Application #	CLIN2-17078
Title (as written by the applicant)	Efficacy and safety of cryopreserved autologous CD34+ HSC transduced with EFS-ADA lentiviral vector encoding for human ADA gene in ADA-SCID subjects
Therapeutic Candidate (as written by the applicant)	Cryopreserved autologous CD34+ HSPC transduced by the EFS-ADA lentiviral vector to express ADA enzyme
Indication (as written by the applicant)	Children older than 1.0 month with Adenosine Deaminase-Deficient Severe Combined Immunodeficiency
Unmet Medical Need (as written by the applicant)	ADA-SCID is often fatal within the first 1-2 years of life from severe infections if left untreated. Although allogeneic stem cell transplant can restore immunity, a matched donor is needed and carries risks of graft rejection or GVHD, significant causes of morbidity and mortality
Therapeutic Mechanism (as written by the applicant)	The autologous CD34+ HSPC have a normal copy of the ADA gene inserted by a lentiviral vector. Transplant of these stem cells leads to engraftment and production of blood cells expressing the genetically missing ADA enzyme. T, B and NK lymphocytes expressing ADA are produced and restore protective immunity life-long.
Project Objective (as written by the applicant)	Establish commercial manufacturing of LVV and DP
Statement of Benefit to California (as written by the applicant)	ADA SCID affects approximately 1 of 500,000 births, with 1-2 new patients born in California per year. Autologous gene therapy provides a safe and effective curative treatment. Besides the health benefits, gene therapy eliminates the need for a more risky allogeneic stem cell transplant or ongoing ADA enzyme replacement therapy, both of which are more expensive. Establishment of FDA marketing approval for this gene therapy may led the way to similar treatments for other disorders.
Funds Requested	$14,798,337
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	• Yes, the project has potential for impact. Adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID) continues to be associated with high morbidity and mortality, especially in patients without a matched donor. A medical need exists for new therapies. • Standard of care currently would be enzyme therapy and allogeneic stem cell transplant with the risk of graft-versus-host disease (GvHD). Because one can mitigate the risk of GvHD, this protocol does offer improvement over standard of care. • Severe combined immunodeficiency caused by defects in adenosine deaminase leads to a fatal form of immunodeficiency in which patients perish in the first few years of life. The current proposal is utilizing an autologous lentiviral gene-modified stem cell transplant which has been ongoing for a number of years at applicant's host institution and is now ramping up for BLA completion/submission. Historically, ADA-SCID had no treatments, but now with the advent of hematopoietic cell transplant (HCT), there is curative therapy for this disease. As the decades have gone by, outcomes with HCT for ADA-SCID have improved dramatically. Nevertheless, because transplant is through an allotransplant, there is a risk of GvHD which can be up to 19% as quoted in the proposal. The use of an autologous product would mitigate the risk of GvHD as proposed. • ADA-SCID is a devastating ultra rare disease that if not treated the afflicted child will die by age 2. This trial does meet an unmet need in an ultra-rare tragic health condition. The treatment/control options are well discussed and the impact of autologous mobilized peripheral blood CD34+ hematopoietic stem cells transduced with lentiviral vector promises to continue past efforts to provide a cure in a more efficient manner with less burden to the patient and less time at the hospital listed. • Of note, a novel and new approach is being taken in this application with a collaboration between applicant's host institution, a public benefit corporation, and a commercial manufacturing partner to make a new model for treatment of rare disease. The public benefit corporation has a mission of sustainably benefiting patients through gene therapy for ultra-rare diseases. Therefore, instead of prioritizing profits as the traditional model has done, the listed public benefit corporation needs to prioritize long-term patient outcomes and public health over financial returns as mentioned. This is a real opportunity to change the landscape of extraordinarily high drug costs associated with these therapies. • The proposed trial has high significance and high potential impact for patients with severe combined immune deficiency due to adenosine deaminase deficiency. • From a non-clinical standpoint, the proposed treatment seems capable to address an unmet medical need, potentially providing improved efficacy and safety over current licensed product and other treatments. • The proposed improvements in design will be less invasive to patients, more efficient for the viral vector development, less costly in the long run compared to current options, and more reasonable for the patient and family in regard to time away from home and cost. Given the cost of polyethylene glycol-modified adenosine deaminase (PEG-ADA) can reach 100,000 USD per year, the use of a one time gene therapy approach has a long term savings even when the upfront costs (which are currently unknown) are higher. • The treatment is a lifesaver for those with this mutation. • Value proposition is difficult to assess. One of the main reasons is that these types of therapies are extraordinarily expensive compared to standard allo-transplant. • Value can only be addressed once the safety and efficacy of the proposed product are known, the product is licensed, and the cost is known. There is potential for value, depending on the details.
GWG Votes	**Is the rationale sound?**
Yes: 14 **No:** 0	• Yes, the rationale is sound. The product has undergone extensive clinical testing and long-term data (10+ years are available); clinical data appear compelling vs allogeneic transplant, although significant manufacturing and regulatory challenges remain prior to BLA filing, licensure, and launch. • Applicant has excellent clinical data showing effectiveness.

	• The rationale is sound and use of an ADA expressing lentivirus has been explored and published upon in many articles. • The data do support continued development of the treatment at this stage. There has been a Type B meeting with the FDA and guidance given for this project. • Interesting model with the public benefit corporation; it's nice to see an attempt at a new model to try to spur development in rare and ultra-rare indications. If successful, this could provide a roadmap for future (similar) therapies. • The rationale for this trial is well explained and excellent. • A key component will be the manufacturing of lentivirus, which historically was done at a university facility, and now will be done at a commercial manufacturing partner. In this case, they will have to show that selected commercial manufacturing partner can display a minimum non-inferiority demonstrated to support the use of their manufacturing material. Again, details are laid out in the application, particularly on page 43. There will be testing of mobilized peripheral blood from three healthy donors, which will be split in half with both sites doing the analysis (host institution and commercial manufacturing partner), to ensure comparable results. • Proposed CMC plan is sound, utilizing proven vendors for vector production, transfection, formulation, cryopreservation, shipping, analytical work and regulatory applications. • Proposed CMC plan utilizes sound scientific principles from currently available information on virology, cell biology, cell culture, purification, and analysis. • Proposed CMC plan has been reviewed with FDA for scientific and regulatory acceptability on multiple occasions. Proposed organization(s) seem open to FDA input to improve proposal based on correspondence and proposal content. • The rationale seems sound.
GWG Votes	**Is the project well planned and designed?**
Yes: 14 **No:** 0	• The applicant had a Type B meeting with FDA to discuss and attempt to align on path forward to BLA, particularly around manufacturing challenges and establishing comparability between existing and commercial processes; the meeting was productive. • The data do support continued development of the treatment at this stage. There has been a Type B meeting with the FDA and guidance given for this project. • Path to BLA appears feasible with minimal additional dosing of patients. • The rationale is sound and use of an ADA expressing lentivirus has been explored and published upon in many articles. • Excellent trial design and plans. • Manufacturing planning is very reasonable in terms of making clinical drug substance and drug product available which meets quality and regulatory standards for investigational products. • Budget and timeline appear appropriate. • Interesting model with the public benefit corporation; it's nice to see an attempt at a new model to try to spur development in rare and ultra-rare indications. • Manufacturing is complex, and in many ways this proposal represents primarily a late-stage manufacturing project. There do not appear to be any remaining significant nonclinical or clinical challenges. • There is one large change: patients receiving this therapy will have the drug product manufactured at commercial manufacturing partner. Although this manufacturing facility supposedly has lots of experience with drug product manufacturing, including lentiviruses, there is very little information about their specific experience with lentiviral manufacturing for human hematopoietic stem cells. In fact, their website lacks data regarding their experience; specifically which trials and for whom other manufacturing endeavors have been pursued. It is unclear whether the manufacturing partner has CD34 experience (but they do have CAR-T experience). • One major concern would be whether or not the drug product historically which has been manufactured at applicant's institution will be the same when it becomes manufactured at commercial manufacturing partner. Therefore, a long, detailed comparability plan of the transition of this manufacturing has been laid out with multiple variables being tested simultaneously between the two labs to ensure that the manufacturing partner product meets or exceeds the standard set at applicant's institution. The FDA will have to approve whether or not the product meets the product and testing is satisfactory. • It is unclear how platform technology designation would be used.
GWG Votes	**Is the project feasible?**
Yes: 14	• Qualified team, including members with long CIRM history. • There do not appear to be significant regulatory risks. • Adequate trial feasibility as proposed.

No: 0	• The proposed program seems possible to achieve objectives within the proposed timeline. • The proposed team has the CMC and regulatory experience and access to resources required to achieve the proposed CMC activities. • The CMC risk assessment seems reasonable, and proposed remedies and contingency plans are appropriate. • The proposed/planned path to commercialization is quite interesting, and it will be worth following this to market. • The project is feasible, though there is a risk of increased costs and delays due to the complexity of manufacturing and tech transfer. • The only concern in the listed activities is the choice of a contract research organization (CRO) for biopharmaceutical services, which has been subject to several lawsuits regarding data breaches as well as internal management practices.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14 **No:** 0	• The applicant understands race, ethnicity, sex, gender, and age-based disparities involved with this kind of a project. • There is a plan for trial outreach, engagement, and enrollment. • The applicant's institution is well suited to fulfill the DEI objectives. • Well explained and adequate DEI plans and approach. • Proposal seems to consider DEI principles.

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

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

DEI Score: 8.5

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

Score	Patient Advocate & Nurse Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
9-10: Outstanding response	3	• Excellent review of incidence and racial distribution since the inclusion of ADA-SCID diagnosis as part of the newborn screening program. • Clear review of past performance of autologous stem cell transplant from the applicant team's clinical trials with their patient's race/ethnicity matching closely with national data for this ultra rare condition. Gender distribution also discussed, and trial participants have matched the gender distribution from national data. • Strong collaboration with a consortium which has a strong national repository of data and access to all patients diagnosed with ADA-SCID among other rare genetic diseases. This center will provide contact to the afflicted patient's families in an equitable manner and in their language in a culturally responsive manner. Other strong collaborations are ongoing with other outreach organizations that outreach families in all areas of the US, even in rural and frontier regions. • There are no exclusion criteria. All patients will have access to this potential cure due to the autologous nature of the trial and plans for coordinating with the patient's home children's hospital base for ongoing follow up (with scheduled follow-up checks) that mitigates long travel leave from home and cost to the families and researchers. • Costs are well discussed and planned and will be coordinated for the patient and family via a strong patient navigation/coordination center. • Cultural sensitivity training is well institutionalized at applicant's institution. There are new plans to develop a patient family diversity panel and to add a diversity board to the Public Benefit Corporation. • Applicant's institution has an excellent track record related to patient selection and management.
6-8: Responsive	3	

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

Application #	CLIN2-17127
Title (as written by the applicant)	Gene Therapy for Artemis-Deficient Severe Combined Immunodeficiency Using a Self-Inactivating Lentiviral Vector
Therapeutic Candidate (as written by the applicant)	The gene for Artemis (DCLRE1C) inserted into hematopoietic stem cells from patients with Artemis deficient SCID using lentiviral vector.
Indication (as written by the applicant)	Artemis-deficient severe combined immunodeficiency (ART-SCID)
Unmet Medical Need (as written by the applicant)	Artemis-deficient SCID is the most difficult type of SCID to treat with standard bone marrow transplantation (BMT) due to increased rejection, poor immune reconstitution and increased sensitivity to chemotherapy agents used for BMT. Gene therapy using the patient's own cells eliminates these issues.
Major Proposed Activities (as written by the applicant)	• Complete phase 2 trial and finalize historical control database. • Purchase commercial grade vector and demonstrate comparability to current phase 1/2 vector in the laboratory and in patients. • Validate potency assay.
Statement of Benefit to California (as written by the applicant)	This trial is the first to treat a disease associated with a defect in DNA repair using gene insertion therapy and will benefit California babies including Native Americans with ART-SCID. The results will help us to treat other DNA repair defects benefiting affected patients from California. This trial will increase our knowledge of lentiviral gene insertion and will form the basis for next generation approaches. California citizens will ultimately benefit from this knowledge and these advances.
Funds Requested	$14,999,999
GWG Recommendation	**Tier 1: warrants funding**
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 1

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

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

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

KEY QUESTIONS AND COMMENTS

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

GWG Votes	Does the project hold the necessary significance and potential for impact?
Yes: 13 **No:** 0	• Artemis-deficient Severe Combined Immunodeficiency (ART-SCID) due to mutations in DCLRE1C, encoding the DNA repair enzyme Artemis, is a severe, ultra-rare inborn error of immunity with absent B and T cell immunity. While allogeneic hematopoietic stem cell transplant is an available treatment it is generally not fully effective and conditioning protocols lead to a variety of side effects due to the DNA repair deficiency associated with the disease. The proposed gene modified autologous stem cell treatment with much milder conditioning would be impactful for patients. • The proposed phase 1/2 trial is of high significance and potential high impact for patients experiencing Artemis-deficient severe combined immunodeficiency. • This was a clearly defined, underserved population with poor treatment options and dismal outcomes. This was a beautiful application and deserving of funding. • There is a clear unmet need particularly in this SCID subpopulation which has demonstrated a poorer response to allogeneic transplantation than the general SCID population. • Although there are some therapies for this disease, they tend to not work well in this specific indication, therefore a strong unmet need.
GWG Votes	**Is the rationale sound?**
Yes: 13 **No:** 0	• Previous results are outstanding and show a strong, effective treatment. • The rationale is strong and supported by the available data. • The rationale and significance have been acknowledged by the FDA in their granting RMAT, Orphan Drug and Rare Pediatric Disease designations. • Well-documented and explained trial rationale. • The preliminary clinical data are encouraging. The bulk of the proposal is the development of a potency assay supportive of licensure along with transfer and manufacturing of the lentiviral vector to a commercial manufacturer and the development and execution of a comparability study followed by treatment of a few trial participants a clinical arm using the commercial vector. • While the high-level rationale is sound, there manufacturing section only covered the cellular drug product manufacturing. There was no outline of the new commercial vector manufacturing. In the ancillary documents the current manufacturing outline was available, but it appears that there will be major changes when transferring to the selected contract manufacturing organization. Without understanding the scope of these changes, it is hard to determine the risk to the comparability studies.
GWG Votes	**Is the project well planned and designed?**
Yes: 13 **No:** 0	• The project is well designed and importantly aligns with the Agency's recommendations for achieving a successful BLA application. • The project plan seems well designed and is informed by good regulatory guidance coming from a number of type B meetings. The proposed strategy for development of a potency assay as well as experiments to demonstrate vector copy number as a surrogate potency assay during the final development plan is well-supported. • While the general plan to follow regulatory guidance on viral vector comparability testing and to develop and request commentary on such a plan is well thought out, the lack of description of the commercial vector manufacturing makes it hard to assess. • Clear and appropriate trial design and plan. • The essential work demonstrates an urgency in particular exploring the potential for an accelerated surrogate endpoint. • A specific population has been identified based upon initial data to increase the potential for early success.
GWG Votes	**Is the project feasible?**
Yes: 13 **No:** 0	• The proposed timeline should be achievable. • The team, including collaborators, are excellent. • This is an outstanding group. • Adequate trial feasibility per proposed plans. • The project appears feasible. For the major project goal of transitioning to a commercial viral vector supplier it was difficult to fully assess. The chosen commercial manufacturer uses proprietary plasmid vectors in their transfection process which will be a major change from the current clinical process. It was unclear if the manufacturing would change from the current adherent process to a suspension process and if downstream purification steps would be changed. Without this understanding it is hard to assess the risk of successful comparability. Nevertheless, the team has put together a well-reasoned plan and has good regulatory guidance on the path to filing a BLA. The assay

	development is well reasoned, and the lentiviral vector plan appears sound, if not well-described.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13 **No:** 0	• Yes, the disease while ultra-rare has a higher incidence in Native American populations due to a founder mutation. • The proposal outlines a strong DEI effort to identify and support patients, with good outreach efforts for this population. • DEI plans and approaches are well documented. • DEI plan is comprehensive and specifically addresses outreach and recruitment strategies.

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	• Ultra rare disease; more prevalent in Native American population. It is important that this population is included in the study, despite low numbers. • Good track record from the institution. • Outstanding track record at the applicant institution related to patient selection and outreach. • Thoughtful patient management and connections with key groups.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*