Application #	CLIN2-14801
Title (as written by the applicant)	Stem-Derived IL13Ra2 Chimeric Antigen Receptor T cells for Patients with Melanoma and Advanced Solid Tumors
Therapeutic Candidate (as written by the applicant)	Adult Stem-Like T cells engineered with chimeric antigen receptor (CAR) to target cancers expressing IL13Ra2, including melanoma.
Indication (as written by the applicant)	Advanced cancers that express IL13Ra2, including melanoma.
Unmet Medical Need (as written by the applicant)	Cancer is a leading cause of death in the United States and worldwide. Patients with advanced cancer lack curative treatment options. Our proposed product provides a potentially curative option for patients with cancers that express IL13Ra2, including deadly cancers like melanoma.
Major Proposed Activities (as written by the applicant)	• Manufacture the therapeutic product to supply the proposed clinical trial • Assess clinical safety of increasing doses of the therapeutic product in a phase 1 clinical trial • Assess the activity of the therapeutic cell product through clinical and non-clinical studies
Funds Requested	$10,211,085
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 proposal have the necessary significance and potential for impact?
Yes: 13 **No:** 0	• The proposed treatment continues to address an unmet medical need for the management of refractory metastatic melanoma, and offers the potential to eventually treat other malignancies, including rare malignancies that lack approved treatments. • The work proposed here will investigate the feasibility of using a novel CAR-T cell product for therapy of refractory metastatic melanoma, a disease that carries a dismal prognosis despite recent progress. • This resubmission is for a CAR-T cell treatment for solid tumors, initially metastatic melanoma, an unmet medical condition.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The authors provide a sound rationale for using the CAR T cells in a subset of patients with melanoma. • The rationale is supported by nonclinical and clinical data. The clinical study is underway. The protocol has been revised based on information from the first few patients. Additional patients have been treated. • The rationale remains sound, and after adjusting the eligibility criteria and adopting a lower initial dose of transferred cells, now we have clinical data from additional subjects treated with these CAR T cells. • Additional safety data provided in this resubmission obtained from additional patients treated at the current dose level assure the feasibility of using the CAR T cells in a systemic disease setting.
GWG Votes	Is the proposal well planned and designed?
Yes: 13 **No:** 0	• The investigators have faced numerous challenges and have addressed them and been able to modify the design of the protocol to better protect the participating subjects while still allowing for an appropriate scientific evaluation of the investigational product. • The project is very well designed and written. • The resubmission addresses comments from the previous submission.
GWG Votes	Is the proposal feasible?
Yes: 13 **No:** 0	• Yes. The experience with patients treated thus far suggests that the completion of this project should be feasible. • The initial results of treated patients indicate that this product may be feasible for expanded clinical trials. • Based on the additional information provided by the authors, including safety data from the current dose level the project is highly feasible, as all the elements are already fully in place including patient recruitment and manufacturing. • Of note, the manufacturing of the cell therapy product at the prior site and its transfer to the current clinical site has been successfully accomplished in all treated patients.
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 13 **No:** 0	• The proposal provides some information on meeting the needs of underserved communities. • This protocol will provide travel and lodging support. • The proposal adequately addresses the planned distribution of subjects by sex/gender, race and ethnicity. • The proposal provides an excellent and detailed rationale for the study population selection criteria. • The application provides adequate justification for the proposed exclusion of groups at increased risk for adverse outcomes if they were to be included. • More detail around outreach efforts would have strengthened the application.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

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

DEI Score: 7.0

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	0	*none*
6-8: Responsive	6	• The investigators provide relevant epidemiologic data on the occurrence rates for melanoma, including information from the California Cancer Registry. • The investigators are to be commended for including statistics on race/ethnicity, as well as gender and age. While melanoma occurs more frequently in non-Hispanic Whites, the mortality rates are higher in Non-Hispanic Blacks. While a phase 1 study with limited enrollment is proposed, the recruitment of diverse patients seems reasonable. • The upper age range is limited to 70 years of age. This limitation is appropriate given the Grade 5 adverse event seen in an older patient. • The initial phase of the study will recruit patients at a large CA academic medical center. The second phase of the study will recruit patients from two other CA academic medical centers. In addition, a collaboration and referral system is established with a network. These sites will assist with the recruitment of a diverse sample of patients. • Very strong institution with excellent track record in clinical trials. • Plans are in place to reduce respondent burden through the following initiatives: coverage of transportation costs, provision of housing, and when clinically appropriate, the use of telemedicine visits to decrease travel and associated burdens on the patient. • The investigators plan to work with CIRM Alpha Clinics to facilitate community engagement. In addition, the researchers state that they will work with the infrastructure at each of the sites to enroll patients from underserved communities. • A weakness is that they only refer to the Alpha Clinics as their outreach but don't go into detail about what they are going to do. • What is missing from this application is details on how the investigators will work within the infrastructure at each site. In addition, no information is provided on the specific strategies for community engagement at each of the sites and which of these strategies the investigators will use to facilitate engagement with the community. Without these details, it is difficult to judge how this work will be accomplished. The lack of details on the specific strategies that will be employed to ensure community engagement with this trial is considered a weakness. • Plan seems adequate.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN1-14845 #2
Title (as written by the applicant)	Neural stem cell delivered oncolytic viro-immunotherapy for ovarian cancer
Therapeutic Candidate (as written by the applicant)	A clinically tested tumor-tropic neural stem cell (NSC) platform for effective distribution of oncolytic virotherapy to ovarian cancer metastases.
Indication (as written by the applicant)	Chemo-resistant, metastatic ovarian cancer.
Unmet Medical Need (as written by the applicant)	At diagnosis, >70% of patients have abdominal metastases. Most patients develop resistance to chemotherapies, leading to a dismal 34% 5-year survival rate. New, effective options are needed. This treatment stimulates the immune system to infiltrate, recognize, and fight the tumor.
Major Proposed Activities (as written by the applicant)	• Manufacture product to supply the proposed trial. • Complete nonclinical safety studies. • Clinical protocol and IND preparation
Funds Requested	$5,314,547
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: 15 **No:** 0	• The proposed treatment addresses an unmet medical need for this lethal malignancy. Importantly, it may be not only more effective but less toxic than the current standard of care. • If successful, the proposed product would address a serious unmet need in patients with ovarian cancer. • Metastatic ovarian cancer still has no good treatment options to prolong life or maintain a quality of life. The product has the potential to treat a hard-to-treat patient population.
GWG Votes	**Is the rationale sound?**
Yes: 15 **No:** 0	• The preclinical data support the proposed novel dual mechanism of action of direct oncolysis and induction of adaptive tumor-specific immunity warranting further development to facilitate translation into clinical trials. • The nonclinical data support the rationale. • The applicant addressed the previous criticisms concerning the proposed nonclinical studies. • They have addressed the previous concerns.
	none
GWG Votes	**Is the project well planned and designed?**
Yes: 14 **No:** 1	• Yes, the changes have certainly streamlined the application. • The project plan was adjusted as suggested with respect to analytical method development activities. • Sufficient responses were provided in this revised proposal for the assessment of manufacturing changes. • As methods are better understood during further development, the acceptance criteria for several methods should be updated to numerical criteria, as requested by the FDA for the product specification. • I would recommend they modify acceptance criteria for their product to include ranges of acceptable values. • The specifications and comparability testing will need further clarification for regulatory agency acceptance as development proceeds. • Yes, although some issues with the budget remain that may not have been completely updated from the previous submission. • There are discrepancies with study start dates between timeline and budget estimates. Please reconcile. • There are discrepancies between the scope of work for biodistribution and toxicity studies and activity budget. Please reconcile. • The applicant should reconcile some differences in project and budget timelines.
GWG Votes	**Is the project feasible?**
Yes: 15 **No:** 0	• The applicant has shown safety in a clinical trial with the same/similar product in another oncology indication. • Yes, they have a good track-record and the experiments are feasible in the labs proposed. • Team has excellent experience in this area. • The project is now streamlined. • Plans to mitigate risk have been provided.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 15	• Well thought out plan to uphold principles of DEI. • The principles and proposed implementation of DEI have been adequately considered. The applicant is: ◦ Providing input to finalize the eligibility criteria, recruitment materials, informed

No: 0	consent and other protocol documents to ensure cultural sensitivity and responsiveness. • Working with medical staff to establish unbiased and inclusive screening protocols and documents that will be available in different languages. • Advocating for the inclusion of any potential participants from under-represented groups that meet the trial's eligibility criteria. • Gathering relevant health information to appropriately target clinical outreach. We expect such information will include but not be limited to cultural characteristics, socio-economic factors, employment and living conditions. • Creating and strengthening alliances with the community: clinics, community centers, faith-based organizations, leaders, and volunteers. Coordinating clinical outreach with other medical affiliates or community health organizations. • Organizing outreach and targeted marketing activities, such as health fairs, urban community centers, and women's advocacy groups. • Creating culturally relevant marketing content using social media and flyers with local businesses and faith-based organizations. Will work to make materials available in the diverse languages spoken in the host institution catchment area. • The proposal outlines the future steps and seems appropriate for a CLIN-1 application. • While theoretical at this point, they do have a good plan to address a wide range of 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	4	• Well described understanding of the population and aspirational DEI plan. • Clearly understands that socio-economic status and racial ethnicity are major factors in receiving care and survival rates. Talks about eventually focusing on socio economic goals based on income, education, and employment ranges. • The host institution will partner with CCARE to provide advice on developing community and culturally responsive study materials and on reaching and interacting respectfully with diverse populations for study inclusion. • Additional activities include hiring staff for the outpatient call center who are fluent in languages other than English. To remove language barriers, host institution makes interpreters available electronically through a vendor and has expanded its staff interpreter certification program to include 10 languages. • Partnerships includes community health organizations, community hospitals, federally qualified health centers, and faith-based organizations. • Community Research Navigator Program trains community health leaders to become research navigators who educate the community about the importance of ethnic minority participation in clinical trials as a significant component to achieving health equity.

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

Application #	CLIN1-15337
Title (as written by the applicant)	Chimeric TGFB Signaling Receptor (CTSR) Enabled Anti-B7H3 CAR T-cell Therapy in Children and Adolescents and Young Adults (AYA) with Recurrent Solid Tumors
Therapeutic Candidate (as written by the applicant)	Engineered CAR T-cells are enhanced to allow their survival in solid tumors
Indication (as written by the applicant)	Children, adolescents and young adults with variety of solid tumors but focus on sarcomas and neuroblastomas
Unmet Medical Need (as written by the applicant)	The survival of children and young adults with metastatic sarcomas has not significantly changed over the last 40 years. The young children and adults also have significant morbidity due to the toxic effects of current standard therapies (e.g. chemotherapy, radiation therapy)
Major Proposed Activities (as written by the applicant)	• Generate the viruses needed to engineer the T-cells • Establish the processes to make the engineered T-cells for patients • Establish the protocols and regulatory documents to conduct the trial and apply for FDA approval
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	2
Count	15
Votes for Tier 1	11
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: 12 **No:** 0	• Pediatric solid tumors typically impact the lives of families for years - often with negative outcomes. The need for novel therapies that provide cures is unquestionable. • Targeted pediatric solid malignancies represent an unmet medical need. The prognosis is very poor and there is no standard effective treatment available. • Yes, there is a significant unmet medical need. In particular the application states that there are very limited options to address progression of disease in children, adolescents, and young adults. • Treatments for relapsed, refractory solid tumors remain a significant unmet medical need, especially for children. • Even though the target(s) are not novel, the two-target approach (CTSR-B7H3) is proposed in three pediatric solid malignancies for the first time.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• The preliminary data presented in the application support continued development. • The scientific rationale for the mechanism of action is supported by strong nonclinical data. • Yes, there is clear preclinical evidence that the added CTSR component leads to enhanced efficacy over a B7H3 CAR alone. • The applicants have tested multiple relevant tumor models to demonstrate the mechanism and concept. However, there is still concern that the CTSR alone can lead to cytokine release syndrome or other adverse effects. • The observed toxicity in the neuroblastoma model is very concerning for the potential for graft vs. host disease, cytokine release syndrome, or other adverse effects. • The insertion of a suicide switch is proposed as a mitigation to any potential severe adverse events due to the cell therapy. • The applicants should test the safety of the approach in an immunocompetent mouse model (using a murine analog for the cytokine switch) as modification of the cytokine could have off-target effects on endogenous T cells that may dangerously self-amplify without sensitivity to the suicide switch. These models could also be used to demonstrate epitope spreading against immunocompetent murine sarcoma models, such as K7M2.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• The proposed timeline and objectives are thoughtful. • Contingencies are well thought out. • The preclinical studies appear to address FDA questions and comments. • Applicant should provide further detail on the plan to develop the identity assay for the detection of the targets individually and in combination by flow cytometry as requested by FDA in the pre-IND meeting. • FDA did not ask for dose-finding studies in mice, but these studies could be informative. • The applicant will need to address dose justification in the IND as the nonclinical models may not be optimal for determining the dose range for the clinical trials.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 1	• The project appears well designed and feasible. • The team is qualified and has access to all necessary resources. • Some activities depend on successful generation of the lentiviral vectors, which could have delays across the program, but overall the activities are appropriately designed and feasible. • One concern is the patient enrollment given the number of competing clinical trials in this space. • Safety and efficacy will be dependent on reaching a significant number of double positive cells while not going over a vector copy number of five. No data have been shown to

	demonstrate this is possible.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• Ewing sarcoma is predominantly a disease impacting Caucasian individuals, though enrollment at the applicant's institution has higher percentages of Hispanic patients. • The investigators are to be credited for looking beyond the typical Caucasian incidence of these tumors. • The outreach plan appears appropriate. • The DEI efforts will leverage partner institutions.

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: 10

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	7	• The applicant demonstrates an understanding of the inequities of underserved communities. • Efforts to "Build Cultural Sensitivity" are well defined. • The applicant's Office of Diversity, Equity and Inclusion is committed to providing support, education, and resources in support of the commitment to build a more diverse and inclusive institution. • The applicant provides a clear understanding of the patient burden and defines steps to overcome those burdens. • The applicant will utilize institution Wellness Hubs for engagement. • Institutions involved in the study are located favorably to attract a diverse participant population. • Applicant intends to include diversity metrics in the trial design. • Applicant provided data related to ethnic distribution of impacted patient population at their institution • The applicant understands inequities of underserved communities; their institution's office of DEI is committed to support the program. • The applicant institution has all around excellent capabilities.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-15547
Title (as written by the applicant)	Phase 1/2a Dose Escalation Study of Autologous Neuron Replacement in Sporadic Parkinson's Disease (PD)
Therapeutic Candidate (as written by the applicant)	Autologous stem cell-derived dopaminergic (DA) neuron replacement therapy.
Indication (as written by the applicant)	Parkinson's disease (PD)
Unmet Medical Need (as written by the applicant)	Parkinson's disease (PD) is a neurodegenerative disorder, affecting over one million people in the United States. PD causes loss of dopamine (DA) neurons in the brain, leading to loss of motor and neurological function, and severely affecting quality of life (QoL) and life span. Current therapies have side effects and are not curative.
Major Proposed Activities (as written by the applicant)	• Manufacture product to supply the proposed trial • Conduct trial to evaluate the safety, tolerability, and preliminary efficacy of autologous neuron replacement in patients with moderate to severe PD • Patient follow-up and data collection
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

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: 13 **No:** 0	• The applicant plans to treat subjects with moderate to advanced Parkinson's disease (PD) using an autologous dopaminergic neuron precursor cell (DANPC) in an open-label phase 1/2 trial. • While other allogeneic and autologous cell therapies are in development for PD, none have marketing approval at this time. Thus, there is a significant unmet medical need for

	a curative treatment for PD, the second most common neurodegenerative condition after Alzheimer's Disease. ● The current standard of care for PD involves dopamine replacement therapy (using L-Dopa) in the early stages and deep brain stimulation, as well as apomorphine treatment, in later-stage disease. Although these agents treat symptoms, only the replacement of lost dopaminergic neurons can potentially cure PD. ● This will be an autologous cell therapy and thus expensive. However, as there is currently no effective treatment for PD, the treatment represents a value proposition likely to be adopted by patients and health care providers if it effectively cures PD. It must also outperform allogeneic cell therapies being developed by others to justify the cost. ● The applicant aims to develop an autologous cell replacement therapy for PD, addressing the need for restorative and disease-modifying therapies beyond symptomatic treatments. ● The proposed product is a one-time therapy that, if successful, would eliminate the need for daily medications and the associated risks and side effects. ● Parkinson's Disease remains challenging to treat. If an autologous product reduces the need for periodic immunosuppression, it could benefit PD patients. ● Given that allogeneic cell therapies in trials for treating PD will not provide definitive data on safety and efficacy for some time, supporting an autologous product may be appropriate - especially if allogeneic products encounter regulatory approval hurdles. ● Longer-term efficacious treatments for PD would significantly impact the disease, improving quality of life and likely reducing the overall cost of treatment. ● Several issues could be better clarified regarding the need for autologous therapy. The rationale is that ESC-derived cells may be rejected by the immune system, whereas iPSC-derived cells are less likely to be cleared. This is an unanswered question. Surviving TH+ neurons from fetal transplants can be found decades later with only transient immediate immunosuppression. Testing the hypothesis is one way to explore the necessity of autologous therapy. Downsides include higher costs, time consumption (over six months from skin harvest to transplant-ready cells), and variability in iPSCs. Whether these neurons cause graft-induced dyskinesias is uncertain, but it's a concern. Additionally, a few animals treated with the therapy exhibited graft-induced dyskinesias, which is concerning due to the aggressive FIH approach of the millions of cells given into each putamen. This could be very problematic.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No**: 1	● Previous work has shown that allogeneic dopaminergic neurons can be effective in curing PD in some instances. Limited supply and side effects (dyskinesias) meant that these trials were more a proof of concept than a product that could be used to treat PD. ● The applicant has used an acute model of PD in rodents to demonstrate effective cure of animals with PD-like symptoms through the implantation of DANPCs, which, over time, differentiate into dopaminergic neurons and integrate into the brain. ● Safety of the proposed product in primates has also been demonstrated by the applicant. The applicant has accumulated enough safety and efficacy data to proceed to the clinic, and the FDA agrees. After several rounds of interaction with the FDA, the applicant has now been taken off clinical hold and are ready to take their product into the clinic. ● While all animal data is subject to interpretation, the current data are sufficiently prospective to move forward into the clinic. ● All patients with PD experience a loss of DA neurons in the midbrain and subsequent loss of DA in the forebrain. Cell replacement therapy aims to replace the lost neurons and thereby restore their function. ● The rationale to use autologous cells to eliminate the need for immune suppression is sound. However, the use of autologous cells poses a risk that the cells will develop PD-related pathology over time, even if patients with monogenetic disease are excluded. This is not sufficiently addressed verbally or experimentally. ● The selected doses are based on surviving DA neurons in mature grafts, which is appropriate. However, the total cell number grafted is constant, while the differentiation capacity in vivo of each cell batch is different. This means that the dosing is not precise and may vary a lot between patients. ● Part of the rationale is an improved understanding of the differentiation process during the manufacture of the product. This is a common question for cell therapies derived from iPSC lines. ● Although the FDA has approved the dosage regimen, the nonclinical data suggest there could be unwanted side effects in humans. This question will not be answered until more human data are available. ● The patients for this phase 1/2 have been pre-recruited, and skin biopsies have been taken. It is quite feasible that they could enroll as anticipated. The applicant has only

	generated iPSCs from a few of the skin samples, so there is a possibility of variability/failure of some of these skin samples. Comparing directly to the other PD transplant that is in the clinic, it seems the competitor's data are more compelling preclinically. ● There are distinctions between the applicant's and competitor's product that might explain the differences above. For example, the applicant transplants later DA progenitors, so the applicant's cells may be less migratory. ● The Principal Investigator (PI) is very accomplished after long stints in academia, pharma, etc. They are well respected and highly productive. ● Is the use of autologous cells necessary? Other studies demonstrate that this may not be needed. The autologous approach adds a lot of variability in the cell product due to differences in the patients. Additionally, genetic aberrations in some patients may have predisposed them toward PD, so autologous cells may not be a good choice. The autologous approach also adds complexity and cost to the manufacture of the cell product.
GWG Votes	**Is the project well planned and designed?**

Yes: 13
No: 0
	● Making the product involves taking a skin punch biopsy, cleaning and dissecting the tissue, and expanding dermal fibroblasts from the biopsy sample. After expansion the dermal fibroblasts act as a starting material for the generation of patient specific iPSCs. The fibroblasts are reprogrammed to iPSCs that then are differentiated to DA neuronal precursor cells (DANPCs) using a series of growth factors and morphogens.
	● The applicant has already enrolled over a dozen subjects and collected skin biopsy samples from all of them. For a few of these samples they have reprogrammed cells to iPSCs, differentiated to DANPCs, and cryopreserved. They are well positioned to achieve their clinical goals.
	● The applicant plans to enroll less than a dozen participants in the trial. Having close to twenty subjects already identified, with biopsy samples isolated, puts the applicant in a good position to execute on this project.
	● The applicant has had a lot of interactions with FDA which led to several clinical holds due mainly to CMC issues. Those issues have all been resolved. From a CMC perspective they are certainly ready to enter the clinic.
	● The project is appropriately planned both in terms of patient recruitment via a run-in group, the staggered dosing, and the outcome measures.
	● The manufacturing plan is well thought out. The budget is reasonable and the timelines can be achieved.
	● The planned evaluation of cells prior to grafting is minimal but sufficient in terms of cell identity and QC.
	● The applicant's preclinical support for the starting dose in the trial is not fully convincing. This can be resolved as the project proceeds and should not be a barrier to funding. Consider the following:
	  ● The doses used in preclinical studies are considerable smaller than proposed for the first-in-human study, even accounting for relative size of the brain.
	  ● The preclinical studies do not yet have adequate follow-up for full characterization of risks associated with the doses tested.
	  ● The FDA gave a 'safe to proceed' in August 2023. However, the submitted preclinical data met minimum requirements for sample size and did not use doses equivalent to the planned dosing for the trial.
	  ● The rationale for bilateral injection is clear although the FDA initially suggested unilateral injection. Thus, there are concerns about the starting dose and it should be further justified. The applicant may see graft induced dyskinesias at very high doses. Why not start at a lower dose, provided it still has potential to be effective? Can we predict from the iPSC-derived DA progenitors which lots/batches might be likely to trigger graft induced dyskinesias?
	● The applicant has four clinical sites to perform this trial. It may be wiser to use one clinical site for a small clinical trial like this one. Having more sites means additional variation, which could be avoided if just one site were used.
	● According to the FDA's guidance, each trial site will need batch production records and meet the requirements for personnel, documentation and qualifications per 21 CFR 211.
	● This proposal suggests manufacturing steps be performed at the clinical sites with quality control tests being performed at each site. This may lead to variability that might impact data analyses.
	● The applicant has not included preclinical studies of disease-related pathology after grafting in relevant preclinical models in their proposal.
	● Would a kill switch for this product reduce the risk of side effects?

GWG Votes	Is the project feasible?
Yes: 13 **No**: 0	• As the clinical hold was lifted by FDA last year, the applicant is able to execute on their manufacturing and clinical plan and meet their proposed timelines. • The team is very well qualified; several members including the PI are pioneers in the use of pluripotent stem cell derived cellular therapies in the clinic. • The manufacturing contingency plans are well thought out. While there could be slight delays to timelines, no showstoppers are evident. • The project is feasible to conduct within the planned timeframe. • The team is well composed and contains relevant and necessary expertise. • The use of four clinical sites is not needed and risks the introduction of site bias. • The applicant has demonstrated that the program as described is feasible. • This is an excellent team with lots of experience in this space. • One of the co-investigators is documented as committing 75% effort to this project, which seems too high. Is this an error? I recommend that CIRM check this.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No**: 0	• The two cohorts for the clinical trial are small and currently reflect the diagnosed incidence of PD in the population (mostly white and mostly male). They note that the incidence is higher in rural areas, possibly because of heavy pesticide usage. The enrollment of participants from these underserved communities in future trials would be helpful. • The applicant recognizes that minorities are probably under-diagnosed or only diagnosed in late-stage disease. The applicant intends to work with trial sites serving significant populations of under-represented minorities to achieve more diversity in their trial population in the phase 2 clinical trial. • One member of the applicant team has isolated iPSCs from diverse genetic backgrounds and intends to undertake a project to look at the differentiation potential of these cell lines. This will be beneficial in the long run, allowing the applicant to either adapt or change their differentiation protocol to accommodate for genetic differences. • Their approach moving further into clinical trials is mindful. • This is well described in the proposal. The applicant has good plans for outreach and patient information. • The applicant presents plans for community engagement to reach underserved communities.

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	• Strong DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-15562
Title (as written by the applicant)	Phase 1 Study of Autologous E-SYNC T Cells in Adult Participants with EGFRvIII+ Glioblastoma
Therapeutic Candidate (as written by the applicant)	Human T cells transduced with a lentiviral vector encoding anti-EGFRvIII synNotch-primed anti-EphA2/IL-13Rα2 chimeric antigen receptor.
Indication (as written by the applicant)	Patients with MGMT unmethylated newly diagnosed GBM (Cohort 1), and patients for whom re-resection of recurrent GBM (Cohort 2).
Unmet Medical Need (as written by the applicant)	Glioblastoma is the most common malignant primary brain tumor, affecting approximately 3 out of 100,000 individuals/year in the USA. Despite surgical resection, radiation and chemotherapy, prognosis remains poor with a 100% recurrence rate and median overall survival of approximately 20 months.
Major Proposed Activities (as written by the applicant)	• We will evaluate the safety of IV-infused E-SYNC T cells in patients with MGMT unmethylated newly diagnosed GBM (Cohort 1). • We will evaluate the infiltration and priming of the IV-infused E-SYNC T cells in the resected tumor tissue (Cohort 2)
Funds Requested	$10,927,618
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: 13 **No:** 0	• The two proposed populations for treatment of glioblastoma have no approved therapies, thus it is an unmet medical need. The product may have the potential to impact the disease. • Glioblastoma is an aggressive malignant primary brain tumor that affects nearly 13,000 new patients annually in the USA., with an average survival of less than 2 years. The standard of care is surgical resection and chemotherapy together with radiotherapy. Newer treatments have used CAR T cells, but these have not proved as promising as when used to treat leukemias. This is probably due to antigenic heterogeneity in solid tumor cells, off-target toxicities, issues with trafficking into the tumor, T cell exhaustion and immunosuppressive activity from the tumor. • There is an unmet need for both patient populations proposed in this study. These include Cohort 1--patients with unmethylated O6-methylguanine-DNA methyltransferase (MGMT) promoter glioblastoma as temozolomide does not add significant value to survival and Cohort 2--patients with recurrent glioblastoma as there is a poor to dismal survival after recurrence. Recurrence for glioblastoma is almost universal, and there is no standard of care for recurrent glioblastoma. The approach of IV infusion of CAR T technology for this proposed study is more feasible than intratumoral delivery, which is better for patients and providers. • In this proposal the investigators will use the first antigen that is expressed exclusively on GBM to prime T cells. These cells are effectively but restrictedly activated for the GBM-specific signal, but do not attack cells outside the CNS. They also persist in the circulation for >100 days and display a more juvenile phenotype and can be infused intravenously. If these innovative CAR T cells are successful with respect to their anti-tumor activity, lack of off-target activity, improved survival and easier administration, they would provide an attractive therapy for this serious malignancy. • A disadvantage would be the autologous origin of the cells, such that a new batch of cells would have to be manufactured for each patient. This could result in 1) a more variable therapeutic product given the potential effect of GBM on the starting cells, 2) a prolonged wait time required to manufacture the product - this could be a major stumbling block, and 3) increased costs in comparison to an off the shelf allogeneic product. It is, however, logical to start with an autologous product for demonstration of potential efficacy. This product offers new and worthwhile insights on how to treat a notoriously difficult disease.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• The applicants present a detailed section on preclinical experiments, which include animal experiments, toxicity studies, and off-target information. They filed an IND application and have received a "study may proceed" designation in October 2023. • The nonclinical data support the rationale for the product development. • Technology involving the development and preclinical modeling of the proposed product for targeting EGFRvIII mutant glioblastoma is demonstrated well in this proposal, and there is substantial preclinical evidence to evaluate this in the first-in-human study. • The authors do not include potential discussion of tumor treating fields for patients in Cohort 1 (newly diagnosed cohort). Tumor treating fields after radiation therapy can be considered with temozolomide therapy in National Comprehensive Cancer Network guidelines with level 1 evidence. Presumably it is not mentioned as temozolomide is not included in the adjuvant setting for this Cohort 1. • The authors state that their genetically modified T-cell therapy is "more likely to infiltrate invasive elements of the tumor and even potentially multifocal tumors." Per the reference cited, they only evaluated resected tumor and not all samples had a positive response. It is unclear if the authors have appropriate background to posit these observations.
GWG Votes	**Is the project well planned and designed?**

Yes: 13 **No:** 0	• Two cohorts of the study to evaluate safety followed by window of opportunity study for recurrent glioblastoma are well planned and designed to meet the primary endpoints. • No concerns with the planning for the project. • In addition to the relatively short manufacturing section provided in the proposal, the CMC section of the IND proposal is provided. This includes all of the information on manufacturing the lentiviral vector which is missing from the application. The application provides basic data on the manufacturing procedure but, again, this is presented in full in the appended CMC section. The CMC provides a thorough, well organized summary of all of the required information and completely supplements the information provided in the CIRM application. • The lot failure rate risks related to the potentially complex clinical status of the donors at the time of apheresis and aseptic technique issues are addressed along with their mitigation and its financial coverage. The release tests are as expected. They have not included a potency assay and recognize that this must be provided by the start of a phase 3 trial. They do perform a CAR induction assay. I am not sure why they would not include an in vitro cytotoxicity assay at this stage of development. • They do not describe delivery and administration of the product in the manufacturing section of the application; however, this is provided in detail in the CMC section, and very briefly in the clinical protocol. Details of the facility are well described as is the quality program. I have no concerns about the ability of the facility and its staff to prepare and release the drug product. • In reference to the clinical efficacy endpoint (Page 6/7 of 78 in the proposal), the authors proposed that they adapted the response assessment in neuro-oncology (RANO) and immunotherapy response assessment in neuron-oncology (iRANO) criteria to account for pseudoprogression. An imaging endpoint for immunotherapy study is challenging to interpret and should be reconsidered to include a time-to-event endpoint. The CIRM application specifically indicates a clinical efficacy endpoint. Moreover, the evaluation of radiographic response should reflect the use of RANO 2.0 criteria.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• Pre-meetings with FDA and IND submission have been completed and well managed per the documentation provided to the reviewers. • The proposed team includes a multidisciplinary, interprofessional team that is well-versed in clinical trials, particularly glioblastoma, first-in-human analyses, and immunotherapy. • The timeline looks feasible. • The drug product manufacturing and product release can be completed in a total of 2-3 weeks, and this should not adversely impact the overall timeline. The GMP director is well qualified and has collaborated extensively with the developer of the drug. The GMP Facility has a track record for producing cellular therapy products for innovative trials. The Facility has a backup-plan to secure alternative reagents and supplies in case of a supply chain problem. The main risks are poor quality of the starting apheresis product and potential aseptic technique failures. These are adequately addressed in the risk and mitigation section and financial coverage is provided. • Timeline from leukapheresis to manufacturing then infusion of their genetically modified T-cell therapy is unclear to this reviewer. One concern is that the patient might progress before infusion of genetically modified T-cells (Cohort 1) or be deemed unresectable, whether from clinically declining or worsening disease radiographically (Cohort 2). Strategies to mitigate these situations are warranted.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• Extensive demographic and ethnic information, trial population goals and their rationale, and sections on outreach and engagement, barriers to trial participation, expertise and experience of the staff and building cultural sensitivity are provided. • The investigators demonstrate an understanding of the race, ethnicity, sex, gender, age-based, and socioeconomic disparities for patients with glioblastoma. It is well documented in the proposal application. They provided institutional-based strategies to expand recruitment efforts for a diverse population. They plan to work with community outreach and engagement to include a diverse participant population. • The proposal includes the institutional resources to support the principles of DEI.

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	• Good data, strong institution, excellent track record. • The average survival for patients with GBM is two years. If successful, this product could narrow the gap between disparities in treatment and the time it takes to start treatment. • Recruitment goals are consistent with reported cases of GBM as documented by the applicant and will consist about 38% white, 13% Asian 6% black and 1% other. 60% male to 40% female. 60% between the ages of 20-64 and 40% between the ages of 65+ across the catchment area of 25 counties. • Personnel expertise to implement DEI-oriented activities include: the PI of the project has completed institutional DEI training and will resolve barriers to trial participation to underserved groups. Also, the clinical PI for the trials has also completed the institution's DEI training and will oversee participant enrollment and treatment, including all aspects of community engagement and outreach to facilitate recruitment and retention of a diverse population. • Applicant mentions prior tactics for Community Engagement and the success they had but no specifics for this study. I'd imagine they will deploy the same approach. • Will utilize a patient navigation service to help streamline the complexities of the healthcare system and overcome any barriers to trial participation. • Expand recruitment efforts with partner clinics in the Greater Bay Area and the Central Valley to encourage referrals from the historically underrepresented populations and more diverse populations. • To address barriers the applicant will facilitate telehealth visits and allow certain assessments to be performed at designated satellite offices. Offer patient support services to guide patients through the trial process, helping them access resources and coordinating care among different healthcare providers. Lodging and food for participants who live greater than 2 hours away and utilize a partner program to assist with transportation and travel. Translation services in several languages, offer social services support and finally child and/or pet care. • The applicant institution collaborates with a Community Outreach and Engagement Office to engage local providers and patients from underserved areas. • They will also utilize a Clinical Research Network Office that works with partner locations across the catchment area to help improve access to clinical trials and leveraging diverse populations. • All members of the team will complete focused training to improve cultural sensitivity in the research and clinical settings including the institution's DEI Certification Program. Staff will participate in regular reviews of trial recruitment goals, efforts to promote recruitment, and

		the resources available to support their efforts. Ensuring strategies are effective in engaging potential trial participants from underserved and underrepresented groups. Ensuring commitment to diversity and inclusion is upheld throughout the clinical trial process.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-16063
Title (as written by the applicant)	A phase 1/2 study to evaluate a bi-specific CD19/CD20-directed CAR T-cell, in refractory lupus nephritis (LN) and systemic lupus erythematosus (SLE)
Therapeutic Candidate (as written by the applicant)	An autologous T-cell product genetically modified to express a chimeric antigen receptor targeting CD19 and CD20
Indication (as written by the applicant)	Active, refractory lupus nephritis (LN) and systemic lupus erythematosus (SLE)
Unmet Medical Need (as written by the applicant)	SLE is a chronic autoimmune disorder that can affect multiple organs, including the kidney (LN). A critical unmet need exists for well-tolerated therapies that offer efficacy with durable disease remission.
Major Proposed Activities (as written by the applicant)	• Manufacture of therapeutic for participants with lupus nephritis (LN) and systemic lupus erythematosus (SLE) participating in the Phase 1/2 trial • Enrollment of up to 12 participants in a Phase 1 clinical trial to demonstrate safety of the therapeutic in patients with active and refractory LN • Enrollment of additional patients to evaluate the efficacy of the therapeutic in people with LN or SLE
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

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	3
Count	12
Votes for Tier 1	9
Votes for Tier 2	2
Votes for Tier 3	1

- 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: 10 **No:** 2	• Individuals with systemic lupus erythematosus (SLE) and lupus nephritis (LN) have no options to treat or mitigate their disease. Current standard of care includes dialysis and immunosuppression, with its attendant side effects. There are no curative options at the present time. • Strength: CAR T-cells that target B-cells hold promise based on previous clinical experience with B-cell depleting agents and preliminary data in a small number of SLE patients. Available therapies in SLE (including biologics) fail to achieve low disease activity or remission in about 40-50% of patients, Thus, there is room for novel approaches. • Strength: CAR T-cells can induce robust B-cell depletion, including in tissues, and thus have the potential to provide sustained, drug-free disease control. Preliminary data (a small case series from Europe) suggest profound reduction in lupus disease activity. • Strength: The proposed CAR T-cell construct is bispecific for CD19 and CD20, therefore capable of targeting CD19-low B-cells and CD20-expressing T-cells which might also contribute to disease pathogenesis. • Strength: The protocol includes both active LN and moderate/severe non-renal SLE. • Concern: The clinical benefit of dual CD19/CD20 targeting has not been clearly demonstrated in lymphoma or any other setting. It remains unknown whether it might carry increased risks over monospecific CD19 CAR-T cells. • Concern: As of the last 3-4 years, three new therapies have been approved for LN and SLE (belimumab, voclosporin, anifrolumab) and there are many others currently tested in phase III trials, thus creating a crowded competitive environment. • Concern: Despite protocol improvements and lack of major safety signals, CAR T-cell protocol includes: withdrawal of background immunosuppression for about a month, leukapheresis protocol, prolonged hospitalization and monitoring, prolonged antimicrobial prophylaxis due to increased risk for infections. • This is a well designed study - it has great potential to upend the therapeutic options for LN. • The value proposition has not been sufficiently made to differentiate with current clinical programs with respect to safety. • It is unclear that this experimental therapy is differentiated from CD19 CAR-T for the autoimmune indications.
GWG Votes	**Is the rationale sound?**
Yes: 12 **No:** 0	• B-cells play a major role in SLE and LN. Targeting/deactivating or depleting B-cells has been efficacious in active/refractory SLE and preliminary data substantiate the potential effectiveness of CAR T-cells in resistant/severe SLE cases. CAR T-cells against CD19/CD20 lymphocytes have the potential to induce long-lasting remission of lupus. • The applicant presents nonclinical data to support the rationale for bi-specific CAR-T cell therapy. • Data from Europe with an anti-CD19 CAR-T product in a small number of patients indicates potential for longer-term curative outcome. • CD19 CAR-T for SLE has shown effectiveness in the clinic.
GWG Votes	**Is the project well planned and designed?**
Yes: 12 **No:** 0	• The study protocol is well planned, including inclusion/exclusion criteria, manufacturing of the CAR T-cells, and plans for monitoring patients for possible safety issues. The study endpoints are in line with those used in other studies. From a manufacturing perspective, the project is well planned and designed. Standard lentiviral and autologous CAR T manufacturing approaches have been developed. Sufficient representative batches have been prepared and met acceptance criteria. IND clearance has been received. • The protocol includes appropriate timing of follow up visits and data collection. • The clinical protocol requires a washout period for participants, which may prove to be a

	barrier to enrollment.
GWG Votes	**Is the project feasible?**
Yes: 11 **No:** 1	• The study sets an ambitious target to enroll nearly 20 SLE patients, which is about one patient/month. Given the existing competition between SLE trials and the specific requirements of the protocol (CAR T-cell approach, need for hospitalization, extended monitoring), recruiting could be challenging. • The proposed objectives and timeline appears feasible, provided that enrollment is not limited by multiple other clinical trials currently enrolling. • There is a sufficient patient population for this study. • The use of preconditioning chemotherapy in autoimmune indications is of concern; the proposed therapy does not provide a solution to this. • The additional targeting of CD20 may add risk to the patients without adding activity. It appears to solve a theoretical problem.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12 **No:** 0	• The applicant will partner with a patient advocacy organization to leverage its existing collaborations with multiple experts in the areas of DEI, cultural sensitivity, and competence. The patient voice involvement in this project is commendable. • Plans are for a multi-center trial incorporating urban settings with diverse populations. • This disease impacts underserved groups of women more than other populations and would have a major impact on their quality of life if the product proves safe and efficacious. It may eliminate the costly chronic treatment options.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

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

DEI Score: 9

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	4	• Very strong DEI plan
6-8: Responsive	1	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN2-16303
Title (as written by the applicant)	A Phase 1 Study in Participants with Moderate to Severe Active Systemic Lupus Erythematosus
Therapeutic Candidate (as written by the applicant)	iPSC-derived CD19 CAR T cell therapy
Indication (as written by the applicant)	Systemic Lupus Erythematosus
Unmet Medical Need (as written by the applicant)	Potential for drug-free remission and reset of the immune system
Major Proposed Activities (as written by the applicant)	• Site Activation and Patient Enrollment • Clinical Trial Data Monitoring, Database Maintenance, and Data Analysis • Drug Product Manufacturing
Funds Requested	$7,934,448
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: 14 **No:** 0	• Systemic lupus erythematosus remains a devastating disease for a large percentage with this disease. The variable multi-organ involvement makes this disease difficult to treat. • The current study includes general SLE (not limited to active renal disease), thus targeting a broader patient population. • The investigators are addressing the unmet medical needs of a broad Systemic Lupus Erythematosus (SLE) patient population, with a focus on underserved minorities lacking access to cellular therapies. The approach, centered on the unique features of the product, is both scientifically sound and innovative. The potential impact is substantial, as the further development of CAR T cell therapy can revolutionize clinical practices and treatments for SLE. • Despite existing and recently approved treatments, SLE poses significant therapeutic challenges and long-lasting remission is infrequent. CAR T-cell targeting specific immune cells represent a novel therapeutic modality supported by the pivotal role of these cells in autoimmunity and preliminary results in a small case series of active/severe SLE patients. • The applicant introduces a novel approach where instead of engineering autologous T-cells, they induce T-cell differentiation in PSCs (pluripotent stem cells) followed by transduction of the chimeric antigen receptor (CAR) recognizing the B-cell marker CD19. This methodology has certain benefits such as ready-to-use stock that can be administered repeatedly, no need for aphaeresis protocol, no need for a priori discontinuation of background immunosuppression and shorter vein-to-vein time. • There is less experience with the specific method (as opposed to standard autologous CAR T-cells) in lymphomas and autoimmunity. The in vivo pharmacokinetics look similar with those in autologous CAR T-cells; however the in vivo behavior of iPSC-derived CAR T-cells might differ. • Yes, however, there is immense competition from autologous anti-CD19 therapies in this autoimmune space.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 1	• B lymphocytes are centrally placed in SLE pathogenesis. Monoclonal antibodies depleting or deactivating B-cells (e.g., rituximab, belimumab) have been effective. However, rituximab is off-label and belimumab is not universally effective and can require 4-6 months to achieve maximum efficacy. CAR T-cells targeting CD19+ B-cells have been used in small case series of patients with active refractory SLE, demonstrating high efficacy (drug-free disease remission lasting several weeks-months). • Engineering iPSCs instead of autologous T-cells is a novel technological advancement that can spare manufacturing time and costs and reduce the need for prolonged patient hospitalization. • Recent clinical data with an autologous CAR-T anti-CD19 product supports the rationale for this proposal. • The proposed project for SLE is built on a strong scientific foundation, targeting autoreactive CD19+ B cells to reset the immune system, potentially reducing reliance on immunosuppressive treatment. Benefiting from the success of CD19 CAR T cell treatments in B-cell malignancies and the efficacy of B-cell modulators/autologous CAR T cells in treating severe SLE, the project is poised for significant progress. With over a decade of expertise in human iPSC products and preliminary data from another phase 1 study, the applicant strengthens the initiative. • Other data from anti-CD19 CAR-T products (autologous and allogeneic) supports the proposed mechanism of action for the pathology, however recent safety signals will need to be included in the informed consent. • The iPSC derived cells have shown less activity than autologous in B cell malignancies and it is unlikely that the allogeneic approach will be more effective nor provide any other advantages (besides cost).
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The applicant has a history of developing iPSC cell lines in various clinical trials for other indications.

No: 0	• The project is well-planned for clinical site activation, patient enrollment, and risk mitigation. Clinical trial monitoring is guided by a robust Data Management Plan. The Advisory Board includes external experts with extensive SLE clinical study experience, emphasizing diversity and inclusion. The recruitment strategy for underserved communities is comprehensive. Manufacturing of iPSC-derived products is in compliant facilities with low risks and ample drug product inventory. The proposed experiments align with CIRM's mission, and the timeline is carefully organized, considering sample size, clinical sites, manufacturing facilities, and past phase I trial experience. • The methodology is well-planned including patient recruitment, inclusion/exclusion criteria, clinical protocol, monitoring of SLE disease activity. • A translational study (genomics) will be performed aiming at the definition of biomarkers of response to the drug product. • The investigators in the proposal recognize the recent FDA safety concern regarding T-cell malignancies linked to CAR T-cell therapy. We recommend thoroughly communicating this risk in the patient's consent document before recruitment. • In the exclusion criteria, it is recommended to exclude autoimmune diseases other than SLE as the primary diagnosis, with a specific emphasis on excluding drug induced SLE. Additionally, the suggestion is to exclude subjects with a history of drug abuse or dependence within one year of the screening visit. • A concern is that safety aspects will also be monitored but are not explicitly detailed.
GWG Votes	**Is the project feasible?**
Yes: 14 **No:** 0	• The likelihood of achieving intended objectives within the proposed timeline is high, supported by a favorable environment, adequate resources, and established collaborations. The experienced team, with over a decade of expertise in iPSC-derived product manufacturing, is well-equipped and qualified. Moreover, a robust contingency plan is in place to effectively address potential risks. • The applicant has sufficient drug product inventory to treat well over 100 patients. On the other hand, there is planning to transition the product manufacturing in accordance with applicant's Quality Management System, which might (or not) be seamless. • A steering committee has been formed to supervise the study implementation and mitigate possible risks. • The applicant has a proven track record in development of cell therapies. • The applicant has supplemented the team with advisors with expertise in treating SLE. • There may be significant competition for clinical trial participants as multiple organizations pursuing the same patient population. • The target enrollment is quite high and will require intensive recruitment. On other hand, the target population (SLE, not limited to nephritis) is broad. • The applicant has differentiated their advantages over other cell/gene therapies, however products that are small molecules or proteins may have more convenience if there is similar safety and efficacy results.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14 **No:** 0	• The applicant demonstrates an understanding of health disparities associated with moderate and severe SLE, upholding and addressing principles of DEI. • The DEI approach is appropriate. Special attention is given to cultural sensitivities. • A strength is the established collaboration with LRA (Lupus Research Alliance). • The applicant proposes an Advisory Board to enhance the outreach to underserved communities.

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

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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	• The description of the potential here does an excellent job of summarizing the benefits that may accrue to a source of supply of renewable clonal iPSC derived material used for the treatment. As this approach offers the possibility of lower cost, shorter treatment time as well as avoidance of complications that can occur from halting current mitigations as is required for an autologous CAR-T approach, there are even greater benefits for underserved populations. • There is very good demographic and socio-economic descriptions and factors that can affect clinical trial participation. One study cited notes that a 2022 CAR-T study review showed that only 7% of the patients were from low-income areas. For those with income less than $50,000 annually, they are 30% less likely to participate in trials. There is also an attempted focus of more severe presentation of the disease that shows up in the age group of puberty to the 30s. • This approach attempts to limit hospital time to a few days as opposed to 1-4 weeks of vein-to-vein time for autologous transfer. It is also likely to be significantly less expensive which for future access will be important. For this trial, there is expected support for patients that include considerations around childcare and use of telehealth to have less impact on patient families. In addition, it is expected that the research team will be making after hours patient visits, which is unusual. • There is a connection with Lupus Foundation of America and establishment of an advisory board. • The board includes VP Research of the Lupus Foundation of America, the DEI Officer and Chief of Rheumatology at a large CA academic medical center, and the Clinical Research Director for Lupus at another large CA academic medical center, as well as expected inclusion of patients. Part of the board function will be to monitor how well sites selected after an assessment are actually delivering which is not often addressed in applications. • Strong DEI plan.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*