommendation	Tier 1: warrants funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 1

Up to 15 scientific members of the GWG score each application. The final score for an application is the majority score of all of the individual member scores. If there is no majority score, the final score is 2. Additional parameters related to the score are shown below.

Highest	1
Lowest	1
Count	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: 13 **No:** 0	• Spina bifida (SB) is the most common congenital cause of lifelong paralysis in the United States, and approximately four children are born daily with this congenital defect. Myelomeningocele (MMC) is the most severe form of SB with an incidence of close to 1 in 2000 live births. • In addition to causing significant morbidity and mortality to patients, care of patients with SB results in significant health care resource utilization and health care expenditures.

	• The pathologic insults to the spinal cord in SB occur before birth via the two-hit hypothesis. The MOMs trial demonstrated conclusively that, for a subset of patients, prenatal MMC repair improves outcomes over postnatal care and that some of the pathology of SB can be reversed via prenatal interventions. • The previously published NIH-sponsored MOMS trial demonstrated the potential for improvement in functional outcomes in patients with MMC undergoing in utero surgical repair. However, 58% of children who underwent in utero repair were still unable to walk independently at 30 months of age. Therefore, a significant gap remains between outcomes of the current standard of care and the achievement of fully independent ambulation and freedom from disability for all patients. This cell product aims to improve the functional outcome over surgical repair alone. • Although game changing, the MOMs trial also demonstrated that over 50% of patients did not demonstrate improvement in motor function highlighting an opportunity for novel therapeutic interventions to improve outcomes, especially motor function outcomes, in patients with SB. The current proposal seeks funding for a phase 2a trial evaluating the safety and preliminary efficacy of fetal repair of MMC using a PMSC-ECM patch approach. If successful, this approach would address a significant unmet need in the care of patients with SB. • If the addition of this cell/matrix combo product applied at the time of in utero surgery increases the percentage of children with a functional outcome, without associated safety concerns, then the addition of this cell therapy would be an improvement on the current standard of care and would likely be adopted by parents and healthcare providers. • Previous clinical studies indicated that MMC prenatal repair indicated that 50% of patients still presented with motor function problems associated with spina bifida. The potential for a cell patch to be utilized in utero has the potential for high impact and clinical potential. • Could be one of the most impactful CIRM projects ever. • Devastating condition with unmet medical needs. • Overall, this is a very strong proposal. Some limitations include the concern that the experimental approach will be compared to historical data from the MOMs trial and since that time improvements in the open fetal surgical repair of MMC have occurred to ensure a watertight closure and minimize postnatal cord tethering. Thus, the baseline against which improvement will be compared is less relevant. This weakness is mitigated by the inclusion of a contemporaneous control group. • Postnatal assessment of cord tethering is an important outcome measure, especially when a patch repair is being performed, that needs to be included in the study.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The rationale appears sound based on a robust nonclinical data set in sheep and dogs showing the potential therapeutic effect and a strong safety profile. • Rationale is based on rigorous and well-performed studies. These studies include in vitro and in vivo studies including in the immunodeficient mouse model and the gold-standard fetal sheep model of MMC. Of note, the studies that are foundational for the rationale for the proposed phase 2a clinical trial were previously funded by CIRM. • The applicant had originally planned to do a larger phase 1/2 a study, but FDA asked that they first conduct a small safety study before moving into a larger cohort. Now that supportive safety data are available from the initial phase 1 phase, moving into the phase 2a in a larger number of patients is a reasonable next step, particularly since the initial cohort will continue to be followed for tumor formation and functional outcomes. • Based on the nonclinical POC and safety data, along with the safety data from the patients with MMC treated in the phase 1 part of this study, the rationale for moving into this phase 2a study appears supported. • There is strong rationale for the proposed studies. • Strong preclinical data.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• The project is well planned to achieve meaningful outcomes that, if successful, will support the therapeutic application of PMSC-ECM in fetal MMC repair. • The main concern from the initial review was more detail about a contemporary control group. In their response to the reviewers, the investigators now provide some detail about the control group—namely, that a number of patients have already been enrolled in the control arm (no PMSC-ECM) and enrollment is ongoing. Furthermore, the investigators highlight multiple times throughout the proposal that this contemporary control group is being generated and funded via another mechanism. This response is very nice and addresses the main concern from the previous submission.

	• Previous issues with the intended therapy included a strong critique on the control arms of the clinical study. These concerns have been addressed. • Answered issue of control groups. • They have already performed GMP manufacturing of the proposed therapeutic so application will not be difficult. • The timeline is appropriate. • The protocol's statistical analysis section does not include a plan for how efficacy data from the phase 2 will be compared to the MOMS data and the contemporaneous surgery-only cohort. This comparative efficacy analysis between 3 different datasets could be complex. Would recommend obtaining input from a statistician familiar with FDA's expectations for efficacy analyses using external control groups. • In the revised protocol, there is a statement under Study Population (page 1) that "In the contemporaneous cohort, subjects will be patients from 0-4 months of age with myelomeningocele who underwent fetal repair without the use of PMSC-ECM or postnatal repair without PMSC-ECM." The remainder of the application implies the contemporaneous cohort will have had in utero surgical repair. To include patients in this control group who had postnatal surgery is problematic given the MOMS study showed the benefit of in utero surgery compared with postnatal surgery. Please clarify. • The contemporaneous cohort differs from the treated group in regard to prenatal and postnatal assessments as the patients are to be enrolled at age 0-4 months of age and therefore will not have the same evaluations as the actively treated group from the time of in utero surgery to 3 months of age. Has the applicant considered modifying the contemporaneous cohort to enroll these surgery-only patients at the time of in utero surgery so that all outcomes, including in utero surgical and post-op AEs, can be compared between groups? • There seems to be an inconsistency in study time points as the protocol's Appendix 4b shows the contemporaneous cohort can be enrolled up to 4 months of age, while Appendix 5 for both cohorts indicates that the first post-hospitalization follow-up visit is to be at 3 months, which is not possible for those in the contemporaneous cohort enrolled between 3 and 4 months of age.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• Yes. Project is feasible and supported by significant preliminary data and previous CIRM supported studies. Excellent team. Excellent environment. • From a clinical trial perspective, this study seems feasible. Only one study site is planned which will result in slower recruitment and treatment. The hypothetical risks outlined by the applicant include transmission of infectious agents, impaired wound healing and tumor formation. None of these adverse events were observed in the patients treated in phase 1, however all subjects will be monitored for infections/wound healing through 30 months and for tumorigenicity through at least 6 years. • Some concerns were raised as to the applicant lack of response to a request for pros and cons of the therapy. However, the data presented collectively showed a robust nonclinical effect in two species and strong value proposition. The clinical approach appears feasible.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• Per the applicant, Latina women give birth to children with MMC at a higher rate than non-Latina white and non-Latina black women, and therefore these women and their affected fetus have been specifically selected as the target for development of this novel stem cell therapy. The goal is to enroll at least 30% Latina women, and as only a single study site is planned, the applicant has already begun advertising campaigns across different platforms in Spanish. This grant request includes compensation for lodging and travel costs, as well as childcare. • The project upholds the principles of DEI. The investigators have modified the proposal to indicate the gender of the fetus is NA in response to previous reviewers' comments. • This appears to have been satisfactorily addressed. • Well written.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

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DEI Score: 9.0

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Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	4	● The applicant's commitment to DEI remains unchanged in their updated submission. ● DEI portion of the application remains unchanged. ● Enrollment seems to reflect traditionally underserved communities. ● Address patient burden appropriately. ● Strong institutional commitment to DEI. ● Good job in addressing all issues and seems complete.
6-8: Responsive	2	● Solid DEI track record, good catchment area.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*