Application #	CLIN1-13315 #2
Title (as written by the applicant)	Hematopoietic Stem and Progenitor Cell (HSPC) Gene Therapy for X-linked Chronic Granulomatous Disease (XCGD)
Therapeutic Candidate (as written by the applicant)	Hematopoietic Stem and Progenitor Cells (HSPC) collected from X-linked Chronic Granulomatous Disease (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. This issue is exacerbated for patients from ethnic minorities.
Major Proposed Activities (as written by the applicant)	• Complete Chemistry, Manufacturing, and Controls (CMC) requirements (vector production and cell manufacturing) • Complete toxicology studies in relevant mouse model and cell culture systems • Initiate documentation required to open a phase 1/2 trial
Funds Requested	$3,999,959
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 average of the individual member scores. 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, 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: 15	• Yes, the proposal does meet an unmet medical need, i.e. a means to accomplish immune reconstitution in a lethal genetically-determined immunodeficiency (XCGD) without the need for hematopoietic stem cell transplantation (HSCT), which carries the risk for further immunosuppression and a high risk of graft-versus-host disease. • The current standard of care for XCGD patients is antibiotics and anti-mycotics for prophylaxis or treatment of infections and HSCT. Pre-transplant conditioning is required to prevent rejection - this process results in further risks of complication. Thus, an approach that would allow correction of the underlying genetic defect without the need for a HSCT would be a definite improvement. • 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. • 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. • The proposed treatment is a novel approach for lentiviral gene therapy for XCGD, where there is a clear unmet medical need. • This approach, if successful, will improve the life expectancy of XCGD patients. • Overall, yes, but I have serious reservations about the scope of impact. I need to better understand what more could be done with this technology. • While there may be indeed impact from this project, it is likely to be as a proof of principle for other uses of this bioinformatics-guided approach rather than for a cost-effective treatment for XCGD. • Yes; however, it's worth noting that the patient population is very small. • I appreciated the applicant's direct responses to the feedback from the GWG.
No: 0	*none*
GWG Votes	Is the rationale sound?

Yes:
15
	• The rationale is clear and sound, and supported by the data available from their extensive pre-clinical studies. Yes.
	• The data definitely support the continued development of the treatment at this stage.
	  ◦ The applicant has explored the approach in proof-of-concept studies and has developed a next-generation lentivirus designed by bioinformatic-guided screening of enhancer/promoter elements to restore physiologically regulated expression of the protein.
	  ◦ In a preclinical head-to-head comparison of their vector to a current lentiviral vector under clinical investigation for XCGD gene therapy, 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, representing a significant advancement over lentiviral technologies currently in the clinic.
	  ◦ The applicant has successfully completed a pre-IND meeting with the FDA, and was also granted Orphan Drug Designation from the FDA for this product for the treatment of XCGD.
	• The novel enhancer/promoter elements provide improvement over current lentiviral constructs based on the preliminary research evidence provided.
	• The superior performance of the applicant’s lentiviral construct in mouse disease model experiments offers evidence of a strong value proposition for its use.
	• The applicant has added some additional preclinical work in the resubmission, which was needed, to add to their understanding of the product before moving to the clinic. They also more clearly explain the benefit of this therapy compared to the current generation vector.

No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 15	• The project is well planned and designed. The studies planned are essential and they do create value that advances CIRM’s mission. • The project timeline is appropriate to complete the essential work and the goal is to advance lentiviral-mediated modification of human HSPC for XCGD to an IND filing within two years.

	• The applicant revised the budget allocation for writing the clinical section of the IND, as we suggested. They have allocated a portion of those funds to additional preclinical work. • I found them responsive to the previous GWG queries on the planning and design of the project. They also responded well to the question about treating younger patients, admitting that it will depend on the data and FDA discussions, but it is a possibility given precedence from other work where pediatric patients were allowed after successful treatment of a few adults. • The additional CMC information in the lentiviral manufacturing plan and comparability plan have reduced my concerns. The detailed reagent information for both viral vector manufacturing and drug product manufacturing shows well controlled reagents suitable for GMP use. The comparability approach, particularly comparability based on potency using gp91phox protein expression and functional oxidase activity to a neutrophil-like cell line, is a reasonable strategy. • There is some risk that the use of engineering run viral vector manufactured with research grade transfer plasmid will not be acceptable to the FDA for use in toxicology studies. The applicant states that this should be acceptable, and references feedback from the FDA which stated (according to the applicant): "Please note that the LV used in the IND-enabling safety studies should be comparable to the LV to be used for the production of GMP (clinical) lots." While I could not find this specific statement in the regulatory feedback upload, it does reduce my concern, as the additional CMC information provided supports the comparability of the manufacturing processes at engineering scale and GMP scale. • I still have some concern regarding the use of research grade transfer plasmid manufactured at a different facility than the planned GMP transfer plasmid, but this is likely an acceptable strategy. • I still have concerns regarding the use of healthy donor material for the three full-scale DP representative production runs given the lack of a readout on potency. • The new information on CMC for vector production appears to address many of the points raised by the FDA in their CMC Type B meeting in November 2021. • The FDA, however, also raises a number of other issues related to product manufacturing and testing and I was unable to find a detailed response or plan in this application. I believe all the FDA's points should have been specifically addressed in the resubmission. • Issues raised by the FDA included a recommendation for potency assays, changes to the stability testing program, lists of all manufacturing reagents and excipients, and issues relating to stability of the apheresis product during shipping.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 15	• Yes, but is difficult to answer this question with certainty. Patient recruitment is always an uncertainty with rare diseases. • There is an estimate of approximately 10 patients born with XCGD per year in the US who do not have an HLA-fully matched potential donor. However, the true incidence of XCGD is unknown, because there is currently no newborn screening for XCGD. Unlike severe combined immunodeficiency, which is currently screened for and fatal in the first year of life, XCGD patients can survive for a number of years with chronic antibiotic and anti-mycotic drug administration. Thus, there are likely numerous potential trial participants. • 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. They plan to use two large medical centers as their trial 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. • The team is appropriately qualified. • The proposed timeline seems appropriate with risks identified. However, given the lack of manufacturing information provided it is unclear if the risks are appropriately mitigated. • In general the timeline appears reasonable. • The contingency plan to manage risks and delays appear reasonable.

	• While not a primary concern for a CLIN1 application, recruitment will be challenging for the clinical trial.
No: 0	*none*
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 14	• 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 the general population. The applicants have joined forces with several primary immunodeficiency organizations to lobby for newborn screening for XCGD. • The proposal provides an appropriate rationale for the study population, which will be all male. Only males are affected. Female carriers have variable inactivation of their good X chromosome, but usually do not have recurrent infections. • The application details how the availability of this product would be beneficial for underserved populations. • The applicant has been responsive to DEI-related feedback from the previous review.
No: 1	• This is an ULTRA orphan disease process.

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: 7.0

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	4	• The proposal demonstrates commitment to DEI, based on
		  ◦ a stated goal of hiring for a key DEI role;
		  ◦ a clear sense of building diversity of thought on the team, with staff who are first in their families to college and staff who speak English as a second language,
		  ◦ hiring staff from CIRM Bridges programs,
		  ◦ specific outreach efforts to drive awareness of STEM in under-represented populations.
		• The program runs through a medical center with excellent DEI resources and DEI-oriented career programs.
		• The applicant will conduct patient enrollment in collaboration with a patient advocacy group/trials network with track record of securing broad patient demographics.
		• The revised proposal addresses and reflects a clear positive intent regarding DEI.
		• The applicant was responsive to the previous critiques related to DEI.

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