Application #	CLIN2-13310 #2
Title (as written by the applicant)	Phase 1 Clinical research program for functional cure of HIV with an in-vivo gene therapy
Therapeutic Candidate (as written by the applicant)	A novel genome editing therapeutic targeting integrated HIV-1 genome to achieve sustained virologic reduction to enable functional cure.
Indication (as written by the applicant)	The product is intended to deplete the reservoir of integrated HIV-1 proviral DNA in immune reconstituted virally suppressed HIV-1 positive individuals.
Unmet Medical Need (as written by the applicant)	Even in the presence of suppressive antiretroviral therapy with undetectable viral load in the plasma, HIV virus persists in the body in the form of integrated proviral DNA in latently infected cells. There is an unmet need to remove this latent reservoir towards functional cure of HIV without the need for chronic antiretroviral therapy.
Major Proposed Activities (as written by the applicant)	• Clinical study enrollment and completion of study objectives: safety, biodistribution and excision of latent proviral HIV-1 DNA. • Implementation of biomarkers for the assessment of the product's immunogenicity, HIV-1 reservoir persistence, and HIV-1 proviral DNA excision. • Completion of manufacturing.
Funds Requested	$6,852,486
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	3
Count	15
Votes for Tier 1	10
Votes for Tier 2	3
Votes for Tier 3	2

- 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 project hold the necessary significance and potential for impact?
Yes: 15	• This is a very exciting proposal to test a strategy of gene editing in people living with HIV (PLWH) to reduce the latent reservoir and potentially enable immune control and/or eliminate infectious virus. To date, only a few people have been "cured" of HIV through transplantation of cells genetically resistant to most HIV strains. That treatment is not safe or feasible for most PLWH. This technology would meet a tremendous unmet need to potentially cure the 40 million PLWH today. • The standard of care currently is antiretroviral therapy. These medications are costly, require strict adherence to remain effective, and are associated with side effects and toxicities. A therapy that could enable PLWH to safely live without taking medications would be an enormous advance for them. • The value of this intervention in terms of cost savings and reduced morbidities would be substantial. • An HIV cure is very important. • A cure for HIV would have a huge impact worldwide, however, scale-up may be a future problem which could limit overall impact.
No: 0	*none*
GWG Votes	**Is the rationale sound?**

Yes: 12	• A latent pool of infected CD4+ lymphocytes is believed to be the reason why lifelong antiretroviral therapy is necessary to suppress HIV replication. Preliminary data - based on humanized mice and large animal models - suggest that successful excision of HIV/simian immunodeficiency virus (SIV) DNA from latently infected cells can be achieved. In the large animal models reductions in intact proviral sequences were 38% 77% and 95%. Whether those will result in the ability to control HIV replication remains to be determined. Nevertheless, no therapy to this point has demonstrated this degree of reduction in HIV DNA and just that is a major accomplishment
	• The response from the proposers to the issue of additional large animal studies was appropriate and convincing. The SIV-infected large animal study does not fully recapitulate HIV infection. Viral loads are usually higher in these animals, virus is more homogeneous, and their vector has not been particularly optimized for SIV. There are numerous examples of different outcomes between SIV-infected large animals (and HIV-infected humanized mice) and people living with HIV. One can draw the wrong conclusion regarding both efficacy and futility by basing a decision fully on large animal models.
	• The preclinical data is difficult to interpret for efficacy due to lack of equivalent animal models. Some safety data is provided, so likely the only way to determine the efficacy is for human trials.
	• There are some limitations to this approach including:
	  ◦ The degree to which HIV reservoir must be reduced to achieve a "cure" is unknown. This study could help address that question.
	  ◦ Pre-existing vector antibodies excludes almost half of adults, although presumably better vectors could be developed in the future.
	  ◦ Because the treatment itself often induces antibodies to the vector, this likely precludes participants from receiving a second dose.
	  ◦ Complement mediated toxicity is a potentially quite serious adverse event.
	  ◦ Off target effects cannot be predicted; that is why this is first in human.
	  ◦ The strategy does not prevent re-infection (neither does Hepatitis C virus therapy, but it is widely used and quite effective)

	• Vector targeting may be limited by preexisting antibodies. • The therapy may lead to serious adverse events in a population that does not have a fatal disease. • Roller bottle production may lead to high proportion of empty virions.
No: 3	• The safety and manufacturing challenges of the vector are still big and this creates concerns about the therapy for large patient populations and not the least in developing countries. • The preclinical data is exciting but also suggests that the therapy could still be optimized to increase efficacy.
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The study is very well designed and the outcomes that are outlined are very appropriate. This is a first in human study, so the primary endpoints relate to safety and biodistribution. Tremendous care has been taken to minimize risks to participants in terms of long intervals between dosing and new recruits, treatment with dexamethasone to suppress immune reactions during the week of the infusion, and careful follow up. • Exploratory endpoints measuring proviral HIV excision, change from baseline in HIV reservoir, change in baseline CD4 count, and time to viral rebound are appropriate and considered state of the art in HIV Cure studies. • I believe the project is well planned and the team is well positioned to carry it out. • The project timeline is appropriate to ensure timely development of the product while taken great care to ensure participant safety.
No: 1	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• The intended objectives are likely to be achieved as outlined. This will be a popular study and recruitment of the proposed participants will be easy. • The proposed team is stellar. The California clinical trials sites are experienced in recruitment of PLWH to clinical trials. Resources appear to be in place to provide the outcomes measures. • Contingency plans for anticipated problems are well spelled out. • Feasibility of the study seems even more robust in the revised proposal. In the last review, concern was raised about the ability to manufacture sufficient amounts of the vector; new information is provided to allay these concerns. First, all the product for cohort A, and 60% of product for cohort B have already been manufactured. Second, they have contracted with a new manufacturer who can make much larger amounts of product due to a superior manufacturing process to the current manufacturer. • There are very few changes to the Manufacturing Summary. The applicants indicate that the drug product manufacturing for Cohort B is ~60% complete and that product for Cohort A is completed, released and in storage. They also state that they may elect to expand Cohort A treatment if the results look promising. They indicate that the vector manufacturing process is proprietary, which is why they have provided little information. This facility has considerable experience in preparation of vectors, and this reduces the concern about the lack of detail. The information about outsourcing future manufacturing is marked as a change, but was essentially covered in the previous application. There are detailed responses to reviewer comments for other parts of the application, and these should be used to base the decision on whether the project is now suitable for funding. • I believe major safety issues exist, however, the FDA has cleared it. The FDA cleared dosing range may not be high enough to produce results. • Alternatives to the vector should be considered. • Scalability may be limiting.
No: 1	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 15	• Addition of a partnering organization to provide commitments to serve underserved populations is strong. Other aspects of DEI are also well considered. • Financial and time barriers were addressed.

	• The team has engaged a community advisory board, which is excellent. • The applicant has selected an investor that is an investment fund formed for the charitable purpose of improving global health. The applicant has signed a written commitment to provide products to underserved populations. It also has made commitments to pursue prequalifying the treatment with the World Health Organization, thereby enabling procurement of the product by UN agencies and other public health agencies. They have made additional international commitments as well, although it is not clear that any of these commitments are binding.
No: 0	*none*

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	1	*none*
6-8: Responsive	3	• A well described DEI plan that addresses the need for the treatment among diverse communities, a robust outreach plan that will likely reach underserved target populations. • Good community outreach and presence, good analysis of patient population and focus on overcoming traditional hurdles
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*