Application #	CLIN1-14840
Title (as written by the applicant)	Prevention of GvHD in patients receiving HLA mismatched related or unrelated allogeneic HSCT for the treatment of hematologic malignancies.
Therapeutic Candidate (as written by the applicant)	An allogenic, off the shelf, engineered regulatory T cell product that mimics the function of T regulatory Type 1 (Tr1) cells.
Indication (as written by the applicant)	Prevention of acute and chronic Graft versus Host Disease (GvHD) in patients undergoing mismatched stem cell transplant.
Unmet Medical Need (as written by the applicant)	GvHD affects patients undergoing mismatched hematopoietic stem cell transplant (HSCT) and is a major cause of morbidity and mortality. Only ~50% of HSCT patients are disease and relapse-free (GRFS) after one year. The proposed product will broaden access to transplants, while reducing the burden of GvHD.
Major Proposed Activities (as written by the applicant)	• Preclinical in vitro and in vivo studies to characterize the product and determine its safety and efficacy in preclinical models of disease. • Process development, optimization and technology transfer to partner CDMO for production of the product to enable IND submission. • Process Development, engineering and clinical manufacturing runs of the product to enable IND submission.
Funds Requested	$4,000,000
GWG Recommendation	Tier 1: warrants funding
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” 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	• The proposed project does hold the necessary significance for impact. The potential for the product to provide a therapeutic against GvHD is demonstrated by the data provided from studies with the proposed products. With updates from the agency allowing for

No: 0	pooled donors, the likelihood for a study with repeatable results may be likely with early efficacy reads in the trial. ● Demonstration of the proposed drug product did show reductions in the incidences of PBMC-induced Xeno-GvHD and is supported by the molecular data provided for the construct. ● Yes. This treatment, if successful, will fill the unmet need of managing steroid refractory GvHD. I am skeptical of this product improving upon the currently available strategies to prevent GVHD such as post transplant Cy and abatacept, which all work via similar mechanisms. That being said, the only way to demonstrate safety and efficacy is through a well done phase 1/2 study as proposed here. Abatacept as an example for a GvHD prevention is priced high, which remains a barrier to its use. I would expect this product to have a similar price tag. I'm not sure how easily it will be adopted even if it is as good as Abatacept. ● This allogeneic "off-the-shelf" cell therapy is intended to support the current standard of care and mitigate GvHD. The applicant's agreement to reduce dose for a planned clinical study gives the product potential to support the current SOC as an adjunct therapeutic. ● It would be useful to add an arm to treat GvHD, and not only look at prevention. ● As it is presented, the project team is able to provide consistent product. ● This therapy is greatly needed.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	● The rationale is sound and worth exploring. The applicant has adequately addressed prior concerns except for one. While prevention may be the best possible use of this product, I would have liked to see the clinical trial amended to include an arm for active disease too where if this fails the first safety step in the prevention trial, they still had an arm with active disease (GvHD) to explore its efficacy, with a more favorable benefit/risk profile. ● Previous updates to the proposal provided evidence to support the safety of the product in regard to any clonal expansion concerns. The content includes lots that do not exhibit cytokine-independent growth which excludes that the proposed construct and manufacturing process result in immortalization of the cells. ● The addition of experiments looking at the impact of CY on the Tregs was helpful. ● Additional engineering runs have been described in the revision of the proposal. These demonstrate consistent drug products, which further substantiates the sound rationale for the manufacturing process. ● Two major changes to the original application were (i) lowering the dose for clinical testing, in alignment with FDA and (ii) an agreement with FDA to assess the number of contaminating cells for safety prior to consideration of higher doses.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	● Characterization of the rIL10 integration and expression is sufficient. FDA's requests regarding IL10 expression may further be de-risked with characterization of the integration profile of the drug products. ● The proposed construct monitors SV 40 poly(A) short tandem repeats as a primary endpoint for donor chimerism. This region would represent the donor population to a suitable extent, based on additional description provided in this revision. ● With selection of cells based on NGFR expression, scoring the genome using Psi packaging signal proximal to the 5' SINLTR, and characterization of the rIL10 expression, the proposal outlines a well planned and designed project. ● My only concern is that FDA has not agreed at this time to increase the maximum level of contaminating cells. Therefore, there may be a delay after the first two patients during which a submission to FDA will be needed. If a safety concern is noted, additional manufacturing development would be required. ● I believe the timeline and the revised design to start at lower dose levels are appropriate. However, one minor comment on study design is that the applicant should include an arm for treating active GvHD. ● While there are no additional in vivo data on the products' safety in this revision, the applicant plans to conduct in vivo safety studies and submit the results with their IND submission. They are confident their products will be safe in vivo models. I have no reason to doubt that assertion. ● Major deficiencies associated with safety concerns have been addressed. There appears to be an appropriate nonclinical model to recapitulate the human condition. ● The applicant has been responsive to the prior review recommendations.
GWG Votes	**Is the project feasible?**

Yes: 13 **No:** 0	• The project is feasible. It is likely the project will elucidate negligible structural impacts from theoretical concerns for the vector substance's profile either way, especially considering there is a selection of cells based on NGFR expression. • The proposed construct monitors the SV 40 poly(A) short tandem repeats as a primary endpoint for donor chimerism. This region would represent the donor population to suitable extent based on additional description provided in the revision. • Updates to the project plans, including granted permission from FDA to pool donors and successful engineering runs, provides substantial evidence to support the feasibility of the proposal. • Yes. Now that they have completed an engineering run and have FDA exemption to pool donors (which was a major concern at the last submission), we have more confidence that the product can be made successfully, and the trial can be initiated within CIRM timelines. • The project now appears feasible taking into consideration prior safety concerns and appropriate changes and explanations. • The risk mitigations seem reasonable.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• Activities associated with outreach and building cultural sensitivity include work with their CRO partner, trial sites, and PIs to design a marketing campaign to reach underserved patient communities. This plan is well matched to the needs of the potential participants. • The applicant's DEI plan also includes addressing barriers to trial participation. For example, they will provide study materials that are customized for varying languages and cultural groups. • The applicant has been thoughtful about diversity, equity, and inclusion. • Yes. Given that the target population of haplo and mismatch recipients comprises invariably unrepresented minorities, this project is consistent with DEI principles. • All DEI concerns have been adequately addressed.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

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

DEI Score: 7.5

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	1	*none*
6-8: Responsive	3	• Documented DEI plans are in alignment with CIRM's mission. • The applicant has not provided any edits to the DEI section. • My previous critique remains an accurate assessment of the applicant's proposal. • The applicant appears to be depending on the clinical sites for their DEI protocols. • The applicant has not documented their own DEI values.
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	• 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

No: 1	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 #	CLIN2-15395
Title (as written by the applicant)	A Phase 2b Study of the Efficacy of a Novel Pro-Neurogenesis/Pro-Plasticity Drug for Bipolar Depression Using a Precision Psychiatry Approach
Therapeutic Candidate (as written by the applicant)	Small Molecule
Indication (as written by the applicant)	Bipolar depression (I or II)
Unmet Medical Need (as written by the applicant)	Bipolar depression is a severe, life-long disorder with high burden of illness and risk of suicide. The only approved treatments are antipsychotic medications, which have limited efficacy, are associated with weight gain, metabolic syndrome, movement disorders, and high rates of non-adherence.
Major Proposed Activities (as written by the applicant)	• Enrollment of 200 participants in a Phase 2b trial to assess efficacy of the drug candidate in adults with bipolar disorder depression • CMC optimization to prepare drug substance and drug product for validation and further scale-up
Funds Requested	$15,000,000
GWG Recommendation	Tier 1: warrants funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." 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	10
Votes for Tier 2	4
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	• This is an excellent proposal with a novel and deeply grounded mechanism for depression in MDD (major depressive disorder) and potentially BD (bipolar disorder). The proposal is to conduct a phase 2b clinical study in patients with bipolar disorder depression (BD-D) with a small molecule that enhances neurogenesis and synaptic integration of newly born hippocampal neurons.

	● The mechanistic basis for this is as follows: Most studies find that untreated depressed patients have smaller hippocampal volume, neuronal and glial number, and cell size compared with non-psychiatric controls. In MDD, the extent of hippocampal gray matter volume loss is related to time spent depressed and hippocampal volume is associated with worse depression scores. Dendate gyrus (DG) granule neuron number and DG volume were smaller in the hippocampus in unmedicated MDD postmortem. ● Based on this observation, the hypothesis is that there are neuroplasticity-related molecular, cellular, and circuit-level abnormalities in the brains of BD-D patients. Deficits in memory, as a behavioral measure of reduced hippocampal neuroplasticity, are common in BD-D and can be used as a 'canary in the coal mine' to identify a subset of BD-D (and MDD) patients who have impaired hoppocampal neuroplasticity and therefore might improve on a neuroplasticity therapy. A drug that enhances hippocampal neuroplasticity may therefore be a promising candidate specifically for memory-impaired BD-D patients. ● Bipolar disorder depression (BD-D) is a common and serious psychiatric condition associated with high rates of disability and suicide. While there are existing treatments for BD-D, most come from the same class of medications and are associated with tolerability issues. Failure to respond to treatment is common in BD-D and few options exist for people who fail existing standard treatments. The proposal mildly overstates this issue, focusing on FDA-approved medications and not discussing other evidence-supported, off label options such as lithium and lamotrigine. This is a minor criticism and the points made in the proposal remain valid. ● If successful in BD-D, the expected benefits on depression of the proposed study medication would add significantly to the existing options for pharmacotherapy. Establishing a novel mechanism of action could have important second order effects. The potential for impact is very high. ● BD-D affects approximately 1% of the adult population in the United States in any given year. The current standard of care for BD-D is antipsychotic drugs which are associated with weight gain, metabolic syndrome, movement disorders, and excessive sedation. A drug that is well tolerated and effectively treats the depressive phase of BD without exacerbating the manic phase would address a major unmet medical need. ● Bipolar disorder is a significant problem and cognitive impairment not always readily detected. ● Bipolar depression is currently very difficult to treat and the potential for impact is considered high. Regular anti-depressants do not always work in subgroups of patients and the potential for a novel therapeutic that can stimulate neurogenesis could be very significant. ● Bipolar depression is often treatment resistant.
GWG Votes	**Is the rationale sound?**
Yes: 11 **No:** 2	● The candidate is an orally active small molecule with a novel pro-neurogenesis/neuroplasticity mechanism of action currently in late-stage development for major depressive disorder (MDD) (not part of the current grant proposal), another disorder characterized by impaired hippocampal neuroplasticity and memory in a portion of patients. ● The candidate was initially identified in an in vitro human fetal hippocampal neuronal stem cell screen for pro-neurogenic compounds, and then tested in initial human studies. In a retrospective analysis of these studies, many of the secondary endpoints were positive and more importantly, the primary endpoint was positive in the subset of patients who had cognitive impairment at baseline (defined by verbal memory impairment). The molecule was tested in a subsequent MDD trial, and this observation was prospectively replicated: that a subgroup of patients characterized by poor memory on a clinically validated objective computerized behavioral test had a greater antidepressant response. This ieads to the phase 2b study proposed here. ● This is a precision psychiatry approach very much in line with FDA guidance in psychiatry (2019): poor memory-stratified phase 2b trial of the candidate in BD-D, which closely follows the already FDA-tested structure of the applicant's recently launched MDD phase 2b. ● The rationale for targeting hippocampal volume and neurogenesis is well supported by in vitro, animal, human post-mortem and clinical studies. The approach is highly novel. ● The use of verbal working memory to identify individuals with cognitive impairment in BD-D is novel and well supported by previous literature and the investigators preliminary data. The selection of BD-D sub-groups that may respond optimally to treatment is a novel approach and potentially powerful. This approach was nicely demonstrated in MDD

	and PTSD suggesting it may be transdiagnostic, but has not yet been validated in BD-D. Critically, the investigators propose additional studies to refine the selection process in BD-D. ● While the investigators have done a good job validating verbal memory in preliminary studies using mobile electronic devices, there is some concern that this method may not be valid in some populations where language or problems using technology could affect the assessment in some users. This is not a score-lowering concern. ● The rationale appears sound although there was some concern expressed over the use of the cognitive enrichment marker which may have limited utility in these patients. There was some concern expressed over the premature use of the drug and readiness for a phase 2b study given that there are no population data to date using this novel drug. ● Neurogenesis failure has been implicated in depression. ● Given the novel mechanism of action of the candidate and the encouraging phase 2a data in MDD, it seems reasonable to pursue the BD-D indication in parallel with the MDD program. However, given MDD and BD-D are different diseases and respond differently to other classes of antidepressant drugs, moving directly into a phase 2b study may be premature. ● The applicant is seeking CIRM funding to conduct a phase 2b study in BD-D based on data obtained in MDD. However, BD-D and MDD are different diseases and it's unknown whether patients with BD-D will have the same depression response as MDD at the proposed dose, or whether the enrichment marker is relevant to BD-D. It's also not known if the proposed dose will cause new significant adverse events in BD-D patients (e.g., exacerbating manic episodes). ● A major concern is that the enrichment marker has not been evaluated in bipolar disorder and may not be appropriate. There has been no dose optimization for bipolar disorder.
GWG Votes	**Is the project well planned and designed?**
Yes: 10 **No:** 3	● The background preclinical data presented for the candidate indicate that chronic administration over the course of several weeks led to an increase in neurogenesis in the dentate gyrus of the hippocampus, the site of adult neurogenesis across species. This was accompanied by increased dentate gyrus synaptogenesis (e.g., synaptophysin expression) and volume. The candidate also increased neurogenesis in rodent models of stroke, radiation-induced cognitive dysfunction, and Angelman syndrome. ● The candidate was tested in extensive IND-enabling studies in two species, which the FDA accepted without comment, allowing long-term chronic dosing in humans. The candidate was also tested in a healthy volunteer phase 1a safety and pharmacokinetics study, followed by a small MDD phase 1b treatment study which showed promising antidepressant effects, published in 2016. The candidate was then tested in a phase 2 randomized trial with two stages of randomization to assess antidepressant efficacy in MDD. Due to insufficient powering for this study design, the study failed to reach statistical significance on the primary outcome, though several secondary outcomes were significant, published in 2020. ● The candidate was then tested in a phase 2a study in patients with MDD and/or post-traumatic stress disorder (PTSD) to identify and prospectively replicate a treatment predictive marker. This work identified patients with poor verbal memory as likely responders across MDD and PTSD. The prior phase 2 trial was also re-analyzed, which provided additional support for the importance of poor memory in driving better treatment response. Identification of a reliable enrichment marker between the two independently conducted trials led to initiation of a phase 2b trial in MDD and to request funding here for a similar trial in BD-D. ● The design looks similar to the major depression trial, should a dose range be considered. ● The project was well planned with robust nonclinical data demonstrating neurogenesis in a nonclinical rodent model. ● The trial design is appropriate and well powered, using gold standard methods for clinical trials of depression. The endpoint is a standard measure of depression. Standard secondary endpoints in anxiety and mania are also collected. Cognition, EEG and actigraphy are included as exploratory analyses. The endpoints are well suited to the study goals and widely used. ● Screening based on cognition makes the design more complicated. The screen fail rate is 74% in the MDD study. Investigators seem well prepared for this challenge. A comparison between high/low cognition scores is a nice feature of the design. ● The design for the use of the candidate as adjunctive treatment may limit the ability to identify responders given the treatment resistance of the population to initial therapy.

	There is no discussion of potential drug-drug interactions with valproic acid, lithium or lamotrigine. These may affect tolerability, but these are minor concerns. • Moving directly into a phase 2b trial in BD-D without any prior data in this population is a somewhat risky clinical development strategy. This program would benefit from a smaller phase 2a study in this new population before investing resources in a large phase 2b. By moving directly into a large phase 2b BD-D study as the first study in this indication, the applicants are missing opportunities to assess dose-response, safety (including impact on manic episodes), preliminary efficacy, and the MDD enrichment marker in the BD-D population. • A major concern is the lack of sufficient justification for evaluating only a single dose level in the proposed phase 2. While phase 2 dose ranging was conducted for a previous indication, MDD, there is not a sufficient justification that the proposed dose level will be optimal in BD-D i.e. not only as safe but sufficiently active. • Data on the enrichment marker in the MDD population will not necessarily translate into the BD-D population, and yet the proposed BD-D phase 2b is designed using the same enrichment marker without first evaluating this enrichment marker in a smaller BD-D population. The enrichment marker and the assessment tool have not been used previously, and there is no FDA precedent for its use in registration studies of BD-D (or MDD). The assessment tool for evaluating the recall index enrichment marker has been created by the applicant and not yet discussed with FDA (it's the topic of an upcoming Type C meeting). However, FDA has made clear that this marker would need to be assessed separately in MDD and BD-D populations as they are different diseases. • If the applicant proceeds directly into a phase 2b study, as proposed, it is recommended to add a second dose as no dose exploration has been conducted in BD-D. This was also recommended by FDA in their non-hold comments. • The study design could be improved by inclusion of two doses. • Only six of the planned 30 clinical sites in this phase 2b will be in California.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• IND submission was completed and the applicant received notification that the study may proceed. The applicants say they will not start up activities until/if the CIRM grant is awarded. The project will benefit from the parallel MDD study as the sites will be similar and they already are enrolling. In addition, the manufacturing campaign has been completed and is sufficient to support both clinical trials. • The phase 2b study appears feasible, although enrollment of BD-D patients able and willing to adhere to a clinical trial will pose challenges given the severity of their illness. The applicant's decision to provide a decentralized/remote option for participants should assist with enrollment and follow-up adherence. • The applicant has launched six phase 2 studies in the last two years and thus has extensive clinical trial experience relevant to conducting the proposed phase 2b. • The team has demonstrated the ability to run similar trials in MDD with good results. There is an extensive network of study sites. The team is experienced with industry clinical trial experience. There are cost and logistical benefits of running the BD-D study concurrently with MDD. • The clinical trial is feasible but the enrichment marker might not be correct. More data are needed to understand whether the enrichment marker is the correct one. • A proposed two-dose strategy would be beneficial enabling an escalating dose based on safety concerns. • Feasibility is not an issue.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• This is well done in the application. The target disease preferentially affects and has disproportionate impact on underserved communities. • The applicant is aware of the racial/ethnic disparities in treatment of mental health disorders, including BD, and has concrete plans of how they will enroll a diverse population into the phase 2b. The plans for increasing diversity appear well thought out and leverage the applicant's experience with conducting clinical trials in psychiatry. • The phase 2 is planned as a hybrid design trial that includes both decentralized and traditional study sites to improve access for underserved populations. Participants at decentralized sites complete most of the study assessments remotely via telehealth, which may better accommodate their schedules and need for transportation. Remote participants are provided with laptops configured for study assessments. For those attending clinic visits, the cost of transportation services and meals will be covered. • The strategy addresses a need to include diverse populations in the study group. The strategy is well justified and supported. Exclusion criteria are based on sound reasoning. The applicants have a history of engagement with this community.

	• The applicant addresses the issue that individuals from marginalized communities often do not participate in trials because they are apprehensive about medical research. In psychiatry, patients tend to look for mental health professionals that match their ethnic and/or racial identity. As part of site selection, the applicant will look for diversity of PIs and site staff. • This is well addressed. • This was adequately addressed with all parameters covered.

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	4	• There is a strong description of the patient population. Appropriate participant selection criteria, and a strong outreach to patient advocacy groups are included. Patient feedback will inform future trial design. • The proposal does an outstanding job in attending to the issues of DEI as it approaches issues related to current treatment of bipolar disorder, patient recruitment, retention and other support issues. • The diversity of sites supports the recruitment of diverse populations. • This is a comprehensive DEI plan.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN1-15450
Title (as written by the applicant)	Human Embryonic Stem Cell-Derived Neural Stem Cells for Severe Spinal Cord Injury (SCI)
Therapeutic Candidate (as written by the applicant)	Human embryonic stem cell-derived neural stem cells.
Indication (as written by the applicant)	Spinal cord injury
Unmet Medical Need (as written by the applicant)	There are more than half a million Americans living with spinal cord injury (SCI). There are currently no approved therapies for promoting recovery in movement, sensation, bowel, bladder or sexual function.
Major Proposed Activities (as written by the applicant)	• Generate clinical grade human embryonic stem cell-derived neural stem cells and qualify release assays. • Conduct GLP in vivo studies in rats. • Conduct GLP in vivo studies in large animal models.
Funds Requested	$6,000,000
GWG Recommendation	Tier 1: warrants funding
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." 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	13
Votes for Tier 1	13
Votes for Tier 2	0
Votes for Tier 3	0

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 12	• This was considered to be highly impactful, well-considered and well-written application for a complex combination product to treat adult traumatic spinal injury. There is a large unmet clinical need. • SCI is a huge unmet medical need. SCI normally occurs in younger people because of sporting injuries and other accidents. After SCI, lifelong support is necessary, costly and quality of life can be miserable.

	• Spinal cord injury (SCI) continues to be associated with significant morbidity, including long-term and severe disability, chronic neuropathic pain as well as high healthcare costs. Per the applicant, the lifetime costs of caring for an individual with paraplegia are in excess of $5 million. There is a high unmet medical need for new therapies for SCI. • Currently there is no treatment for someone that sustains a SCI injury and there is a notable disparity in access to rehab care. SCI includes loss of movement, sensation, bowel and bladder function and sexual function. Many also suffer from chronic neuropathic pain and dysreflexia. The success of a therapy would mitigate some resulting conditions and a return of greater independence. • Any improvement would be significant given the current standard of care does not actually have any impact on the SCI. The lifelong costs of caring for SCI patients is very large so any stem cell treatment that impacted the injury would offer a significant value proposition. • This could be one of the most impactful CIRM projects to date. There are no effective restorative treatments, and this is the exact type of injury/disease that should be the focus of CIRM. • Yes, the proposed project holds the necessary significance and potential for impact. • There have been a number of attempts to treat SCI with stem cell therapies. These include attempts by Stem Cells Inc, Neuralstem, Geron and Asterias going back more than 20 years. While all these approaches failed the applicants are using a different approach by delivering neural stem cells (NSCs) fated to become spinal cord neurons and other components directly into the lesion. • The applicant's proposed approach, if successful, has potential to offer a new treatment option for patients with sub-acute SCI (5 days to 6 weeks post-injury) and thus is not anticipated to be a treatment option for patients with long-term/chronic SCI. • The applicants intend to treat patients with a recent SCI (5 days to 6 weeks) which I think is the rational place to start this work in humans although 5 days may be a bit early. If there is no impact in these patients, it would be much less likely to have impact on patients injured for longer. • Yes, it is built on extensive prior work and adds neurotrophic factors and a support substrate to improve graft survival.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The PI lays out a beautifully illustrated evaluation of this approach based upon years of evidence that they have painstakingly developed. • The nonclinical testing package was considered robust utilizing two species to establish safety and efficacy. • This program was previously awarded a TRAN1 grant from CIRM, which reported good progress including a successful pre-IND meeting; scientific rationale continues to be sound. • The applicant has conducted numerous pharmacology and proof-of-concept studies, including published studies in spinal cord transection model in immunodeficient rats, C7 right hemisection lesions in large animals, and contusive thoracic and cervical SCI, which provide sufficient evidence to justify further development and initiation of human clinical testing (assuming continued sufficient safety and bioactivity profiles from remaining work). • The applicant hypothesizes that the direct implantation of H9 ESC-derived neural stem cells into the lesion/site of SCI will support regeneration of injured host axons into and through stem cell graft forming synapses; with this approach, applicant hypothesizes that new axons have the potential to extend upwards into/through the graft, resulting in significant functional recovery. • The applicants have provided significant pre-clinical animal model data to support the application. The data provided from both rodent and large animal models looks compelling and I believe justifies moving forward with the project. • Target patient population is patients with SCI 5 days to 6 weeks prior; this timing appears sufficient to allow for manufacturing of cell product after a patient is identified but this should be confirmed. • The functional improvements are undeniable. I assume that the re-wiring has a number of off-target synaptic connections, meaning an arm motor neuron connects to the leg, etc... How is this explained, and/or is there some plasticity argument around this? • As far as manufacturing is concerned the project plan is based on FDA comments from the pre-IND meeting. The plan does address comments from FDA, and I believe the path forward for the manufacturing component of this project is well laid out.

	• There are a few considerations regarding the rationale and methods. • Methods of dose level extrapolation from rats to large animals to human clinical scenario is unclear. It is reasonable to explore dose level in planned clinical trial which the applicant proposes. As lesion size is increased from rat to large animal and then large animal to human clinical scenario, it is unclear if similar effects will be seen across species (and lesion size). There is some non-trivial risk that animal findings will not translate to a human clinical scenario. • This is a highly complex product, incorporating a gel containing several factors in addition to ESC-derived neural stem cells. The MOA of product and relative contributions of each component is unclear. The complexity of product may pose regulatory challenges related to qualifying reagents, collaboration with companies, developing potency assay, dose level selection and eventual marketing, including potential regulation as a combination product. Applicant appears to be aware of potential challenges and has already has some discussion with FDA (to which FDA provided extensive comments). Applicant may be underestimating potential challenges to long-term development. • It will be challenging to have this combination therapy approved by FDA and it is somewhat inaccurate to call the trophic factors excipients. They are clearly biologically active. • It is hard to believe that pain has not been observed in these extensive studies since it occurs often after experimental spinal cord injury. • A central myelotomy in an AIS B subject may injure intact axons.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 12	• The nonclinical testing strategy included two species: rats to be tested at one- and three-months post treatment and large animals up to 6 months to inform on biodistribution. The studies were well-designed and considered dose responsiveness with time, including safety parameters. • The project is exceptionally well designed in terms of cell production, IND enabling studies in rodents and transitioning to large animals. • Yes, project is well-designed and planned. • The applicant is planning robust set of animal studies which incorporate FDA feedback from the pre-IND meeting; clear path forward to IND filing (assuming data continue to be supportive). • Given animal use concerns, the planned animal numbers for the large animal study are reasonable; additionally, data to be generated in athymic rats (with larger animal numbers) will provide important complementary data; the applicant's plan is reasonable. • Applicant's plan for immunosuppression in animals to support conduct of studies (and required long-term engraftment) is reasonable; don't foresee regulatory issues as long as long-term engraftment at the final scheduled sacrifice is seen (at levels and numbers expected clinically). • The manufacturing component of the project is designed to bring all aspects into regulatory compliance to enable the submission of an IND and entry into the clinic. • FDA have provided extensive guidance on manufacturing and the plan does address the points raised by FDA. • There has been some genetic instability in the manufacturing of NSCs shown by some runs producing abnormal karyotypes - this is low level and to be expected when growing cells in culture for extended periods - I am not worried by that but it is something they will need to keep a close eye on. Given the product is cryopreserved, they will be able to test cells before they are used to treat any patients. • The product is quite complicated as the cells will be implanted with a gel as well as several growth factors and a small molecule. While the gel has been used clinically it has not been used in the spinal cord. The growth factors are GMP grade but made for the manufacture of cell products and so used in vitro and not in humans. The small molecule is not GMP grade. I think all these issues can be addressed by appropriate testing and a risk analysis, so my only concern is around time and cost and not whether or not it is feasible. • The budget and timelines look appropriate for the scope of the manufacturing work. • I have one moderate concern related to the modeling. The large animal studies are using cord hemisection. This is well-established in regenerative medicine studies. However, it isn't really representative of the overwhelming majority of SCI (I suppose a SW to the spine would be one). The PI recognizes all of these limitations, and points

	most of them out; I'm not sure there is a reasonable alternative but may be why this project sputters in translation. ● Depending on conduct of animal studies and type of injury, applicant may face restrictions on the target patient population in the planned clinical trial (i.e., thoracic vs cervical SCI); sponsor modified design appropriately. ● As an allogeneic product the applicants intend to use immunosuppression for the first 12 months. As SCI patients are already compromised, I am not sure if the immunosuppression will be well tolerated. ● I do have two other major concerns that can be addressed but are significant for the trial design. (1) the vast majority of patients with a clinically significant SCI will undergo some type of spine stabilization procedure early in their index hospitalization, often with hardware. While I am not a spine surgeon, I do appreciate that this will require re-operation in a field with potential previous fusion/hardware in the setting of post-operative immunosuppression. Infected hardware is a major, often life altering complication. This aspect of "repeat laminectomy" was glossed over in the application and is something that may come up once there is a FDA review with a true clinical spinal trauma expert. (2) it is reasonably well known that the level of SCI (above or below the innervation of the spleen) significantly impacts the incidence and severity of sepsis both in pre-clinical and clinical circumstances. I would hope that the early phases of this study could be done in those injuries below the spleen for safety evaluation, and in those without hardware. Also, to that end, I think it would be wise to add an animal group with injuries above/below the spleen who get cells and immunosuppression with an inoculum of typical nosocomial pneumonia species (Pseudomonas, Klebsiella, etc.). If there is no impact, I think this would go a long way to reassuring everyone that this is safe in the real world. I am thinking of a difficult choice of halting immunosuppression in a patient with serious pneumonia post procedure. The more this can be understood/mitigated, the better off going forward. ● The earliest time point is probably a high-risk period and it may be better to delay until 14 days. This is due to the following reasons: high pulmonary infection risk at 6 days, immune depression syndrome of SCI is active, and the MRI may have substantial longitudinal reverse edema causing subjects to fail screening. ● A psychologist should be involved in the consent process to help dispel therapeutic misconception and for support during the study. ● An MRI should be obtained within the post-transplant day as its important to understand the cord changes that are associated with grafting, and these may be non-obvious 2 weeks after transplant. ● The cell line being used for this work was originally derived on mouse feeder cells in a research laboratory. They clonally propagated these cells to produce GMP master cell banks. Because of the intimate contact with mouse cells during the differentiation process the product may be considered to be a xeno-product by FDA.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 12	● The proof-of-concept studies were robust, and the authors presented a clear path to IND. ● The cell production and planned studies can easily be accomplished by this group. These data are in direct response to FDA communications and will be important for the ultimate IND submission. ● This is a strong team with track-record of success with CIRM funded projects. ● The manufacturing team is experienced in GMP manufacture of ES cell banks, testing and manufacture of differentiated cell products so I am confident they can execute on this project. ● I believe the timelines are reasonable but aggressive - the path laid out for manufacturing is well thought out and closely follows guidance from FDA. ● Considering the complexity and relative high-risk of the proposed product, appreciate the applicant's frequent interactions with FDA to get advice on development pathway (including successful INTERACT and pre-IND meetings). The FDA provided an extensive and sobering list of comments. The applicant appears to have reasonably incorporated FDA feedback into planned studies to support IND filing. ● Timelines may be overly aggressive and optimistic, especially the planned rat and large animal studies; there is likely a medium risk of delay to IND submission due to high number of assessments and analyses required from animal studies that may be delayed and/or time consuming (i.e., appear to be planning for only 12 weeks following final scheduled sacrifice).

	• Device compatibility with the final cell product should be completed before initiation of animal studies. • The large animal study incorporates both 3- and 9- month timepoints (and rat study incorporates timepoints at 1, 3, and 9 months); applicant may want to consider confirming engraftment in animals sacrificed at earlier time points to justify continuing the study to the planned 9 months. If engraftment is not seen at 9 months, there may be significant regulatory challenges with opening the IND; thus, the study could potentially be modified based on data from earlier time points. • Recruitment may be relatively challenging for a single center, given reduced rates of motor complete injury. Enrolling the target number of subjects at a single center could take 4-5 years. • The contingency plans appear reasonable. My only concern would be how well tolerated to 12-month immunosuppression regimen will be tolerated. • Probably yes, with the caveats as noted above. Majority of patients will have to travel while acutely post-injury and/or sub-acute. This will require some significant infrastructure support (ICU bed availability, etc.). This is for post-IND but is a consideration in the design.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• Phase 1 clinical trial will consist of under two dozen patients with recruitment of African Americans and all minorities into the clinical trial. The trial site area has a large minority population. Proposed enrollment is equal to California's population with the exception of African Americans, representing about 6% of the population and targeting 10% due to higher incidence of SCI. • Applicant plans on having a community engagement program with DEI Advisors, a Community Advisory Board, and a Community Engagement Manager. • The only barriers for participation are outlined in the "Exclusion Criteria" which is typical for this type of study. • Recruitment will take place throughout California and participants will need to travel to the trial site; all participants will be transferred by ambulance at no cost. Those in the surrounding area for follow-up visits will be provided mileage reimbursement or wheelchair transportation service with lodging costs and meals. For out-of-area participants a member of the study team will travel to the participant. The applicant will also provide affordable or free accommodations and meals for primary caregivers while participants are enrolled in trial activities. • To achieve recruitment in underserved populations applicant will notify all California trauma centers but emphasize contacts with trauma centers that serve traditionally underserved populations in large urban areas and the Central Valley. • To increase cultural sensitivity staff will be provided training in-person from experts in cultural sensitivity in the medical space. • Will have a study panel for guidance and oversight of cultural sensitivity. • The applicants seem to have done a comprehensive job of accounting for DEI. • This appears to have been well considered.
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: 8.0

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	4	• Robust DEI plan with reimbursement of costs incurred by patient and family.

		• Cultural sensitivity training of staff is included.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-15607
Title (as written by the applicant)	Phase 3 (Pivotal) Clinical Trial for SPG50
Therapeutic Candidate (as written by the applicant)	AAV9/AP4M1 is a recombinant serotype 9 adeno-associated virus (AAV9) encoding a codon-optimized human AP4M1 transgene
Indication (as written by the applicant)	Spastic Paraplegia Type 50 caused by the AP4M1 gene
Unmet Medical Need (as written by the applicant)	Today there is no treatment of any kind beyond supportive care for SPG50/AP4M1
Major Proposed Activities (as written by the applicant)	• Plasmid Manufacturing • cGMP Vector Manufacturing • Phase III clinical trial with 8x patients and 16x matched aged controls
Funds Requested	$15,000,000
GWG Recommendation	Tier 3: sufficiently flawed, cannot be resubmitted for 6 months
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 3

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

Highest	2
Lowest	3
Count	14
Votes for Tier 1	0
Votes for Tier 2	4
Votes for Tier 3	10

- 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:	• The treatment definitely addresses an unmet need. The treatment would definitely provide an improvement over standard of care (SOC) in this patient population. The

8 **No:** 4	SOC is symptom control and is not intended to be curative or in fact to mitigate the course of the disease. If this treatment is successful it would definitely be "adopted" by both patients and health care providers as a treatment for this disease. ● This disease has no treatment. ● The proposal targets unmet medical needs. ● The primary aim of this program is to conduct a Phase 3 (pivotal) clinical trial for AAV9/AP4M1, a recombinant serotype 9 adeno-associated virus carrying a codon-optimized human AP4M1 transgene, in patients with spastic paraplegia type 50 (SPG50) disease, a variant of hereditary spastic paraplegia (HSP). ● SPG50 is an ultra-rare condition in which there is a the disruption of adaptor protein complex 4 (AP-4), which gives rise to progressive neurodegeneration. SPG50 results from biallelic pathogenic variations in the AP4M1 gene. The disease trajectory is characterized by the gradual onset of spastic paraplegia during the initial decade of life, which escalates to quadriplegia during adolescence or early adulthood. This transformation renders patients reliant on wheelchairs for mobility, with few managing to surpass the age of 30. Notably, epilepsy emerges as a prevalent comorbidity among SPG50 cases. ● The phase 3 clinical trial is designed to treat 8 patients aged 1 to 4 years old, as this age group is expected to benefit most from the treatment. Additionally, 6 more patients will receive treatment on a compassionate use (patients > 4 years old) basis at European sites in Spain, Germany, and Italy. ● Within North America, an estimated 16 individuals grapple with SPG50. Among this cohort, approximately 5 subjects fall within the age bracket of 1 to 4 years, rendering them eligible candidates for the Phase 3 clinical trial since the investigators rightly feel that >4 years of age represents potentially fixed and severe disability with less of a therapeutic opportunity. ● The investigators have done an excellent job of moving this program to the clinic. They have had a robust bidirectional dialogue with the FDA, they have been responsive to FDA feedback and have incorporated those changes. They have conducted an excellent preclinical program and the proposed clinical trial is as good as one could hope for. They are using AAV9, which is the best available AAV vector for CNS correction. They are giving the highest dose justifiable by the tox package. They are giving it intrathecally which makes a ton of sense to try to get the most to the CNS. So, all of this is very impressive and the investigators should be lauded for all their excellent and rigorous work. But there are deep concerns articulated in response to other questions below. ● It is not clear that sufficient cells in the CNS would be corrected to have a clinical effect. ● The ultra-rare patient population would be required to be treated before and up to the age of 4 to have any impact on disease outcome. ● The AAV-mediated gene supplement strategy fits nicely with SPG50 and related gene mutations. However, the current AAV vector design (promoter, serotype, delivery approaches, etc.) does not provide very supportive data for its expression and beneficial effects in pre-clinical models.
GWG Votes	**Is the rationale sound?**
Yes: 5 **No:** 7	● The proposed project is based on sound scientific and clinical rationale as it seeks to literally replace the defective gene (which is causative for the disorder) with a corrected gene. The project included preclinical data to document safety and efficacy. The project included toxicity data in patients. However, the clinical data is limited, possibly related to the small number of subjects available for treatment. It would be interesting to know the clinical efficacy outcomes (or indications of outcomes) in the patients treated in the phase I/phase II study because although those studies weren't designed to prove efficacy the potential for benefit in those studies did exist. ● The rationale is sound but this is such an incredibly difficult disease that the project is quite likely to not be successful for several reasons: ● First, the preclinical data are modest at best and suggests that there will not be enough cells transduced in the CNS to have an effect. The vector biodistribution in mice, rats and NHPs suggest that somewhere between 1 in 10,000 to maybe at best 1 in 100 cells will express the corrective transgene. So, 99% to 99.99% of the CNS neurons will be uncorrected. And for an intracellular protein and a cell autonomous, intrinsic disorder, this means that it may be very unlikely to have a clinical benefit. ● When one looks at the vector biodistribution in NHPs using the 8.4 x 10(13) dose, which is the scaled dose that will go into the clinic (Figure 4), one sees about 0.1 vg/dg, meaning that only 1 in 10 cells are even getting the vector. Now, many of those vectors will be cleared or silenced and therefore will not

	express transgene. In mice, RNAscope assesses how many cells are expressing transgene mRNA and that number at the mid-dose (the scaled equivalent to the human dose) is about 2 in 10,000 cells expressing transgene mRNA. It is very hard to imagine having a clinical effect when the percentage of transduced cells is so low. ● As one might expect from the biodistribution data above, the 'rescue' in transgenic mice is quite limited. In terms of rescue, unfortunately the preclinical data are quite limited. The mid dose is the one equivalent to the scaled human dose and there seems only to be protection in male mice, and only when treated at postnatal day 90, not when treated at p7-10, not in female mice and no rescue on the elevated + maze test. ● Clinically, it is going to be extremely difficult to demonstrate benefit even if the drug does work. There are only 16 such patients in North America, and only 5 of them are in the 1-4 year age range (the entry criteria to the study). And yet the study hopes to enroll 8 treated patients (open label) plus 16 matched prospective controls. It seems very unlikely that this can be achieved given the ultra-rare status of SPG50 disorder. ● Even if enrollment goals are met, it is unclear what is achievable from this study. Certainly some patients will drop out, there will be data loss as patients cannot get to clinics, this is an open label study (and so even with blinded evaluators reviewing video, one cannot eliminate the likely bias), and the study is not powered to detect a significant benefit. It has maybe 80% power to detect a change of 5.6 points between the groups and the GMFM-88 has a standard deviation of 6 points. This is not the fault of the investigators. They have done everything they can. But the likely scenario here is that this takes 3-5 years to enroll, they may not fully enroll even then, there will be data loss due to patient drop out prior to the primary endpoint in 3 years. This will lead to ambiguous data that won't lead to an approval, and following this study there are very few patients to enroll in any subsequent trial. ● It is not clear that sufficient cells in the CNS would be corrected to have a clinical effect. ● The biodistribution data showing mRNA expression in NHPs is unconvincing that the drug can get to enough cells. ● Although the rationale in terms of the basic science is excellent, it is concerning that the applicants will initiate a phase III clinical trial without strong preclinical basic science. The limited information from the phase I/II trial is a weak point. ● The utility of AAV9 may be rate-limiting for this disorder. This vector's limited impact on biodistribution within the CNS is considered to be rate-limiting and variable in mice. To have an effect on reversibility of symptoms, a high number of cells need to be transduced and off-target toxicities might occur at the dose levels required for efficacy. ● The very low transfection rate is a serious problem.
GWG Votes	**Is the project well planned and designed?**
Yes: 8 **No:** 4	● The investigators have had engagement with the FDA and have received and have incorporated excellent feedback from the FDA with regard to the clinical protocol. The type C meeting led to a revised protocol submitted on September 11 which led to the FDA request for an informal meeting on October 12. The meeting was held on October 18 and the primary endpoint was changed to be a derivative of the GMFM-88 based on major motor milestones. ● Outstanding issues included qualification of the ddPCR assay under CGMP conditions (underway, expected March 2024), potency assay (complete), compatibility (complete) and some clinical items: FDA recommends a smaller age difference between treated and untreated participants (with which I agree), updated matching criteria for treated versus control participants (by epilepsy type and motor milestone achievement by age), video primary efficacy with blinded evaluators review (with which I agree), and clarify the imputation method for loss of data. ● The clinical trial is designed well overall but there are too many outcome measures with the burden on participants being too high. The preclinical data are not convincing. ● The project was extremely well written, well-designed and received. However, the potential to treat is limited by the number of cells that can be potentially targeted to reverse symptoms. ● The study seems to have been re-designed to match criteria provided by the FDA that would allow outcomes for this trial to be evaluated as a phase III (pivotal) data. Unfortunately at this time the FDA has not yet provided a response to the submission of the re-designed study. Similarly, the FDA had concerns and provided feedback related to the manufacture (and specifically the potency assays) for the product. The company

	has responded to those queries; however, at this time the FDA has not yet provided a response to the submission of the modified CMC plan. ● If this study (inclusive of the manufacturing plan and clinical protocol) is allowed to proceed by the FDA it would provide significant information not only for this indication but for other rare diseases caused by single gene defects. CIRMs support would benefit not only patients with this condition but also patients with similar conditions. This project definitely advances CIRMs mission. ● The proposed timeline seems appropriate and indicates urgency. Unfortunately, the timeline of regulatory review is slightly lagging review by the CIRM and at this time the Grants Working Group are unable to assess whether or not the proposed manufacturing plan and proposed clinical trial will be able to proceed and serve to support this as a phase III pivotal trial.
GWG Votes	**Is the project feasible?**
Yes: 3 **No:** 9	● The proposed project is feasible in terms of scientific resources and administrative process for phase III trials. ● Assuming regulatory approval by the FDA can be secured, it seems likely that the stated objectives can be achieved within the proposed timeline. This is a patient population (family population) that is desperate for treatment and motivated to engage in research options. ● The proposed clinical team is top notch providing disease expertise but also covering different geographic regions. I am especially impressed with the inclusion of the investigator from NINDS (NIH). ● From a clinical trial perspective the team seems to have considered the risks to patients. ● I did not see a plan to manage risks (supply chain issues, unexpected toxicities, etc) that might result in risks to the company or in delays in the completion of the clinical trial. I am not certain that there are viable contingency plans for these types of risks. The primary feasibility issue at this time is the lack of agreement from the FDA regarding their approach to responding to CMC and Clinical issues raised by the FDA. FDA response is likely to arrive in the next couple of weeks. ● It's not clear that this study could enroll in North America if there are only five patients who fit the enrollment criteria of age 1-4. ● The limited number of patients available mean the clinical trial is unlikely to be feasible. ● The early preclinical data provided by the applicant do not sufficiently support the amount of gene correction needed to support a likely therapeutic for the indication. Marking would ideally demonstrate a more suitable target tissue biodistribution in animal studies which would represent delivery of genes to more cells. ● Efficacy data in mice indicated limitations in rescue of disease based on dose limitations with limited and inadequate biodistribution to be impactful. Protein expression was missing and uncertainty regarding which cell types were transduced.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	● This appeared to be adequately addressed. ● Due to the limited size of the patient population the investigators seem to have a very good understanding of the race, ethnicity, sex, gender and age composition of the target patients. The trial has been designed to allow for inclusion of the involved race, ethnicity, sex, gender of the patient population. The trial has been designed to treat only patients <4 years old so at this time it does not include all ages of the target patients. The rationale for the age limitation is explained in the protocol and is acceptable. ● The proposed plan for outreach, engagement, enrollment, and retention seems adequate for all patients being targeted inclusive of underserved demographic groups.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

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

DEI Score: 7

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	3	• The proposed phase 3 trial will treat patients with a rare genetic disorder called spastic paraplegia type 50 (SPG50). The exact number of patients to be treated is stated as 5 on page 5 and 8 on page 8. This point warrants clarification. • Given the rareness of SPG50, limited information is available on its epidemiology. However, the investigators indicate that it occurs equally in both genders and is seen in all ethnic groups and geographic regions. • The investigators have a number of outreach activities planned including: working with patient advocacy groups (e.g., CureSPG50), engagement with patient communities, and development of culturally sensitive materials for recruitment and education. However, given the small number of cases, it is not entirely clear how all of these activities will be achieved, as implied in group settings (e.g., information sessions and workshops). • Plans are in place to decrease barriers, promote recruitment, and decrease respondent burden. For example, patient navigators will be employed, patients will be treated at the nearest center to their home, and reimbursement will be provided for transportation and lodging. It would have been useful to have information on which of these strategies were useful in the recruitment of patients and family members in the previously treated patients. • A plan for staff education on DEI is included in the application. • No information is provided on how principles of DEI will be applied to the children and family members in the control group (e.g., gender, ethnicity). • No information is provided on the composition of the Data and Safety Monitoring Board. • Their plan covers the basics but lacks the specificity required for a stronger score. • Sufficient DEI is described.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*