Application #	CLIN1-13315
Title (as written by the applicant)	Hematopoietic Stem Cell Gene Therapy for X-linked Chronic Granulomatous Disease (XCGD)
Therapeutic Candidate (as written by the applicant)	Hematopoietic stem and progenitor cells collected from XCGD patients modified with a highly regulated lentiviral vector
Indication (as written by the applicant)	X-linked Chronic Granulomatous Disease (XCGD)
Unmet Medical Need (as written by the applicant)	Allogeneic transplant, while curative, is not available to patients without a matched donor, an issue that is particularly exacerbated for patients from ethnic minorities.
Major Proposed Activities (as written by the applicant)	• Complete Chemistry, Manufacturing, and Controls requirements (vector production and cell manufacturing) • Complete toxicology studies (in relevant mouse model and cell culture systems) • Initiate documentation required to open a phase 2/3 trial
Funds Requested	$3,999,959
GWG Recommendation	***Tier 1: Has exceptional merit and warrants funding, if funds are available.***
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

SCORING DATA

Final Score: 1

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

Highest	1
Lowest	2
Count	15
Votes for Tier 1	8
Votes for Tier 2	7
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, and the same project should not be resubmitted for review for at least six months after the date of the GWG's recommendation

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: 14	1. Yes, the proposal does meet an unmet medical need, i.e., it offers a means to accomplish immune reconstitution in a lethal genetically determined immunodeficiency (XCGD). 2. The current standard of care for XCGD patients is antibiotics and anti-mycotics for prophylaxis or treatment of infections, and Hematopoietic Stem Cell Transplant (HSCT) where possible. Unfortunately, in XCGD, T cells are present and functional; therefore, pre-transplant conditioning is required to prevent rejection in HSCT. Conditioning results in further immunosuppression making lethal infection an even higher probability and increases the likelihood and severity of GVHD. An approach that would allow correction of the underlying genetic defect without the need for allogeneic HSCT would be a definite improvement. 3. XCGD is a serious and life-threatening disease without good treatment, and this therapy has the potential to positively impact patients. 4. The value of the proposed treatment, if shown to result in immune reconstitution equal or superior to current approaches to HSCT, would also be a significant cost reduction to patients. In addition to cost reduction, the proposed approach would make immune reconstitution possible for any XCGD patients who are not candidates for HSCT because their physical conditions are too frail. 5. Based on the applicant's preliminary findings, the novel enhancer/promoter elements in the applicant's lentivirus (LV) improve upon current LVs. 6. The superior performance of the applicant's vector in preclinical mouse studies provides a strong value proposition. 7. Yes. However, if successful, this therapy will be difficult to commercialize given the case rate of about 1:300,000. The impact of this project will likely be in the proof of principle for other uses of the applicants' bioinformatics-guided approach.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• The project plan is supported by the data available from their extensive pre-clinical studies. The applicant has developed a next-generation lentivirus (LV) designed by bioinformatics-guided screening of enhancer/promoter elements from the human genome to restore physiologic expression of the causal gene for this indication. In a head-to-head comparison to other LV technologies currently in the clinic, the applicant's vector shows superior correction of oxidase function in neutrophils derived from XCGD patient HPSC and produces 100% survival in an infectious challenge of the XCGD mouse model. • The rationale for the project appears sound. The applicant follows a standard approach used in other ex vivo LV therapies. • The data are promising for the stage of development. The FDA's response to the product information presented at the Pre-IND meeting was, overall, positive. • The applicant was granted Orphan Drug Designation from the FDA for this product for the treatment of this indication. • Yes. However, the rationale for potential efficacy is based on mouse studies with small sample sizes in each group. Larger studies would be more convincing. • This product is a relatively straightforward gene replacement therapy using a vector that may be incrementally superior to related vectors that are currently in trials.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• The project is well-planned and well-designed. The studies planned are essential and they create value that advances CIRM's mission. • The project timeline is appropriate to complete the essential work and the goal is to advance LV-mediated modification of human hematopoietic stem and progenitor cells for XCGD to an IND filing within 2 years.

	• Overall, yes. However, there is limited description of the viral vector manufacturing, and the strategy for demonstrating comparability between manufacturing processes at the former facility and the new facility is not clear. • It would be helpful if the Proposal better defined which cytokines are to be used in the manufacturing process. • The cell manufacturing section also lacks some detail on reagents to be used, including media. • The first figure is not labeled or numbered (and therefore is not referenced in the text) and has no legend.
No: 3	• The budget for the clinical development seems high. From my read, the Protocol is drafted, but an additional $250,000 is requested for the writing of the IND. I believe that funds would be better used for another preclinical efficacy study. • The FDA asked for the phase 1 trial to be complete before the applicants move forward from adults to younger patients; however, the proposed phase 1 study includes pediatric patients. There is risk that the limited preclinical data and the trial data from the adult patients will not be sufficient to justify proceeding with pediatric patients. • Another animal model, and perhaps a different catalase-positive bacteria, could bolster the risk-benefit profile for pediatric patients. • Very little information is provided regarding the LV vector manufacturing process and plans. The application would benefit from a detailed list of reagents along with cGMP suitability status including plasmid, media & reagents used for both viral vector and drug product. More information regarding the tech transfer plan for viral vector production to the CDMO and any changes between research process and proposed cGMP process. Additional details around comparability planning between research, engineering, and cGMP lots would be beneficial in understanding manufacturing risks.
GWG Votes	**Is the proposal feasible?**
Yes: 13	• According to available estimates, there are ten XCGD patients without an HLA-matched potential donor born in the US per year. However, the true incidence of XCGD is unknown because there is no newborn screening for the condition. Unlike severe combined immunodeficiency, which is currently screened for and fatal in the first year of life, XCGD patients can survive for several years with chronic antibiotic and anti-mycotic drug administration. • The applicants have enlisted the aid of several national organizations for primary immunodeficiency to identify patients and physicians of patients with XCGD, and to promote newborn screening for XCGD. • The timeline for this CLIN1 appears reasonable. While not a primary concern for a CLIN1 application, recruitment will be challenging for the clinical trial. A related study of this indication enrolled nine patients over more than three years, with four sites. • The proposed team has ample qualifications to perform these studies and appears to have access to all the necessary resources to conduct the proposed activities. • Overall, yes. I recommend that the applicants clarify whether GMP vector is required for preclinical testing; this may impact project timelines. • The product may have limited commercial potential due to the small population, but the impact to the few patients with XCGD could be life changing. • This is an excellent team. • The contingency plan to manage risks and delays appear reasonable. • Overall, the timeline appears reasonable.
No: 1	• XCGD is an ultra-orphan indication. It will be difficult to commercialize the product with so few patients.
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Setting the cost and complexity of the product aside, providing an alternative to allogeneic HSCT would benefit underserved populations. • Yes. This approach obviates the need to match XCGD patients with donors by HLA, thus benefitting racial and ethnic minority patients.

	• Yes, the proposal provides an appropriate rationale for the study population. • Potentially, yes. However, the small patient population poses a challenge. • XCGD is an X-linked disease that is not currently screened for at birth. Currently there is no way to ascertain whether underserved populations have a higher incidence than in the general population. The proposers have joined forces with several primary immunodeficiency organizations to lobby for newborn screening for XCGD. • Only males are affected. However, female carriers have variable inactivation of their good X and some manifest as low as 15% of normal oxidative function in their neutrophils. This is usually sufficient to keep them from having recurrent infections.
No: 2	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate 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: 5.5

Up to 7 patient advocate 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 Votes	Has the applicant sufficiently addressed how they have or will incorporate perspectives from individuals with diverse experience and from underserved groups in the implementation of the proposed project?
9-10: Outstanding response	0	*none*
6-8: Responsive	2	• The applicant has done impressive work with advocacy groups to advocate for newborn screening for this disease. • The team has an accomplished track record of mentorship for diverse trainees. • The recruitment activities leverage the CIRM Bridges Program. • The application demonstrates a strong history of inclusive patient selection and ensuring DEI in employment practices. • The applicant plans to hire a Chief DEI Officer. • The applicant will cover all costs for patients and family members (i.e., medical bills, travel. airfare, housing) to receive this treatment. • It's important to note that trial participation will require entire families to relocate for months at a time. Even with financial coverage for housing, etc., the burden here will disproportionately impact lower income families. However, the therapy may represent a best path forward for under-represented groups as compared to the difficulties of accessing standard treatment.
3-5: Not fully responsive	2	• The team appears to embrace principles of DEI. • Travel and relocation expenses will be covered; this will remove a barrier to participation. • I don't see clear intent nor a clear plan to enroll a diverse trial population. • Relying on registries is unlikely to achieve inclusive trial enrollment goals, as underserved and underrepresented communities are likely also underrepresented in registries.
0-2: Not responsive	0	*none*