Application #	CLIN1-17103
Title (as written by the applicant)	Expression of Ube3a by the hematopoietic system for the treatment of Angelman syndrome
Therapeutic Candidate (as written by the applicant)	Autologous human CD34+ hematopoietic stem and progenitor cells transduced with a Ube3a expressing lentiviral vector
Indication (as written by the applicant)	Angelman syndrome
Unmet Medical Need (as written by the applicant)	Currently there is no effective therapy for patients for Angelman syndrome and palliative care is the only option. The development of our therapeutic candidate has the potential to provide functional Ube3a to affected neurons.
Major Proposed Activities (as written by the applicant)	• Perform in vivo toxicity, tumorigenicity, and vector transduced cell engraftment and Ube3a expression studies. • Manufacture the clinical lot of the Ube3a lentiviral vector for use in a Phase I trial. • Submit and IND to the FDA for a Phase I trial for adult patients.
Statement of Benefit to California (as written by the applicant)	The continued development of stem cell and gene therapies for neurodevelopmental disorders, including those that require innovative approaches will not only affect the Angelman syndrome community but will also help in developing therapies for similar disorders. These would include those affecting the pediatric and adult populations.
Funds Requested	$4,487,656
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	• This proposal would be filling in some requested murine data on pre-clinical trials heading into a human trial of CD34+ HSPC lentiviral transduced UBE3A for the

No: 0	treatment of Angelman Syndrome (AS), AS is a monogenic pediatric-onset orphan disease without any approved targeted treatments. The project has high significance and impact, given the lack of treatments and the applicability of the technology to other disorders. ● There is a significant decrease in quality of life for patients with AS. They have seizures, ataxia, and intellectual disability including impaired communication. Therefore, a potential treatment is a step forward, and as this murine data is an obvious next step, it would be important piece of data even if it fails so the field can move forward in other ways. ● The proposed treatment strategy, if successful, would address an unmet clinical need by improving the quality of life of AS patients. ● The proposed drug product could potentially address a severe rare disease and improve over the current standard of care. ● It is important to note for AS that there is a relatively normal lifespan for these patients, it is not a life-limiting illness, so the risks of bone marrow transplant have to be put into that context. ● The reviewers have an extensive amount of preliminary data that address the main concerns about adverse events as best as can be expected for a novel therapy. ● The applicant has refocused proposed IND-enabling studies to support an adult trial as prospect of direct benefit has not been established. ● Although mechanistic data would be interesting, the lack of biological mechanism is unlikely to be a major barrier to approval.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	● The rationale is sound based on preclinical studies. The sound rationale for this therapy warrants continued development. ● The rationale remains sound, no new issues are raised in the revised application and focusing on adults makes the proposal more targeted and feasible. ● The CMC plans are well developed, and the CMC details for a successful IND have been included in this updated proposal with respect to FDA concerns and requests. ● The rationale is sound despite an unclear understanding of the biological mechanism. ● While understanding the biological mechanism may be of value, lack of understanding will not prohibit clinical development. ● No additional studies have been provided to support impact on clinically relevant physiological parameters, e.g., induced seizure thresholds, spontaneous polyspike activity and sleep disruption.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	● The proposal is much stronger with the plan to add the requested data from the FDA. Reviewers appreciate the rationale for not including it previously but agree that it will ultimately ease the process to be in alignment with their expectations. ● The project as revised better aligns with FDA's recommendations. ● The CMC is appropriately planned to meet the objectives for both time and budget. ● The formal studies of the needle/syringe compatibility are also noted and improve the study. ● The FDA asked for neurobehavioral analysis in a mouse model to assess any neurological deficits that may arise from Ube3a overexpression. The applicant should consider addressing this by detailed clinical observations during the proposed toxicity study, e.g., by assessing activity, movement/gait/trembling, alert/sleeping. ● The fact that the mice will not have endogenous Ube3a does not negate the utility of an overexpression study. It is very possible that cells in the deficient mice (and humans) will be exposed to supranormal levels of Ube3a protein, perhaps beyond those in the studies mentioned. This is not a make or-break point for the study for me. ● The proposed toxicity studies do not fully address the FDA's concerns specifically measurement of Ube3a expression and activity levels in serum, CSF and spinal cord and neurobehavioral analysis to assay any neurological deficit that may result from Ube3a overexpression. No justification of dose level is provided nor proposed time points for interim evaluations. ● We appreciate pointing us to the secondary transplantation information and addressing the single dose issue. ● The FDA gave an option to justify not performing secondary transplantation - that the data from the Tay-Sachs program could be leveraged especially with the stated challenges of this model. ● It is unclear what significant additional information is being derived from Milestone 3 vs Milestone 1.
GWG Votes	**Is the project feasible?**

Yes: 13 **No:** 0	• The proposed studies should be able to be completed within the suggested timeline. • With the additions of the FDA-requested data this is in good shape leading to an IND. • Yes, from a CMC perspective, this project is feasible and achievable within the proposed timeline.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• There is an excellent outreach program planned, including a large catchment area. AS is not an ultra-rare disorder, making it easier to include a diversity of patients in multiple ways. • It would be helpful to see outreach (recruitment materials) specifically in languages other than English, and specific language that the IRB allows enrollment in languages other than English. • Strong enrollment plan with good community support. • While the majority of AS patients in North America are Caucasian, recruitment will not have limitations on race, ethnicity, sex or gender. • The study team has cultivated resources from the institution including outreach to community groups, such as the National Organization for Rare Disorders maximizing the offering and leveraging partnerships. • The Center for Reducing Health Disparities (CRHD) conducts community-engaged research programs and interventions, socioeconomic education programs, research on community health outcomes and involvement of underserved, in cooperation with the Office of Community Outreach and Engagement (OCOE) center. • The study team plans to meet regularly with the institution's Clinical Trial Diversity Task Force to include underserved genders, races, and ethnicities in the clinical trial through quarterly reviews of data. • They will engage with a Alpha Stem Cell Clinic (ASCC) to foster collaboration with clinicians, nurses, clinical trial coordinators, and researchers from diverse departments. The ASCC will be managing the future clinical trials in AS patients and will provides access to a patient population that would otherwise be less likely to access them through outreach to rural and underserved/ under-resourced individuals. • Outreach will be conducted through collaboration with the Center for Reducing Health Disparities (CRHD) Community and Collaboration program and through Bidirectional Community-Researcher Education Forums. • The Alpha Stem Cell Clinic (ASCC) will expand access to clinical trials by training physicians, Clinical Research Coordinators (CRC) and patients to increase patient recruitment, create a network of private and government support systems to improve participation of low-income participants, collaborate with collaborative the Alpha Clinic Network to conduct clinical trials throughout the state and expand their Telehealth Program to include stem cell and gene therapy clinical trials to increase enrollment at remote sites. • The applicant will create a network of private and government support systems to improve participation of low-income participants and participants who do not have the appropriate social support system needed for these trials. • The applicant participates in an annual Supporting Educational Excellence in Diversity training which is focused on educating faculty and physicians on applying diversity to both teaching and research.

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	5	• Angelman syndrome affects both males and females and all racial/ethnic groups equally. However, the majority of cases in North America are from Caucasian descent. • The research and therapeutic candidate would help all individuals affected by AS. There is no limitation on the development or with the therapeutic candidate itself that would exclude anyone. • Trial participant goals align with the demographics of the California population in terms of race and gender. • Added new strategies to ensure representation in the study sample. • Good demographic data.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-17080
Title (as written by the applicant)	[Redacted] for prevention of GvHD (graft-versus-host disease) in patients receiving HLA mismatched HSCT (hematopoietic stem cell transplantation) for the treatment of hematologic malignancies
Therapeutic Candidate (as written by the applicant)	[Redacted] is a CD4+ T cell , investigational allogeneic, off-the-shelf cellular therapy product for the prevention of GvHD
Indication (as written by the applicant)	Prevention of GvHD in patients undergoing allogeneic HLA mismatched related or unrelated HSCT for the treatment of hematological malignancies
Unmet Medical Need (as written by the applicant)	With [Redacted], we plan to enroll patients receiving a mismatched related (haploidentical) or unrelated (PBSC) grafts, to prevent the emergence of GvHD.
Major Proposed Activities (as written by the applicant)	• cGMP manufacturing and full release-testing of clinical production runs #1 and #2 • Enrollment and dosing of all subjects in Cohort 2, 3 & 4 • All correlative translational work associated with Activity 2
Statement of Benefit to California (as written by the applicant)	The [Redacted] trial will enroll patients in California at one of its sites, it will also represent the opportunity to develop an entirely novel solution for Californians requiring mismatched stem cell transplants for treatment of their hematological malignancies. California as a state performs more HSCT than any other state, representing 11% of transplants, meaning this trial will provide significant benefit for its residents, particularly minorities, which in California are >50% of residents.
Funds Requested	$8,000,000
GWG Recommendation	**Tier 1: warrants funding**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” 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

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13	• GvHD (graft-versus-host disease) is a significant issue for patients receiving an allogeneic transplant. The potential for this intervention to address this risk is significant.

No: 0	• Allogeneic hematopoietic stem cell transplantation is a potentially curative therapy for malignant and non-malignant hematologic disorders, however acute and chronic GvHD occurs in 16% to 77% and 32% to 77%, respectively according to the publication cited. With improved prophylaxis, the incidence of acute and chronic GvHD is below 25%. The chances of finding a matched donor are reported to be approximately 75% for Caucasians, 40% for African Americans, and 50% for Hispanics. The proposed allogeneic cell therapy may address the unmet medical need for those individuals that are in candidates for human stem cell transplants without the ability to find a suitably matched donor. • The applicant has assuaged the majority of concerns about significance and potential impact. The allogeneic, pooled approach is innovative and could make a significant impact. The note that it is still an allogeneic gene-modified drug in the context of a donor/recipient transplant is still relevant and riskier than other indications. • This reviewer continues to maintain that this is a well-designed proposal and represents a continuation of a prior preclinical study funded by CIRM. Compared with the first submission, this reviewer is more enthusiastic about this proposal to see if the product actually does anything to lower GvHD now that they have treated 6 patients and demonstrated some evidence of safety. • The applicant has adequately addressed the committee's comments from the last review. • The applicant did provide most of the data requested. The only outstanding data that make it difficult to evaluate the impact is the batch-to-batch variability on efficacy. All batch-to-batch data show phenotype, viability, cell yield, etc. but not function.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• Preclinical data demonstrates potential protection from GvHD when this product is included. • 6 patients have been treated, none of whom experienced an SAE (serious adverse event) related to the product. • No updates regarding rationale. It still feels like there is a better indication for this but more comfortable with it in GvHD. • The reviewer, like the other reviewers (including when this as a CLIN1 proposal) was skeptical about administering an allogeneic cell therapy during the critical early post transplant stage after post-cy, but this is somewhat overcome by the fact that they have already cleared the IND and enrolled 6 patients, with good safety profile to date. The reviewer now understands their rationale to finish this trial and propose efficacy trials as the next step if the trend of safety continues. • The applicant states that a process improvement plan has been developed to address increasing yield. The plan was not outlined and the impact on the potential cost was not estimated. It may be possible to review during the budgeting process as the current stated cost ["both ICER (U.S.) and NICE (U.K.) frameworks would support a high six-figure price tag—likely $300,000–$400,000 (typical U.S. thresholds)"] may impact commercial viability. Recent removal of an expensive gene therapy is noted. Commercial aspects will be resolved as development progresses. • Helpful to explain why pooling of three donors is optimal (why not more than 3 to reduce batch to batch variability even more)? • Some concern regarding potential loss of GvT (graft-versus-tumor effect) response, as at least part of GvT is due to allogeneic recognition of the cancer cells.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• The proposed plan is designed to meet the stated goals that would lead to commercialization upon completion of a successful clinical trial. • Significant preclinical data supporting the hypothesis. • The study will evaluate that engraftment issues (decreased engraftment), early mortality, and infections are not increased by introducing this product into the treatment plan. • To date 6 patients have been treated without SAEs related to the product. • Data was provided demonstrating the persistence of these cells in patients' post-infusion. • The project follows a traditional design of a phase 1 trial with safety as the primary objective. This reviewer likes the emphasis on stopping rules for graft failures and also monitoring for immune recovery after receiving a potentially immunosuppressive therapy. Applicant still do not have a formal treatment "arm" for patients with active GvHD that have failed all lines of therapy, but based on their preclinical work this is not an area where this treatment might be effective. • It is good to see that applicant may consider compassionate use of their product in such situations. This maybe a missed opportunity, because if their treatment did show efficacy

	in treating GvHD without toxicity, that could be a faster route to FDA approval and importantly would be fantastic for patients. There are no concerns with their manufacturing plan and "scale-out" strategy using the CliniMACS Prodigy system to meet trial demands and potentially eventual commercialization.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The proposal details adequately the contingency plans to manage the perceived risks and delays. • The proposed team has the necessary experience and resources to conduct the activities. • Data was provided demonstrating the role of HLA (no role) and batch to batch variability. • Yes, they have now bolstered the feasibility aspect of this study, by demonstrating that Dose Level 1 is safe and Dose Level 2 is almost complete too and that they have kept pace with their planned recruitment. Applicant has also successfully answered concerns about having enough cells or a contingency plan for if cells do not meet release criteria, by successfully completing 1 of the 2 or 3 clinical production runs to make enough cells to complete this project. • Have already treated 6 patients. • With an active IND and patients treated the clinical protocol is indeed feasible. • The study team provided robust justification of the projected timeline. • Applicant have successfully produced 8 batches of product to date and only 1 failed to meet release specifications. • Some concerns about scaling up (or as applicant proposes, scaling out) in that the highest dose levels may not be entirely cost effective.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• Given the lack of sufficient numbers of matched donors for individuals with Asian, Hispanic or African American genetic backgrounds, the proposal outlines the outreach for these populations. • Improvements were made to the DEI catchment and the fact that the majority of enrolled patients to date have been underrepresented minorities is a plus. • Yes, and applicants have bolstered their outreach plan by instituting frequent PI and NMDP (National Marrow Donor Program) meetings, where donor issues can be discussed. As already indicated, their project is designed to serve those patients, often minorities, who are unable to find a suitably matched stem cell donor since the donor pool is largely of Caucasian descent. • There are disparities in access/utilization of mismatched, allogeneic HSCT (hematopoietic stem cell transplantation) in Black and Hispanic populations. From there the incidence of GvHD is also disparate. • The company is seeking to enroll a representative population across all races in the US. Their current enrollment is predominantly Non-White (5/6 patients). • Importantly, one goal of the research is to identify ways to decrease GvHD. Were that to decrease the success rate of mismatched HSCT would improve. This improvement would allow for better success in mismatched HSCT recipients (which skew towards non-white patients).

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	6	• Patient enrollment has already incorporated success in reaching under represented populations. • Expanded catchment area. • Build on existing relationships with community partners. • Align study visits with clinical treatment.

3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-17135
Title (as written by the applicant)	Inhibitory Interneuron Cell Therapy for the Treatment of Drug-resistant Bilateral Temporal Lobe Epilepsy
Therapeutic Candidate (as written by the applicant)	The proposed cell therapy is an inhibitory interneuron cell therapy derived from human embryonic stem cells (hESC)
Indication (as written by the applicant)	Focal epilepsy; bilateral drug-resistant mesial temporal lobe epilepsy (MTLE)
Unmet Medical Need (as written by the applicant)	Current treatments for drug-resistant mesial temporal lobe epilepsy (MTLE) include surgical resection or ablation of the hippocampus; both are tissue destructive and can cause irreversible adverse effects. There is a clear need to develop non-tissue destructive, and long-lasting therapies that are safe and effective for MTLE.
Major Proposed Activities (as written by the applicant)	• Initiate and conduct a Phase 1/2 trial of an inhibitory interneuron cell therapy in subjects with drug-resistant bilateral MTLE. Includes training and activation of trial sites. • Manufacturing of an inhibitory interneuron cell therapy clinical lots. Includes preclinical and technical support. • Outreach activities to identify and support underserved populations who have drug-resistant bilateral MTLE.
Statement of Benefit to California (as written by the applicant)	Epilepsy affects more than 3M people in the US and >500,000 in CA. 30-50% of epilepsy patients have seizures that are drug-resistant. The proposed inhibitory neuron cell therapy is a novel therapeutic strategy that has shown promise in preclinical and clinical studies and could potentially provide a non-tissue destructive therapeutic option for suppressing seizures in people with drug-resistant focal epilepsy. California medical institutions will participate in the clinical trial.
Funds Requested	$13,999,983
GWG Recommendation	**Tier 1: warrants funding**
Process Vote	All GWG members unanimously affirmed that “The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG.” Patient advocate members unanimously affirmed that “The review was carried out in a fair manner and was free from undue bias.”

SCORING DATA

Final Score: 1

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

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 14 **No:** 0	• The proposed allogeneic cell therapy product may address an unmet medical need in individuals with drug-resistant bilateral mesial temporal lobe epilepsy (MTLE). • The Sponsor cites the 2018 CDC report from a nationally representative household survey excluding institutionalized individuals. Approximately 1% of the US population reported having active epilepsy with approximately 90% on anti-epileptic therapies. • The 2011 Kwan citation references another European study where the proportion of noncontrolled epilepsy is approximately 16%. the Epilepsy Foundation cites 30% to 40% of individuals with epilepsy will have uncontrolled seizures while on anti-epileptic medications at some point in their lives. • The applicant intends to use allogeneic hESC derived inhibitory interneurons to treat subjects with drug resistant bilateral mesial temporal lobe epilepsy (MTLE). Drug-resistant patients' treatment options are limited to resection, ablation of the hippocampus, or insertion of seizure-dampening neuromodulation electrodes. These surgical options can have severe impact on memory, mood, and vision. This patient population does represent an unmet medical need, which this approach may remedy. • The applicant has promising findings already from a prior, ongoing clinical trial using two doses. The current approach may only require one treatment for life. That is yet to be established, but durability of effect has been shown in a small number of patients out to two years. • Because the cell therapy is allogeneic subjects receive a immunosuppression for 12 months, after which it is withdrawn. Use of immune suppression drugs has led to some adverse effects (AEs, i.e., signs of safety concerns). • Given that surgical ablation or resection are not feasible to perform bilaterally, this treatment option provides an improvement over current standard of care. • This treatment is likely to be adopted by drug-resistant MTLE patients. It is unclear what the treatment will cost but given it is proposed as a "one and done" treatment - if that proves to be the case it would represent a tremendous value proposition. • The proposed allogeneic cell therapy is designed to be a one-time treatment and thus may better control epileptic seizures and reduce the need for multiple drug administrations that may have adverse side effects. • Patients with bilateral MTLE have no standard treatment leading to seizure reduction or cessation. If this product is successful, it would be a significant improvement in care for these patients. • The applicant has provided further information regarding the difficulty of treating patients with bilateral MTLE, their lack of surgical and other options, and the distinctiveness as a clinical population. • The applicant has provided further information regarding per subject costs emphasizing the large amount of imaging and other testing, in addition to the cell and surgery costs.
GWG Votes	**Is the rationale sound?**
Yes: 14 **No:** 0	• The candidate is an inhibitory neuron cell therapy derived from hESCs for the prospective treatment of drug-resistant mesiotemporal lobe focal epilepsy (MTLE). It is an allogeneic cultured ES cell line differentiated to a post-mitotic GABA-ergic pallial (medical ganglionic eminence) interneuronal phenotype that is a cryopreserved product. • The scientific rationale for the product - inhibition of excitability through release of GABA - is an important target for anti-seizure therapeutics. The approach proposed here should lead to integrated GABA-ergic inhibition without the need for repeat administration. • The candidate is proposed to be delivered by intracranial administration into bilateral hippocampal seizure foci and is intended to distribute locally, functionally integrate into the neural circuitry, and release the inhibitory neurotransmitter GABA. The cells are expected to persist long-term following a single dose, and not require repeated administration. • The applicant has both pre-clinical and clinical data showing robust efficacy of the product in patients with unilateral MTLE. Given these data, both the scientific and clinical rationale are sound. • The data do support the continued development of the product. The applicant has another CIRM grant supporting the ongoing clinical trial. • The applicant has clarified that they will not need to scale up the manufacturing process for the clinical trial or commercial manufacturing. • Their pre-clinical model reflects both safety and efficacy of the product. Additionally, 18 subjects treated in the unilateral study have not had product-related serious adverse effects (AEs) and there have been some decrease in seizure activity (efficacy). There is good reason to believe that this study will be beneficial to patients.

	• The applicant has addressed the clinical need and rationale for improved treatment of bilateral MTLE, and provided additional evidence of safety and efficacy from the unilateral transplant trial that has enrolled 18 subjects at two doses.
GWG Votes	**Is the project well planned and designed?**
Yes: 14 **No:** 0	• This is a Phase 1/2 trial in bilateral MTLE building off experience with the product in unilateral MTLE. Patients will receive immunosuppresion for one year which will be tapered starting at the beginning of year two. The study includes appropriate long-term follow up of these patients as well as appropriate stopping rules and enrollment gaps to maximize protection of enrolling patients. • The manufacturing process has already been developed and the applicant has made three batches of product which they have used in their ongoing clinical trial. One of those batches will be used to treat the first patients in this proposed clinical trial. • The applicant has clarified the GABA release potency assay and it appears ready for use in these trials (though a potency assay is not strictly required to commence clinical trials). • The applicant has clarified that they will not need further cell manufacturing scale-up for these trials or commercial development. • The Sponsor has provided an appropriate plan for conducting the manufacturing and clinical development of the product. • The Sponsor has deleted the information about comparability and characterization of the product (to be) manufactured for the drug product to be used in this clinical study. The potency assay has also been deleted. What is the potential impact on successful approval and commercialization of the product? This can be addressed at a later date. • One patient with an RNS system (Responsive Neurostimulation for Seizures) has been implanted and shown an improvement in seizure frequency. The first sentinel patient in the new trial will not have RNS. The screening will assess if RNS precludes a surgically reasonable trajectory. Only those with MRI compatible RNS will be enrolled. • RNS may provide exploratory seizure readouts. • Injection device not larger in diameter than stereoelectrodes. • The applicant argues they have accomplished scale-up and development of a potency assay based on GABA release.
GWG Votes	**Is the project feasible?**
Yes: 14 **No:** 0	• If the applicant can get consensus with FDA on comparability testing, the manufacturing goals are very achievable within the proposed timeline. • The manufacturing team is very qualified and they have all the right structures in place (Quality being independent and reporting to the CEO) to be successful in manufacturing the cell product. • The contingency plans for manufacturing are viable. There is only a small risk that they won't be able to manufacture clinical product in a timely fashion. • Yes, based on the current, ongoing trial that has enrolled 18 subjects. • The proposed plan is feasible with staff experienced in producing the needed doses of the cell therapy from an existing cell bank. • The proposed manufacturing enhancements are appropriate to assure adequate production for larger clinical trials and commercialization. • The ongoing unilateral study shows that this approach is feasible.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14 **No:** 0	• The applicant has engaged a diversity and equity consultant to assist them. The ongoing clinical trial includes minority populations. • Their plans are appropriate and build upon previous CIRM applications. • The applicant presents a well-constructed DEI plan. • The Sponsor has provided an outline for incorporating the principles of DEI that appears to be appropriate for this early phase of clinical development. • Although the disease seems to be more prevalent in White populations (according to data provided by the applicant) they are working to identify and enroll patients at sites that are ethnically diverse in order to treat a wider group of patients.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

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DEI Score: 8.0

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	3	• This is a good example of how companies, which have different limitations from those of universities, can meet DEI criteria and achieve solid DEI scores. The applicant presents thought-out patient target data using the Trinenex database and focuses on a proxy population which is a reasonable, parallel demographic set. In addition, there is a direct patient demographic assessment from 4 of the enrollment sites, so their conclusions are well-founded. • In addition to working with the Level 4 centers where treatments in general are carried out, there is a well-considered plan to broaden work at Level 3 centers and in particular to improve diagnoses. Diagnosis can be difficult and even more so in under-represented populations. Part of the plan is related naturally to the low prevalence of the condition. There is also a broad catchment area for the 20 sites under consideration. • The group consulting on the patient recruitment and the work with the the Epilepsy Foundation also is the organization behind the patient access focus.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*