CLIN2 AWARDS

12/11/25

$34,999,933 GWG RECOMMENDED

$42,999,933 CIRM TEAM RECOMMENDED

$135,000,000 AMOUNT AVAILABLE

$0 BOARD APPROVED

								Score Range		Number of GWG Votes			
APP #	**TITLE**	**BUDGET REQ**	**GWG Recmd**	**CIRM Recmd**	**SCORE (MEDIAN)**	Mean	SD	Low	High	Y	N	Previous CIRM Funding	**Disease Indication**
CLIN2-19068	A Phase 1 trial of RNDP-001, a dopaminergic progenitor drug product, in idiopathic parkinson's disease	**$8,000,000**	**Y**	**Y**	**90**	87	4	75	90	12	2	Y	Parkinson's disease
CLIN2-18731	Clinical Development of [redacted], a Gene Regulation Therapy for SCN1A+ Dravet Syndrome	**$15,000,000**	**Y**	**Y**	**86**	84	4	75	90	10	3	N	Dravet syndrome
CLIN2-18595	Phase 1B/2A study of the safety and tolerability of human neural stem cells for Huntington's Disease [redacted]	**$11,999,933**	**Y**	**Y**	**85**	81	7	70	90	8	7	Y	Huntington's disease
CLIN2-19061	Phase I/II Clinical Trial for CMT4J	**$8,000,000**	**N**	**Y**	**80**	81	4	70	86	4	10	Y	CMT4J

Application #	CLIN2-19068
Title (as written by the applicant)	A Phase 1 trial of a dopaminergic progenitor drug product, in idiopathic Parkinson's disease (PD)
Therapeutic Candidate (as written by the applicant)	An off-the-shelf cell therapy of dopamine-producing neurons to restore motor function in Parkinson's disease (PD).
Indication (as written by the applicant)	Idiopathic Parkinson's disease
Unmet Medical Need (as written by the applicant)	Parkinson's disease (PD) affects over 1 million Americans, including >90,000 Californians, with no therapy that stops its progression. This treatment aims to restore lost motor function by replacing dopamine neurons with stem cells, offering the potential for durable benefit from a single procedure.
Major Proposed Activities (as written by the applicant)	• Dosing of cohort 2 and cohort 3 to select optimal dosage • Conduct PET imaging to assess graft survival and network effects post transplantation • Manufacture GMP Run 3 to enable contralateral dosing of cohort 1 and 2 • Complete all trial visits to enable database lock for final data analysis
Statement of Benefit to California (as written by the applicant)	This research offers hope to over 90,000 Californians living with Parkinson's disease (PD) by advancing a potentially transformative, one-time cell therapy that targets the root cause of the disease. By restoring lost brain function and reducing long-term care burdens, the project supports CIRM's mission to deliver stem-cell based regenerative treatments while strengthening California's leadership in biomedical innovation, job creation, and advancing access for patients.
Funds Requested	$8,000,000
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
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: 90

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below.

Mean	87
Median	90
Standard Deviation	4
Highest	90
Lowest	75
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	12
Tier 2 (1-84): Not recommended for funding	2

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.

Key Strengths and Weaknesses
• The applicants have developed a cryopreserved allogeneic iPSC derived dopaminergic progenitor cell product which shows promise for the treatment of Parkinson's Disease (PD). • Currently the only treatments for PD are aimed at ameliorating the symptoms of PD but do not address the underlying cause (progressive destruction of dopaminergic neurons). • If successful the proposed product would be a substantial improvement over current therapies. Having said that, other groups are also developing both autologous and allogeneic stem cell products for treatment of PD. Some of these products are in phase 1/2a clinical trials but none has been approved. • Today's therapies for PD are mainly based on increasing dopamine levels with drugs. While that can be effective initially, it has less benefit and severe side effects over time. Moreover, current therapy treats symptoms but is not disease modifying or regenerative. Stem cell therapy, where new healthy dopamine cells are transplanted into the brain to replace those lost to disease could be transformative for how we treat PD in the future. • The proposed therapy is a one-off treatment that could work as well as current therapy, but sustained and without side effects. • This is a very well developed proposal and contains all aspects necessary to efficiently and effectively drive clinical development. • The patient population is well described and well justified. • The project team is exceptionally strong, comprising leading experts in CMC, cell transplantation, neurosurgery, neuroimaging, and Parkinson's disease clinical care, including individuals with direct experience from previous fetal tissue trials. All necessary resources appear to be in place to support successful execution of the study. • The rationale for performing surgery at three different sites is less well supported, as this design could introduce variation into a small trial and thereby affect interpretability — a concern also noted in Barker et al., Nature Biotechnology (2025). This reviewer recommends one single surgery site and bilateral dosing. • The novelty is low, as there are ongoing clinical trials for similar cell therapies in PD. Nonetheless, this warrants funding due to the potential benefits. • Well designed and population appropriate with readiness for clinical data; applicant just needs to expand oversight and communication plans.
Value Proposition
• There are more than 1 million PD patients in the US with approximately 100,000 in California. The promise of a stem cell treatment to cure PD has been on the horizon for more than 20 years because of promising work done with fetal cell transplants in the US and Scandinavia. These transplants often led to dyskinesias thought to be due to contamination in the transplant material. • While there are other products in clinical trials, there is room for distinct approaches - meaning, differences in cell lines, differentiation processes, formulation and delivery. • Approaches which use a defined starting cell population like iPSCs are likely to be reproducible and scalable and, this reviewer believes, will eventually lead to a treatment for the underlying cause of PD. The impact and durability of the approach are still questions that need to be addressed. • The study population and inclusion criteria are well designed and clinically appropriate. Future patient populations that could benefit from stem cell therapies once safety and efficacy are demonstrated are clearly described. • Today's therapies for PD are mainly based on increasing dopamine levels with drugs. While that can be effective initially, it has less benefit and severe side effects over time. Moreover, current therapy treats symptoms but is not disease modifying or regenerative. Stem cell therapy, where new healthy dopamine cells are transplanted into the brain to replace those lost to disease, could provide a one-off treatment that potentially could provide the same benefits as conventional dopaminergic therapies, but in a sustained manner and without the long-term side effects associated with chronic medication. • Parkinson's disease affects over 1 million Americans, including >90,000 Californians, with no therapy that stops its progression. This treatment aims to restore lost motor function by replacing dopamine neurons using stem cells, offering the potential for durable benefit from a single procedure.

- The value of the screening study is to ensure the most defined population to receive the treatment would be selected to move forward.
- The unmet need is getting to the root of the disease to change the pathway of progression.
- The potential for a single treatment that would prevent further progression and mitigate the need for additional drug treatments would be meaningful and a substantial improvement to currently available therapies. Current therapies require daily medications and all have side effects to some degree or another.
- A successful therapy for PD that would stop or reverse progression would have a significant impact on the patient, caregivers, and the healthcare system.
- The current cost of PD therapy is estimated to be approximately $15-20K per year in both drug and medical care costs. There is the additional economic cost of lost work by the patient due to the illness, lost work by caregivers, and lost work due to shortened lifetimes. The long and complex surgical procedure, as well as the cost of the drug, will likely make this therapy quite expensive. Uptake of this therapy will likely be dependent upon whether this is truly a single procedure and the efficacy is enduring.
- This is an early stage project and it is too early to assess feasibility and practicality of the therapy's uptake by patients, healthcare providers and payors. Likely, the treatment will need to be performed at specialized centers.

Rationale

- The applicants have developed a process that involves thawing and expansion of a cryopreserved iPSC WCB vial and a 4-step differentiation protocol to produce and expand dopaminergic progenitor cells. The final product is then cryopreserved and can be shipped to clinical sites.
- The applicants have also developed an MRI-compatible delivery device to deliver cells to the putamen using MRI to guide the delivery to the desired site. This device has been assessed by FDA for use in the clinic
- The applicants have used a 6-hydroxydopamine lesioned rat model of PD to demonstrate dose-dependent efficacy with the highest doses, leading to complete correction of symptoms in this model. They have also utilized a primate model to assess the delivery device.
- The applicants have had extensive interactions with FDA and they are now cleared to enter clinical trials.
- No further animal studies are warranted before initiating clinical trials. As with all animal models, there are limitations; the remaining questions are best addressed in a clinical setting.
- There is a strong scientific and clinical rationale for cell-based therapies in PD from early fetal tissue trials and more recent stem cell trials. This is a very well-developed and comprehensive proposal, addressing key aspects required to efficiently and effectively drive clinical development and based on a substantial body of pre-clinical data.
- This would establish that the ability to screen appropriately so that the disease progression would have a similar pathway for each eligible patient would lead to a more significant efficacy response.
- With over 1 million patients in the US with PD and over 90,000 patients in California, this is a significant disease with the need for a new disease-modifying drug. Current oral therapies are available, but typically lose efficacy over time due to disease progression and all have unwanted side effects. The therapeutic approach has the potential to be a single procedure for the life of the patient, which would be truly significant. However, the route of administration will require a long and complex surgical procedure.
- In the large animal model studies, the engrafted cells remain and produce dopamine, which, if confirmed in clinical research, would be a transformative therapy for this disease.
- The issue that resulted in the clinical hold was related to the device that will be used to implant the cells in the putamen portion of the brain. The applicant adequately addressed this issue, allowing the IND to go into effect. This indicates that the proposed manufacturing process and the preclinical models used to show both safety and potential efficacy were sufficient for a first-in-human study.

Project Plan and Design

- The proposed clinical trial uses dose escalation with ~10 subjects to assess the safety and tolerability of the approach. While the number of subjects is small, it is hoped that some signal of efficacy can be seen.

  The trial is an open label study and should generate data to allow the applicants to assess next steps in the clinical development of the product.
- The applicants are working with three (3) centers and should have no difficulty enrolling subjects.
- The manufacturing process is robust and should be scalable. The applicants have developed in-process and final product assays which will allow them to monitor the manufacturing process. Further work will be needed to assess comparability of commercial scale development of the manufacturing process.
- The applicants are using a surrogate to assess potency. They are aware that a more directed potency assay will be required for comparability and release of commercial product and development plans are in place.
- It is not clear what changes are envisioned for commercial production and at what scale they are aiming to achieve with commercial production. of course some of that depends on clinical data on efficacy signals - it

is unclear what dose shows a robust impact in the clinic. The applicants gave more clarity on their scale-up plans in response to a reviewer inquiry.
- While it appears that the applicants have thought about the types of training that will be required at clinical sites, it is always a concern when a number of steps and assays will need to be completed at the clinical sites.
- The application is well written making it a pleasure to read and assess.
- This is a very well-developed proposal and contains all aspects necessary to efficiently and effectively drive clinical development.
- The patient population is well described and well justified. Staggered dosing is mentioned but not well described.
- The plan is to do unilateral grafting for the first two (2) dose cohorts. The rationale for that is unclear and deviates from what has been done in other studies.
- Moreover, there is a plan to offer the patients in the first two (2) dose cohorts a second transplant BUT this carries significant risks including an additional invasive surgery with long term global anesthesia, increased time for immune suppression, high risk of graft rejection if same cells are implanted twice, and a second breach of blood-brain-barrier.
- Risks are well assessed and mediated for, with the exception of the risk of immune suppression in this patient population.
- The rationale for three (3) surgery sites is not well justified and will introduce variation in a trial with few patients and can affect the ability to make conclusions (see Barker et al. Nature Biotechnology. 2025).
- It would be helpful to include timing between these screening assessments and the next planned study to begin dosing as some of the assessments within the screening period could have a significant change in output due to disease progression within certain periods of time. For instance, it would be helpful to say that they should then be dosed within [X] period of time or re-screening would need to be done.
- The section on partner oversight and communication comprised one brief statement. It will be important to have a proper plan that covers how communication between the applicant organization, their major subcontractor, other vendors, and the investigative sites will be effective. This plan would include the high level RACI highlighting key channels and players, the anticipated schedule, frequency, purpose and expectations along with the outline for escalations and resolutions. It should also list other plans that support communications such as a Monitoring Plan, Recruitment and Retention Plan, Protocol Deviation Plan, Regulatory Submissions Plan, and Safety Monitoring or Medical Monitoring Plan.
- The protocol will utilize FDG PET and wearable technology to capture motor symptoms to help assess the effectiveness of the treatment. Both these assessments, as well as safety and objective clinical assessments, should allow stage-appropriate go/no-go decisions on this approach.
- The study envisions four medical centers that will perform the surgical procedure to engraft the cells into the putamen portion of the brain. The study plans for ~10 subjects, which should be achievable within the required timeframe. In addition, the company will use an experienced CRO to manage the trial.
- The manufacturing process is considered acceptable by the FDA, as well as in the initial tests for potency. The FDA did state that the company should continue to work on a more sensitive potency test for the product.
- The study's budget and the timeline to complete the study appear likely to be achievable.
- The company addressed potential project risks by having a pre-IND meeting with FDA, addressing clinical hold issues associated with their IND submission, adequately responding to the clinical hold issues that allowed the IND to be in effect, and responding to additional FDA non-hold comments.

Project Team and Resources

- The team is well qualified and they have engaged a CMO with the facilities and expertise to execute on the manufacturing plan.
- The team has access to all the resources they need to complete manufacturing. They have already completed manufacturing for the first two (2) cohorts in the clinical trial. If successful this grant will support the manufacture of clinical material for the third cohort.
- The team has an extensive track record in development of stem cell products. One of them previously helped set up a manufacturing facility at a major academic medical center and also worked for a biotech company with a stem cell product for PD in clinical trials.
- The project team is exceptionally strong, comprising leading experts in CMC, cell transplantation, neurosurgery, neuroimaging, and Parkinson's disease clinical care, including individuals with direct experience from previous fetal tissue trials. All necessary resources appear to be in place to support successful execution of the study.
- The lead researcher has included institutions with leading neurologists in whom they have 100% confidence.
- Considering geographical diversity with the three (3) sites, along with the experts and clinicians in each

area, the project team and resources will have varied input with the drive to have a successful eligible group for the dose escalation phase. ● The company has experienced individuals in all critical roles. The company has also hired an experienced CRO to manage the trial. ● From the information provided, it appears that the team will be able to successfully execute the study. The company has identified four medical institutions that have the capability to perform the surgeries critical for the success of the trial. ● The company has contracted for manufacturing of the product and has completed appropriate shipping studies to send the product to the medical institutions involved in the study. ● The collective team appears to have the requisite experience to support this cell-based project through early clinical trials.
Population Impact
● The applicants have explored populations affected with PD and have taken this into account in their development plans. ● To ensure that representation goals are met, the applicants used population-level and PD specific prevalence data from the CPDR to determine enrollment targets. ● The applicants have set enrollment benchmarks that aim to slightly exceed the observed prevalence rates for underrepresented groups. ● The applicants' projections are accompanied by site-level recruitment plans focused on inclusivity. ● The study population is well described and justified. Inclusion criteria are well developed and make sense. Future populations that can benefit from stem cell therapies once proven effective and safe are well described. ● No major efforts for patient retention are described, but retention tends not to be a problem in these types of studies with few patients. Assessments in OFF is limited to only necessary which is good for retention and adherence to protocol. ● The application was not specific as to the patient population; they only state that the therapy could benefit 90,000 Californians. This reviewer doesn't know enough about minorities impacted with PD, but if something can help 90K Californians it is of interest. ● The PD population is well defined, with sensitive detection/diagnosis of the condition. There is extensive data on the impact of PD on the affected individual, their caregivers, on health systems, and the overall economic cost of this disease to society. ● The proposed trial study population is clearly defined. PD is primarily a disease of the elderly, and the age inclusion criteria cover the appropriate age range. ● The inclusion/exclusion criteria for the proposed study population are appropriate to achieve an appropriate distribution of subjects, appropriate to the proposed indication and the stage of clinical development. ● PD is treated by a well-defined subset of neurologists who treat patients for the lifetime of the patient. These neurologists are present in most medical centers, making it achievable to identify potential participants for this study.

Application #	**CLIN2-18731**
Title (as written by the applicant)	Clinical Development of a Gene Regulation Therapy for SCN1A+ Dravet Syndrome
Therapeutic Candidate (as written by the applicant)	The therapeutic candidate is an AAV-delivered gene regulation therapy
Indication (as written by the applicant)	Dravet Syndrome
Unmet Medical Need (as written by the applicant)	There are no effective treatments for Dravet syndrome (DS). Combinations of the latest antiseizure drugs fail to stop frequent, prolonged seizures. With 20% of patients dying before adulthood and 100% at risk for severe developmental delays, an effective DS treatment is an unmet medical need.
Major Proposed Activities (as written by the applicant)	● Manufacture sufficient product and sham material to supply Part 2 clinical study ● Complete Part 2 clinical trial to confirm safety and preliminary efficacy ● Perform regulatory tasks to enable BLA and MAA submissions ● Disseminate info about the Part 2 clinical trial and the potential of the product as a therapeutic for SCN1A+ DS ● Perform health economics and outcomes research (HEOR) and value demonstration studies to support access and affordability strategies ● Execute global market access planning to support pre-commercialization
Statement of Benefit to California (as written by the applicant)	The proposed research will benefit California and its citizens by providing jobs, improving the health and quality of life of the study participants at the clinical site in California, and reducing the burden of Dravet Syndrome on the California health system by reducing the number of emergency visits and hospitalizations related to duration and severity of patient seizures.
Funds Requested	$15,000,000
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
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: 86

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below.

Mean	84
Median	86
Standard Deviation	4
Highest	90
Lowest	75
Count	13
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	10
Tier 2 (1-84): Not recommended for funding	3

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.

Key Strengths and Weaknesses

- The applicants appear to be making good progress with FDA. The project is worth supporting, with contract milestones to provide flexibility if there need to be any updates based on FDA feedback.
- Strengths - clinical data de-risks moving forward; manufacturing at commercial scale where the product is currently being used in Part 1 de-risks scale-up comparability; possess requisite FDA designations to support accelerated approval path.
- From a clinical operations perspective, the team and plans proposed will lead to clean and accurate data.
- Good potential for improvement of quality of life.
- Positive Regenerative Medicine Advanced Therapy (RMAT) designation is admirable.
- Agree with expert reviewers that bias in efficacy assessments should be minimized and placebo effects controlled. Recommend use of methods such as standardized video recordings to ensure consistency and reduce bias, particularly where parent involvement could influence outcomes.
- It would be good to have a manual to ensure the assessments are captured in an order/flow that does not risk full attention and/or energy required for each one.
- Weaknesses - RMAT and Scientific Advice (SA) advice meetings are not yet complete; new manufacturing facility at commercial scale needs to demonstrate CMC comparability.
- CMC deficits need clarification.
- Financial ask for some redundant needs noted.
- Access/affordability has some deficits to be worked on.

Value Proposition

- Dravet syndrome is one of the worst forms of intractable pediatric epilepsy with mostly ineffective treatments that do not slow progression of neurologic disability. The condition is life long. If the animal data results are also seen in human cases in the proposed study, this treatment would be a significant breakthrough. The methodology could represent a new approach to other genetic disorders.
- Despite available therapies, Dravet continues to be associated with patient mortality and high patient morbidities including seizures, seizure burden, developmental delays, sleep disturbances, etc...
- The current medications for Dravet syndrome have many undesirable side effects that limit their use, particularly with polypharmacy. The medication costs are high, so a novel therapy as proposed may actually be cost effective if is truly a one time treatment.
- The applicant is developing a gene therapy that could potentially provide an improvement of the current standards of care for the treatment of Dravet Syndrome. If successful, this treatment would provide a better approach for treating this rare disease.
- Proposed gene therapy offers compelling value proposition for patients with Dravet syndrome.
- The proposed therapy is administered intraventricularly only one-time and presumably has a lasting benefit targeting GABAergic neurons.
- Proposed gene therapy approach has generated compelling data in animals, and early clinical data show promising safety profiles and reductions in seizure burden.
- Very compelling need and plausible mechanism of action. Therapy has the potential to arrest disease.
- The product's route of administration is fairly standard in the field, and the reviewer does not anticipate issues.
- Caregivers of patients would be alleviated of care burden as patients would experience restoration of neural function (restoration of self-reliance, age-appropriate cognitive and motor skills, extended lifespan, overall improvement in quality of life).
- Impact on healthcare providers is likely a caution due to nature of treatment modality

  - payors may initially resist due to upfront cost.

Rationale

- Rationale is sound, including route of administration and gene therapy approach in this severe disease with high unmet need.

- The Sponsor is completing the first part of a clinical study using the therapy for the treatment of DS, and there is strong rationale to continue the clinical development.
- Scientific rationale makes sense - its precise and based on understood biology and uses an efficient delivery system.
- Preliminary clinical data from Part 1 of clinical study show a favorable safety profile and, while only early data are available, promising signals of potential efficacy (e.g., reductions in seizure burden).
- Preclinical proof-of-concept data in animals are compelling; while noting some potential safety issues in animals, these appear fairly representative of class effect with AAV gene therapy and issues resolved with FDA.
- Preclinical animal models recapitulate the disease and mechanics of administration and clinical data (treatment of over a dozen patients to date) is supportive with promising results at dose level three and a reasonable safety profile.
- The animal data presented is compelling for the animal models of Dravet syndrome. Few patients have been treated, and there were no serious adverse events. Clearly long-term follow-up is needed.
- The study drug is delivered surgically and diffuses to the target GABAergic neurons by the adenovirus vector. The DNA targets the SCN1A genes, both wild type and mutated, and increases production of both proteins. The applicants say there is no evidence the mutant protein increases have adverse effects, but the increase in levels of the normal peptides provides the therapeutic benefit.
- FDA awarded program Fast Track and Regenerative Medicine Advanced Therapies designations, which reflect the promise of the program and available data.
- The CMC development and CMC-related milestones are solid, and there is sufficient rationale to perform the CMC activities prescribed.
- Part 2 study design appears robust (double-blind, sham controlled, randomized, delayed-treatment control).
- Risks of the drug delivery by stereotactic injections carries some risk, probably similar to intracerebral depth electrodes used for epilepsy surgery evaluations where there can be hemorrhage, usually not fatal but it can occur. Infection is another risk. One rodent in the animal studies had a tumor develop when the drug was injected intracerebrally rather than intraventricularly. Applicants postulated that the tissue dose was so high that it may have been the etiology.

Project Plan and Design

- A reviewer recommends gating initiation of either planned activities (or CIRM funding) to completion of successful RMAT meeting and alignment on key aspects of proposal, as well as dose level selection for Part 2.
- Funding for all of the proposed activities may be premature, which may be a function of when this CIRM grant was submitted versus when we're reviewing it now.
- Applicant notes Part 1 clinical data justify expansion into Part 2. The panelist tends to agree, but notes only minimal early Part 1 data are currently available (or at least were submitted in the application). Case in point - the applicant hasn't selected whether to take forward 1 or 2 dose levels, and data from the highest dose level aren't yet available.
- The applicant notes initiation of patient dosing imminently, but hasn't yet conducted their RMAT initial comprehensive meeting. This meeting could provide valuable insight into the design of this Part 2 of the clinical trial. Considering Part 2 may generate pivotal data to support future marketing application, alignment with FDA in advance is advisable and may significantly de-risk planned activities.
- The CMC activities proposed are critical to the success of the program. The Sponsor and subcontractors have a proven track record of success, with little risk involved.
- The CMC activities to be performed at the applicant organization are dependent on the FDA acceptance of the comparability protocol and successful execution. This risk is mitigated with an established CDMO as an approved back-up.
- Applicant also is proposing fairly extensive CMC late-stage development work (e.g., support of PPQ activities, other). Certainly appropriate to plan for this activity, but prior to having a complete picture of the Part 1 clinical data and RMAT meeting with FDA, there is potential for these plans to change significantly in the near-term.
- The facility change is a major one that will have to be accepted by regulators - RMAT and SA meetings need to be scheduled and completed.
- Supportive of increasing to fundable score of 85 if funds are gated to successful RMAT meeting.
- Applicant requests funds for site activation; this may or may not already be complete.
- Pivotal clinical study design (approximately 20 patients, sham-controlled) should generate sufficient data to determine ability to apply for marketing approval - timely enrollment will depend on patients' willingness to risk receiving sham.
- Estimating seizure frequency by parents' observation in Dravet is problematic, since they may not see all of

the events or even recognize the spectrum of seizure types unless trained to recognize them. Why not do a 1-3-day ambulatory video-EEG in these cases several times during the 52-week study duration, not just at the end of the trial or at baseline? The EEG systems are readily available for outpatients. The application did not state what type of EEG would be performed other than the 52-week EEG would be done overnight. If the gene therapy is effective, it may reduce EEG interictal abnormalities and allow normal EEG maturation in the treatment group but not the placebo group. EEG should be interpreted by an ABPN board certified physician in clinical neurophysiology, preferably a pediatric epileptologist with fellowship training. ● When the product is delivered, this reviewer suggests that the delivery system parts that made contact with brain tissue be analyzed for DNA to make sure the brain tissue has the same mutation as determined by other means in case the patient displays mosaicism. DNA can be extracted from cells that adhere to intracerebral depth electrodes used long term. Also, consider DNA testing in parents and siblings.
Project Team and Resources
● This appears to be a good team with no major gaps identified in functional representation of subject matter experts. ● The Sponsor's team and subcontractors have a proven track record of success. ● Generally, the project has the appropriate team and expertise. ● The research and clinical teams include well respected persons in epilepsy research. Facilities are good as well. Funding should ensure adequate staffing of ancillary persons. The care teams will require education to standardize data collection, and any complications would need to be shared quickly. ● Recommendation to revise needed clinical operations support to meet goals. ● Some discussion may be needed on the approach to clinical operations; it appears that they've budgeted for up to 5 clinical operations personnel to activate site and enroll up to 18 patients over a 1+ year period (in addition to CRO contracts with two organizations). This doesn't appear to be the most efficient and may be an opportunity for cost savings. ● Onboarding the new manufacturing facility means CMC oversight and strategy relies solely with the applicant organization, without relying on their previous, experienced CDMO for support - unclear whether sufficient expertise exists in-house.
Population Impact
● The gene therapy could impact the DS community in a positive way, offering a potentially better therapeutic option over the current standards of care. As DS is a rare disease, the population itself is quite small. ● Applicant appears to understand indication, disease burden, care and health outcomes- proposed Part 2 clinical study population appears reasonable, to include providing travel assistance for families to participate. ● Appears sufficient. ● There are competing clinical trials, however, applicant is enrolling different age patients, and this is a different kind of therapy, which may positively impact patient decision to participate. ● The research plan is to genetically characterize the patients with Dravet syndrome since the therapy is very specific and will not work with some cases with the syndrome, for example, gain of function mutations in SCN1A. ● This small study would not be powered to detect specific demographic risks and benefits. The condition is so rare that any case that meets the diagnostic criteria for Dravet syndrome should be considered if the caregivers are willing to have the child participate. Not all good candidates will have willing parents.

Application #	CLIN2-18595
Title (as written by the applicant)	Phase 1B/2A study of the safety and tolerability of human neural stem cells for Huntington's Disease
Therapeutic Candidate (as written by the applicant)	The therapeutic is a human pluripotent stem cell-derived neural stem cell.
Indication (as written by the applicant)	The target indication is Huntington's disease, a progressive, neurodegenerative disorder that causes cognitive, psychiatric and movement impairments.
Unmet Medical Need (as written by the applicant)	Managing HD is demanding on the patient, family members and other in-home caregivers as well as on health care resources. Currently, there are no FDA approved treatments available that alter onset or progression of HD and only symptomatic relief is provided by available drugs.
Major Proposed Activities (as written by the applicant)	• Enroll approximately 10 HD patients in Phase 1b clinical trial to demonstrate safety and tolerability of hNSC • Enroll approximately 10 HD patients in Phase 2a clinical trial of striatally-delivered hNSC • Phase 2a to demonstrate safety and preliminary evidence of efficacy at the maximum tolerated dose
Statement of Benefit to California (as written by the applicant)	The direct medical costs and costs of disability and care giving for HD patients are substantial, can stretch for over 10 years and pass from one generation to the next. Estimated annual cost for HD patients based on hospitalizations only in California range between $3 million up to $25 million. The proposed therapy could allow patients to live independently for longer periods after diagnosis, result in saving considerable costs for healthcare and care giving and provide revenue for CA.
Funds Requested	$11,999,800
GWG Recommendation	**(85-100): Exceptional merit and warrants funding, if funds are available**
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: 85

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below.

Mean	81
Median	85
Standard Deviation	7
Highest	90
Lowest	70
Count	15
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	8
Tier 2 (1-84): Not recommended for funding	7

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.

Key Strengths and Weaknesses

- Huntington's Disease (HD) presents a definite, significant medical need.
- Substantial unmet medical need coupled with annual costs of this disease make this an area that would benefit highly from a successful outcome.
- The applicants propose to use human neural stem cells derived from human ES cells (hNSC) to treat Huntington's disease (HD) a devastating condition that affects approximately 10 in 100,000 people.
- There are no current therapies to treat HD, and, as such, a cell therapy that could impact the disease would be an important step in the treatment of the disease.
- There are currently no disease modifying products for HD, though a number of products are in development. A number of FDA interactions have led to the lifting of a prior clinical hold and addressing most regulatory concerns.
- Strength is the overall design and plan for patients that could provide a reduction in burden of illness for both patient and family.
- While there are a number of products under development, this product stands out in a number of ways: 1) delivery directly to the striatum 2) off the shelf therapy that can potentially slow progression. Uptake may be challenging due to the complexity of the delivery system. This system introduces risk, and requires extensive training. The sponsor originally proposed a 50-year long term follow up but has reduced this to 15 years. This change would be more palatable for patients.
- The complex delivery procedure risks are potential issues for the product.
- Manufacturing concerns are a weakness.
- Access and affordability (A&A) reviewers comments that the applicant has inadequately budgeted to support conduct of the proposed A&A activities raises concern.
- Key strengths - Well designed clinical study. Supportive preclinical data, in particular for safe, open IND, outstanding principle investigator and team.
- Key weaknesses - Concerns about expected clinical efficacy, because of limited understanding of mechanism of action and the intracerebral injection strategy. Potentially difficult position for the therapeutic in the current competitive environment, which has several ongoing programs with molecular therapy drug candidates (gene therapy, ASO and siRNA administration).
- The current hESC line carries with it xeno- risk and regulatory complications. Transitioning now to a xeno-free cell product avoids costly repeat of CMC and clinical work later.
- The product has a very invasive delivery mechanism and presents risks. The sponsor also needs to address manufacturing issues, including regarding the cell line and plans for comparability. Additionally, potency assay feedback should be addressed. Overall, trial design is reasonable and the development team appear experienced to carry it forward.

Value Proposition

- HD progresses over 10-20 years with the patient becoming increasingly dependent on caregivers over time. With no treatment currently impacting the trinucleotide repeat cause of the disease, there is a considerable medical need for treatments that impact disease progression.
- Any treatment that could impact the root cause of HD would be very significant - current treatments only address symptoms of HD, and even then, they have significant side effects and are not very impactful.
- Huntington's disease is one of the most devastating neurological diseases. It progresses over many years, is ultimately fatal, and it generates a most painful and difficult burden for patients, their families and caregivers. HD currently has only minimally effective palliative therapy but no disease modifying therapy. Any even only mildly effective treatment will provide a significant improvement. A positive impact of effective treatment will make a major difference by reducing effort and cost for the healthcare system. Given the severe nature of the disease and the lack of effective therapies, the patient population is very eager to participate in clinical trials and will enthusiastically embrace any effective therapy, even if the therapy requires neurosurgical procedures and needle insertion into the brain.
- There are several other currently active experimental therapeutic approaches for HD. They include direct knockdown of the Huntingtin gene using AAV gene therapy. Initial signs of success have been recently reported with this approach by UniQure. Other knockdown approaches using ASOs or siRNA are at various

stages of development, but have not received clinical validation as yet. Gene knockdown efforts have been extended to the modulatory protein MSH3. Furthermore, there are attempts to modify the Huntingtin gene using gene editing. These approaches are well defined molecular therapeutic efforts, whereas the cellular approach by the applicants lacks similar scientific precision.

- The direct medical costs, costs of disability and care-giving for HD patients are substantial and can stretch for over 10 years, costs are over $2.5B/year in the US. HD is a devastating neurodegenerative disease that strikes in the prime of life, and carries a 50% risk for a patient's offspring. There are currently no FDA or EMA approved treatments that change the course of disease. One Huntingtin lowering gene therapy trial has reported interim results that appear promising in press releases (UniQure), suggesting feasibility of disease modification. However, this is an early-stage study with interim results and may represent a partial treatment. In contrast to the palliative treatments, the proposal is for using a single dose, cell-based approach to treatment which may prevent or slow disease progression, particularly in the earlier phases of disease when there is less tissue loss.
- Slowing the progression and potentially improving behaviors such as irritability, apathy, anxiety and depression would provide a meaningful outcome for this intended population.
- With no current treatment, the burden of illness on patients, their families as well as the increase in healthcare required, this therapy would offer delay in the onset and decreasing the time for hands on care prior to end of life.

Rationale

- The applicants have generated pre-clinical data which appear to show a positive effect of human neural stem cell (hNSC) transplantation in animal models. The applicants speculate that the hNSCs engraft and supply trophic factors that support endogenous neurons. In addition, the engrafted cells show longer term survival that may impact disease.
- It is proposed to administer pluripotent stem cell (PSC)-derived neural stem cells into the basal ganglia (Putamen and Caudate Nucleus, the brain areas most affected by HD), to compensate for the loss of neural cells, a key feature of HD pathology. The approach reflects early thinking in the field of stem cell science, namely that stem cells will exert positive effects by differentiating as needed by the environment.
- The precise mechanism of action of the cells is poorly understood. In mouse models of HD, they form synaptic connection with intrinsic neurons, exert trophic influences by secreting brain derived neurotrophic factor (BDNF) and they produce mild but reproducible behavioral effects.
- After implantation in animals (mice and large animals), the hNSC remain largely confined to the needle track with very limited migration into the striatum and putamen and no migration into other areas. For some of the biochemical measurements (e.g., reduction of Huntingtin aggregates) it is not clear whether they reflect the injected cells or the surrounding tissue.
- The following concern and question was sent to the applicants: The studies in mice and in large animals show that injected cells remain largely confined to the close proximity of the needle track and that they do not migrate substantially. The clinical protocol states “The cannula will be advanced into the putamen and striatum for single injections along two trajectories (dorsal and ventral) and cells will be deposited 1-2mm apart while withdrawing the cannula”. The human striatum and putamen are significantly larger than those of mice and large animals. Even with two injection tracks, the areas beneficially affected by the injected cells might be too small to impact the overall function of the entire Putamen/Striatum area of the human brain. The applicants provided a thorough answer, stating that the First-in-Human study focuses on safety, and that a small number in injection tracks are therefore preferable. This makes sense, but it makes it unlikely that efficacy signals will be observed in the first study.
- Pivotal IND-enabling safety/tumorigenicity studies have been carried out in HD mice with no negative outcomes, supporting safety of the clinical product and approach. Biodistribution and safety were also demonstrated in large animals. GMP master and working cell banks have been generated with enough cells to support this Phase 1b/2a clinical trial, and the FDA has cleared the IND.
- The sponsor hypothesizes that due to the loss of striatal medium spiny neurons and loss of cortico- striatal circuitry, transplantation of neural stem cells might provide neuroprotective or neurorestorative outcomes. Because treatment is delivered bilaterally to the striatum, it is targeted. Data show the cell product can replace/support striatal neuron classes, reestablish synaptic connectivity (including cortico-striatal inputs), improve host medium spiny neuron physiology, and supply BDNF, all of which back the claim that hNSC transplantation may deliver neuroprotective and neurorestorative benefit in HD. FDA comments/concerns highlighted with the potency assay will need to be addressed.

Project Plan and Design

- The trial design is an open label, phase 1b/2a study of striatally-administered hNSC in subjects with early manifest Huntington’s disease followed by a phase 2a dose expansion study at MTD in less than ten subjects. According to FDA, the study is too small and underpowered to “establish” safety. FDA also wants additional endpoints. Dose escalation risks are appropriately called out as follows: 1) surgical risk 2) graft rejection 3) risks due to cells 4) immunogenicity 5) tumorigenicity.

- It is proposed to conduct an open-label, not placebo-controlled First-in-Patient dose-escalation clinical study to establish safety of the procedure and to, hopefully, obtain tentative signs of clinical efficacy. The overall approach and the goals are very reasonable. Timelines appear reasonable. It is likely that conducting the proposed study will lead to a meaningful go/no-go decision for further clinical development. The clinical trial design and the manufacturing plan has been vetted by the FDA. There is an open IND allowing the applicant to proceed with the studies, providing significant external validation of their approach.
- Major concerns relate to manufacturing. The applicants are using a human pluripotent cell line that was derived on mouse feeder cells. That means the product will be regulated as a xenotransplant going forward. While the cell line provider manufactured several cell lines that met the requirements for GMP, they were all derived on mouse feeder cells, and any therapy derived from these cell lines will be regulated as xenotransplant products.
- FDA has released a clinical hold on the trial allowing the product to enter the clinic, but a reviewer remains concerned about the longer-term prospects of this product which is regulated as a xenotransplant.
- The differentiation process is quite simple, but a manufacturing expert expresses concern that the applicants have not characterized the product in enough depth to assure there is no lot-to-lot variability. Hand picking neural rosettes and expanding them in culture is bound to lead to variability. In particular the applicants need to ask what "off-target" cells are made and also determine the lot-to-lot variability in these contaminating cells.
- In addition, the above panelist found the application hard to read, not well written and confusing in multiple places.
- The project plan is laid out well with clear goals and timelines.
- The applicants should consider external data mapping plans to associate the data from external sources to their primary data sets.
- The applicant should ensure parameters around reimbursement and compensation for patients are within regulations.

Project Team and Resources

- The manufacturing facility and staff are appropriate and well versed in GMP manufacture of cell therapy products.
- Reading the correspondence with FDA, a reviewer found it obvious that the application was put together by individuals who are not experienced in dealing with FDA.
- The proposed clinical trial will be conducted in academic settings a major California medical centers. The PI is a renowned expert in HD and is very active and well-integrated in the international research community on HD. They were one of the founders of an HD patient clinic, are a member of the Huntington Study Group Scientific Affairs Committee and Enroll-HD Clinical Trial Committee, and very active in the HD community. The PI is an active member of advisory committees to HD foundations, and Co-Editor in Chief of a Huntington's Disease relevant journal. The neurosurgical team lead is well qualified to conduct the procedures. Patients will be evaluated by experienced and well-qualified physician experts in HD. Overall, this is a highly qualified group able to conduct the proposed studies.
- There is a strong team associated with the clinical trial that builds on the successful work from an earlier CIRM award.
- The team is appropriately staffed to complete the aspects laid out in the protocol.
- The resources consider all of the vendors and required oversight.
- The applicant team seems trained and experienced; extensive site training is required to ensure proper administration and human subject protection; strong clinical operations and quality teams will be required. The data safety monitoring board has been defined and instituted; a multi-suite ISO-7 GMP with experience in cell/gene products is designated for hNSC manufacturing, release, sterility, stability, and packaging.

Population Impact

- The population assessment has been exceptionally done with clear definitions regarding the needs and the reach of the potential treatment. The large unmet need along with the progress made to date makes this an exciting application.
- Being that this could impact not only the affected patients, but their families and healthcare providers, there is a much wider demographic that would have a decrease of the burden of illness.
- If successfully developed, hNSC will be enthusiastically embraced by HD patients and caregivers. It will have significant beneficial effects for the entire health care system and society in general. HD affects most, if not all, human subpopulations and is not restricted to specific genders or human population groups. The application attests that the applicants are making strong efforts to enroll a diverse group of clinical trial participants.
- HD is quite rare and mostly runs in families where it is passed down from parents to children (not always but mostly). This is a small, single center trial. Given those limitations, the applicants have done a reasonable

job evaluating and addressing affected populations.

- According to FDA, the potential target population may be limited, given the risks associated with delivery. FDA feedback requests enrolling subjects with at least 40 (≥40) CAG repeats in the Huntingtin gene. In addition, subjects with longer CAG repeats and more rapid progression may be more informative with regard to achieving an understanding as to the potential activity of this product. The sponsor has addressed a number of points from FDA in the updated protocol.

Application #	CLIN2-19061
Title (as written by the applicant)	Phase I/II Clinical Trial for CMT4J
Therapeutic Candidate (as written by the applicant)	An AAV9 vector carrying a codon-optimized human FIG4 transgene under a CBA promoter with modified AAV2 ITRs and a synthetic polyA signal.
Indication (as written by the applicant)	Charcot-Marie-Tooth disease, type 4J (CMT4J)
Unmet Medical Need (as written by the applicant)	CMT4J is a severe, progressive neurodegenerative disorder with no disease-modifying treatments. Current care is limited to symptom management. The proposed AAV9-based gene therapy, aims to restore FIG4 expression, correct lysosomal defects, and potentially halt or reverse disease progression.
Major Proposed Activities (as written by the applicant)	• Complete activities to extend CMT4J NHS study within 3 years. • Complete start-up activities for Phase I/II clinical trial. • Enrollment of 2 sentinel patients in Phase I/II clinical study. • Enrollment of remaining patients in a Phase I/II clinical study.
Statement of Benefit to California (as written by the applicant)	The AAV9/FIG4 gene therapy for CMT4J will benefit California by addressing a fatal neurodegenerative disease affecting children and young adults, for which no treatments currently exist. Advancing this therapy will strengthen the state's leadership in gene therapy innovation and reduce long-term healthcare costs. It offers California families affected by CMT4J the hope of a life-changing therapy that targets the disease at its genetic root.
Funds Requested	$8,000,000
GWG Recommendation	**(1-84): Not recommended for 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: 80

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below.

Mean	81
Median	80
Standard Deviation	4
Highest	86
Lowest	70
Count	14
Tier 1 (85-100): Exceptional merit and warrants funding, if funds are available	4
Tier 2 (1-84): Not recommended for funding	10

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.

Key Strengths and Weaknesses
Strengths ● This project addresses an unmet medical need: a pediatric demyelinating condition. The applicant has financially sound plans for future studies and holds rare disease status. ● This is an area of high unmet medical need, and the proposed approach is scientifically sound. ● The preclinical efficacy data are strong and provide good supporting evidence. ● There are several notable strengths in the application, including the team's expertise, the lower patient burden associated with an AAV delivery modality, and the broad geographic representation of recruitment sites. ● The clinical and preclinical experience of the team is strong, and the data appear clear and well received by FDA. ● The team includes the CMT guru, leading neuromuscular specialists, and experience in clinical studies and trials. The proposed trial sites are perfectly adequate. ● The centers of testing are well established and are expected to attract strong patient participation. ● The proposed trial is well complemented—particularly in patient identification, recruitment, and endpoint refinement—by an ongoing natural history study (20 patients over 2 years), which the team plans to extend for an additional 3 years. This effort will support recruitment, patient selection, and familiarity with testing sites. ● Broadening enrollment to younger age groups makes sense. ● The two trial sites are also sites for the ongoing natural history study – with existing communications, data exchange, regulatory compliance, patient recruitment / interaction. ● The team has adequately considered risks based on their existing clinical experience with AAV-9 gene therapy and a similar, ongoing trial for a different ultra-rare disease. ● From a clinical operations standpoint the application is considered fundable based on strengths in pre-planning and patient recruitment. ● Given the ultra-rare nature of the condition, the pre-planning of the natural history study—with patient recruitment and genetic and clinical characterization—is a significant strength. Weaknesses ● The major score-driving weaknesses include the lack of detailed plans to address accessibility and affordability, the absence of patient-reported outcomes, and only a limited description of challenges related to diagnosis and care—particularly those linked to geography and access to care—with no clear discussion of how these barriers will be overcome. ● There are gaps in the Chemistry, Manufacturing, and Controls (CMC) development plan. ● CMC comments from regulatory interactions highlight the need for improvements. Even for a Phase 1 study, it is important to balance an early start with forward-thinking preparation for the next phase.
Value Proposition
● This project addresses an unmet medical need: a pediatric demyelinating condition affecting approximately 100 patients in the U.S. The applicant has financially sound plans for future studies and holds rare disease status. ● This is an entirely unmet need with no currently approved therapies. ● The applicant is developing an AAV9-mediated gene therapy for the treatment of CMT4J, an ultra-rare disease. As there are no treatment options available, the proposed therapy could provide a vast improvement in treatment for this rare condition. ● A single durable treatment that improves function would have clear medical value, even with a small patient population. ● The target indication is a very rare condition, with an estimated 300-500 patients. Success depends on better diagnosis and patient identification, similar to what was done for spinal muscular atrophy (SMA). The application does not include adequate discussion on how much effort that requires. ● The proposal does not provide quantitative or well-developed analysis of healthcare impact or system value. ● To have real commercial viability, the program needs to serve as a platform or gateway for treating other related disorders, not just CMT4J. ● There is currently no FDA-approved disease-modifying therapy for this ultra-rare form of CMT. ● CMT4J is due to loss-of-function variants in FIG4 (encodes a lipid phosphatase), and this therapy is a

rational attempt to replenish FIG4 (by AAV-9 gene therapy via IT administration) as a disease-modifying therapy. ● CMT4J is a pediatric-onset, severe form of CMT and an unmet medical need with Orphan Drug & Rare Pediatric Disease designations. ● It is estimated that there are approximately 100 patients in the US - so the total cost of therapy may be palatable to payors. ● This population is in need of options beyond supportive care. Registry database (CT.gov) research confirms there are no options, even within the clinical trial space. If successful, this study could be significant for the population when it comes to delaying the development or curing the condition. FDA seems to agree based on reviews and designations granted to date. ● This group currently has a product further along in the development pipeline, which will inform the process for seeking access and affordability for the therapy in this proposal. However, this suggests that the team lacks experience with this process currently, and the plan for access and affordability is underdeveloped.
Rationale
● The preclinical efficacy data are strong and provide good supporting evidence. ● The proposal includes sufficient proof of concept. ● Restoration of the FIG4 protein expression could correct this rare disease. Intrathecal administration is appropriate. ● The proposal presents data on vector copy number but not corresponding functional improvement, so the potential translation of biological correction to clinical benefit has not been well demonstrated. ● A related paper did not show meaningful gains in grip strength or distance traveled, and the application does not adequately address these findings. The claimed major improvement at P7 is not well supported by published data, and the time course or extent of slowed progression remains uncertain. ● The more severe, rapidly progressive mouse model limits confidence in translating results to humans, given the slower and more variable disease progression clinically. ● Replenishing FIG4 expression is a rational strategy. ● Thoughtful presentation and interpretation of pre-clinical data and trial design. ● There is some concern regarding dose-dependent neural degeneration seen in pre-clinical studies (i.e., dosing of FIG4 may be very sensitive). ● The sponsor has an ongoing clinical trial with similar dosing and IT administration for another ultra-rare indication. ● The inclusion criterion for patients to have at least one I41T allele (because it is common and the phenotype is more uniform) makes the study population a bit different from the Plt null mouse. ● Discovery and preclinical work being accomplished under a previous CIRM award and IND clearance shows robustness of the program. ● AAV therapy is a single dose infusion, minimizing patient burden compared to modalities that require repeated dosing.
Project Plan and Design
● The natural history side study and plan for broadening to younger age groups are strengths. ● The proposal needs a more robust clinical development plan on how they'll continue to develop product as data emerge. ● The project plan for CMC is unclear and may be missing some key elements. The Gantt chart only lists Q3-Q4 for manufacturing, with no further details on timing for lot release. The inclusion of stability is missing. Storage and shipping to clinical sites from the source is not detailed. ● The timeline is overly simplistic and lacks clarity on primary endpoint timing or transition criteria to the next phase, making feasibility hard to judge. Also it does not include some of the required elements. ● There is not enough detail on plan for patient access, outreach, or diagnostic funneling; *[organization name redacted]* doesn't address the need to actively identify and test more patients for potential inclusion in the study. ● The applicant indicates that families will relocate to near the study site for up to two months, which is highly disruptive and likely to limit participation/enrollment. ● Sponsor-funded direct support for travel, housing, and caregiving, recruitment and retention is not clearly laid out for this study. The applicant relies on how it is done in the natural history study. ● The application treats enrollment as secondary and minimizes the challenges, assuming the small natural history cohort will supply enough participants, which is unrealistic for such a rare disorder. ● This is a phase 1/2 open-label trial for an ultra-rare condition (n=8 participants) and a first-in-human gene therapy for replacement of FIG4. It is designed to essentially test for safety and tolerability – which are the

primary endpoints – with some carefully designed preliminary efficacy and reasonable exploratory readouts. • The proposed trial is well complemented (patient identification / recruitment and endpoint refinement) by an ongoing natural history study (20 patients over 2 years) which they plan to extend for a further 3 years. This will support recruitment and selection of patients – and familiarity with testing sites. • The age-stratified study is appropriate – starting with a narrow age range and then, following DSMB, approval proceeding to a wider age range. Essentially single dose, with lower doses for young children. • The project design and timeline are adequate for the main readouts. Exploratory biomarkers may or may not yield useful info – but digital / wearable data is a plus. • Risks are adequately considered – especially given the existing clinical experience with AAV-9 gene therapy – and their ongoing, closely related trial. • Future hurdles relate to the Pre-IND FDA Response to Question 8a (part 1 and 2). The agency's comment may foreshadow a potential IRB review issue. Be prepared to significantly justify why those < 18 should be included at all, especially within the sentinel patient cohort. Over the years, in IRBs' handling of gene therapy DMD trials, oversight/pediatric risk determinations can stall study progression (justified or not) during the review process. • This reviewer recommends the applicant consider participation in FDA's CMC readiness and development program, if possible. • There are three clinical sites that are geographically distinct. • The study plan includes diagnosis adjudication by an external consultant. • The study incorporates multiple measures of outcomes using multiple modalities across domains (e.g., musculoskeletal, immune), but no assessment of patient reported outcomes.
Project Team and Resources
• The team includes the CMT guru, leading neuromuscular specialists, and experience in clinical studies and trials. The proposed trial sites are perfectly adequate. • The two trial sites are also sites for the ongoing natural history study – with existing communications, data exchange, regulatory compliance, patient recruitment / interaction. • The teams appear satisfactory, with outsourced CMC activities being completed by an experienced CDMO. • The team at the applicant organization and their academic collaborators are major strengths. • Weakness: Given risks of enrollment (always slower than predicted), it is concerning to see no 'plan b' or backup plans for patient identification, diagnostic access, etc. • The Bespoke Gene Therapy Consortium (BGTC) will provide preclinical, regulatory, manufacturing, and clinical guidance. • The team includes expertise in muscle MRI, FIG4 biology; wearables; and stats with experience in CMT studies. • The team appears capable and experienced. The academic partners have strong therapeutic centers capable of managing this type of study. The support of public and private organizations will be critical in population and community awareness. The consulting and vendor teams have helped with the preclinical, manufacturing and regulator successes to date, so no concerns there. When it comes to financial resources, it is very good to see that they have secured Rare Pediatric Disease Designation (RPDD) for the AAV9/FIG4 gene therapy (granted by the FDA in 2024). The future sale of the voucher could be critical in keeping future development progressing. • This team is currently conducting a natural history study that is likely the largest cohort of CMT4J affected individuals, and will recruit from this cohort.
Population Impact
• The centers of testing will draw good participation; not enough detail is provided for access and affordability. • The impacted population for this ultra-rare disease is quite small, but could provide insights into AAV treatment success for ultra-rare neuropathies. • Access and affordability – the applicant should be thinking about how to improve availability of diagnosis and related testing. • Given this is an ultra-rare condition, the pre-planning of the natural history study, with patient recruitment and genetic and clinical characterization is a strength. • The same sites involved in the natural history study will be involved in the trial. • The relative uniformity of I41T patients is an appropriate stratification. • The applicant has active engagement with leading patient advocacy groups. • This team seeks to represent the population's community on every level. Consideration of affected populations is confirmed via the credentials of key team and organizations participating in the study. The rationale given for recruitment availability and difficulty is clearly discussed and rationalized within the

application. The current Natural History Study is a valuable resource for the recruitment efforts.

- The team acknowledges the likelihood of diagnosis bias based on geographic and access to care factors and the additional challenges for patients from these marginalized groups, but does not provide a plan to attempt to overcome some of these barriers in recruitment.
- The application does not include description of any differences in prevalence of disease based on ancestral genetic characteristics, which seems applicable for the NHS.