Application #	CLIN2-14265 #2
Title (as written by the applicant)	A Phase 1b, Randomized, Blinded, Placebo-Controlled Dose-Ranging Study Evaluating [Product] Safety, Pharmacodynamics, and Biomarkers in Knee Osteoarthritis
Therapeutic Candidate (as written by the applicant)	An adeno-associated vector (AAV) expressing an optimized form of IL-1Ra, a naturally occurring protein that blocks IL-1 signaling.
Indication (as written by the applicant)	Osteoarthritis of the knee
Unmet Medical Need (as written by the applicant)	Osteoarthritis is a degenerative joint disease that is the leading cause of disability. Current treatments are only palliative; nothing can slow or stop osteoarthritis progression. This product is injected into the knee, blocking IL-1 signaling to reduce inflammation, pain, and joint degeneration.
Major Proposed Activities (as written by the applicant)	• Enroll 50 osteoarthritis patients in a Phase 1b trial; assess safety and pharmacodynamics of the product at two dose levels. • Evaluate the effect of the product on symptoms and biomarkers of disease progression over time. • Prepare for next phase of development by scaling up the product manufacturing process and meeting with FDA to discuss requirements for approval.
Funds Requested	$11,637,194
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	14
Votes for Tier 2	0
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, 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: 14	• Osteoarthritis (OA), a degenerative joint disease, is the most prevalent joint disease and a leading source of chronic pain and disability in the United States. CDC estimates that 1 in

	4 (or 54.4 million) US adults have some form of arthritis, a figure that is projected to reach 78 million by the year 2040. ● The proposed phase 1b, multi-center, randomized, dose-ranging, placebo-controlled study aims to assess the safety, pharmacodynamics, biomarker effects, and efficacy of the product in 50 subjects with knee OA. ● Yes, there is unmet need of treating OA which affects over 32.5 million Americans and is the leading cause of disability among the elderly. Current therapy is palliative, and there are no approved therapies that can slow or halt disease progression. ● As OA is the leading cause of disability among the elderly, improvement in OA treatment will have a substantial impact on patients' quality of life and on the burden of health care providers. ● Yes. There is good potential for impact in the management of osteoarthritis (OA) in a non-operative fashion.
No: 1	● Osteoarthritis is a major unmet medical need for which there is only symptomatic therapies. ● This general approach is novel for OA, and relevant since knee osteoarthritis is problematic. ● The practical issue relates to IL-1 as the target for therapy because there is lack of human data to support the thesis that IL-1 is an important causal factor in the pathogenesis of OA. Neither intra-articular injection of IL-1 antagonist or systemic therapy with IL-1 antibody support the notion that IL-1 is a major causal factor in OA.

GWG Votes	Is the rationale sound?
Yes: 14	● The rationale is sound for this phase of a study. ● The development of the product is scientifically sound and targets interleukin-1 (IL-1), a known pathophysiological mediator of disease in joints with OA. ● The proposed study aims to assess the safety, pharmacodynamics, biomarker effects, and efficacy of the product.
No: 1	*none*

GWG Votes	Is the project well planned and designed?
Yes: 14	● The project is well planned and designed. ● This phase 1b trial is very well designed. The multi-arm design is adequate and very efficient. The sample size calculation is mainly based on the key secondary outcome - change in synovial fluid IL-1Ra levels from baseline to Month 12, which is adequate and makes sense. ● The primary, secondary and exploratory outcomes are clearly stated and logical. The randomization process, and statistical analyses such as Safety and Tolerability Analysis, Pharmacodynamic Analysis, and Exploratory Efficacy Analysis are well described, clear and appropriate. ● Overall, the study design, sample size, randomization, statistical methods and analyses are mostly adequate with a high standard. ● The treatment exhibits a low risk of adverse effects when administered concomitantly with other medications, an important consideration for OA patients as many have other conditions. ● The revised gated approach addresses concerns. ● Details regarding manufacturing needs to be consistent through the manuscript.
No: 1	*none*

GWG Votes	Is the project feasible?
Yes: 15	● Yes. The project is feasible. ● Yes, this appears to be the case. The applicant asserts the first-in-human single ascending-dose study, the product administered by injection in subjects with moderate knee OA was safe and well tolerated, with no serious adverse events nor any adverse events leading to study withdrawal. ● They propose to alter the manufacturing procedure to produce larger quantities. They will perform comparability to the material used for phase 1 studies. This plan appears to be acceptable. Curiously, these changes are not reflected by any alterations to the original manufacturing section which still describes the use of adherent HEK293 cells.
No: 0	*none*

GWG Votes	Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?
Yes: 15	• The DEI section has been revised to be very comprehensive and critical now. The implementation is key for such small sample size, but the support of a specialist DEI company is reassuring. • The applicant's plan going forward includes incorporating diverse patient voices into a future trial plan design and a robust health economics outcomes research program to support value-based pricing and widespread reimbursement. • In section 4 of the resubmission, the applicant provides an additional rationale intended to satisfy concerns associated with the reliance on a DEI company to uphold principles of Diversity, Equity, and Inclusion.
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

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	7	• Responsive to comments made by reviewer previously in relation to DEI and outreach efforts. • Much improved DEI plans. • The applicant has added information highlighting OA health disparities in symptoms, access to care, health outcomes, and clinical trial access. • The applicant provides information elucidating the economic burden of OA, and how it disproportionately impacts minority and socioeconomically disadvantaged patients. • Good data analysis, including impact of OA on African American population related to risk, severity of symptoms and access issues. • The selected trial sites draw from diverse populations. • A research organization is driving DEI for the clinical trial.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*

Application #	CLIN1-14299
Title (as written by the applicant)	Ex vivo Engineering of Autologous Hematopoietic Stem Cells for the Treatment of Hypophosphatasia
Therapeutic Candidate (as written by the applicant)	Hematopoietic stem/progenitor cells collected from patients with hypophosphatasia and genetically modified with a lentiviral vector to release TNALP (tissue non-specific alkaline phosphatase)
Indication (as written by the applicant)	Hypophosphatasia (HPP)
Unmet Medical Need (as written by the applicant)	The only approved enzyme replacement therapy (ERT) for HPP requires multiple and expensive weekly injections for life and is associated with compliance issues due to common site injection reactions. We are proposing a more affordable, one-time and stable cell-based ERT treatment for HPP.
Major Proposed Activities (as written by the applicant)	• Optimize the clinical manufacturing of the therapeutic product • Complete toxicity and efficacy studies in cell culture and in mice • Complete the regulatory requirements to initiate a Phase 1/2 clinical trial
Funds Requested	$3,999,980
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	2
Count	14
Votes for Tier 1	13
Votes for Tier 2	1
Votes for Tier 3	0

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- 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: 13	• This proposal is for the treatment of hypophosphatasia (HPP), a metabolic disease that is due to a loss of function mutation of the gene that encodes for the tissue non-specific alkaline phosphatase (TNALP) that is required for mineralization. HPP manifests as short stature and abnormal development of bones, with symptoms ranging from tooth deformities to bowing of the long bones with metaphysis and abnormal rib morphology. It can occur at any age with severity ranging from fetal death to fractures that start in

	adulthood. Mortality in perinatal and infantile forms of the disease is 58-100% within the first year of life. The incidence of severe forms is ~1 in 100,000 live births in the USA with a carrier incidence of ~1 in 200. In California there are ~400 HPP patients, and every year 4-5 children are born with the severe form of HPP.
	● The drug asfotase alpha was approved in 2015. It is an enzyme replacement therapy for perinatal/infantile and juvenile onset HPP and effectively prolongs survival of these patients. Its major disadvantages are:
	  ● The required frequency of treatment (3-6 times per week for the life of the patient) with resulting non-compliance
	  ● Side effects, consisting of erythema, pain, lipodystrophy, hypersensitivity reactions, ectopic calcifications and possible immune-mediated effects
	  ● The drug is extremely costly at over $1M per year for a 100lb patient (the drug is dosed by weight). Express Scripts coverage is capped at $1.5M per year for adult patients, and this results in $42,400 per patient out-of-pocket expenses.
	● The current treatment is high-cost and has a number of side effects that negatively impact the patient's health. The product proposed in this application is worth investigating as an alternative to see if it will mitigate the adverse health effects of the existing treatment. Even if the cost of the proposed product is high (which is likely, based on costs of FDA-approved similar treatments), the one-time treatment would still result in significant savings over the lifetime use of the current approved enzyme replacement therapy.
	● The proposed treatment would represent a one-time, potentially curative therapy by transplanting lentiviral vector genetically-modified autologous hematopoietic progenitor cells. It overcomes the disadvantages of allogeneic transplantation for HPP by avoiding the risk of graft-versus-host disease and the scarcity of HLA-matched donors. It could be performed at any stem cell transplant facility with access to a GMP facility that can manufacture the modified progenitor cells. Additionally, it would result in substantial cost savings.
	● This project has the potential to provide significant improvement over existing standard of care in this rare disease population.
	● Supplanting the extraordinarily expensive lifelong treatment enzyme replacement with the one-time treatment proposed in this application has great potential impact.

No: 1	*none*

GWG Votes	Is the rationale sound?

Yes:
13
	● The genetic defect resulting in HPP is well characterized. The application includes multiple lines of preliminary data supporting the rationale:
	  ● The investigators have shown that autologous cells can be effectively transduced with the appropriate lentiviral vector.
	  ● Pre-clinical data from a mouse model shows that genetically-modified mouse progenitor cells can engraft mice and correct premature death while improving skeletal malformations.
	  ● Human progenitor cells transfected in vitro show high biological activity and these cells can be manufactured in clinically-relevant numbers.
	  ● Overall, the disease appears to be appropriate for this type of therapy and the preliminary data look encouraging.
	● The rationale is excellent based on prior preclinical data.
	● The investigators are leveraging their experience with the indication and knowledge of the mechanism of action of the approved therapy.
	● The proposed project is well-considered. The applicants are incorporating most of the FDA's pre-IND comments to ensure they are performing the necessary IND-enabling studies.
	● One concern is with the plan to conduct the study in pediatric patients less than 16 years old. The FDA requested that the applicants perform a preclinical study to support the prospect of direct benefit in pediatric subjects.
	  ● Specifically, the FDA proposed that the applicants do a study in which the transduced hematopoietic stem/progenitor cells are derived from the same mouse model used to evaluate the treatment. The applicant claims that this study is not feasible, and it will be critical for the applicant to provide data to the FDA to support this claim.
	● The conditions for transduction require further optimization.

No: 1	● This is a disease that is osteoblastic in nature, which makes transplant with the intended cell population counterintuitive due to the fact that osteoblasts are not derived from this

	cell population. However, it is possible that the engrafted cells can supply the deficient enzyme, and the animal model survival data presented in the application are compelling. ● The promoter used in the intended construct is very strong. There are new data emerging in the gene therapy field concerning the development of cancer associated with the lentiviral backbone that should be considered. ● In animal models, the therapy is delivered via intrahepatic injection, which is not relevant to human translation. Although data in the application provide proof of concept, the lack of testing delivery via the intended route calls translation into question. The applicants should consider testing intraperitoneal injections in animal models, as these can be performed in neonatal mice.

GWG Votes	Is the project well planned and designed?

Yes:
14
	● Concerning the manufacturing aspects of the proposal, the proposed activities are well designed and show a systematic approach to the development of a qualified manufacturing and release procedure for both the vector and the cell product:
	  ● The vectors will be manufactured by a CMO with a track record of supporting many biotech companies and which follows both EU and FDA regulations. This CMO has already produced a lot of the required vector that was used to support preclinical development studies.
	  ● The manufacturing procedures are very well described in regulatory material supplied by the applicant to the FDA.
	  ● Manufacturing of the drug substance/drug product will be performed at a facility with experience in manufacturing genetically-modified progenitor cells for existing INDs. The facility has performed two pilot large-scale process development runs.
	  ● Following collection of the starting cells, the appropriate cell population will be selected using a commercially available device following qualified standard operating procedures. Pre-stimulation culture of the selected cells will be performed in the device. It is proposed that transfection will also be performed in the device; however, pre-clinical work has produced relatively low vector copy numbers per cell. The applicants propose a new approach and device to increase vector copy number.
	  ● The proposed release tests are all relevant and well described, as are some supplemental analytical tests.
	  ● The applicant will also initiate manufacture of a lot of GMP-grade vector and perform all release testing. This lot will be used to treat the early phase trial patients.
	  ● It is notable that this applicant has had zero lot failures.
	  ● Recent comments from the FDA do not raise substantial CMC issues.
	● The proposal is a well-planned and designed study with a detailed thought process outlining all the inter-dependencies of each study.
	● The application addresses all the potential pitfalls and includes mitigation strategies.
	● The timeline is realistic.
	● The applicants have an opportunity to treat stem cells from mice lacking TNALP, but suggest the mice don't live long enough to harvest neonatal bone marrow. However, the survival curves included in preclinical data in the application indicate that this may be feasible. In normal mice, one does expect marrow hematopoiesis to take place in the neonatal period. Testing TNALP-deficient mouse stem cells would substantiate the applicants' therapeutic hypothesis.

No: 0	None

GWG Votes	Is the project feasible?

Yes:
14
	● The series of experiments in this application is described well, and reasonable timelines are provided.
	● From a manufacturing standpoint this project is feasible:
	  ● The staff are experienced in preparing cells of this type and the vector CMO has a good track record.
	  ● The applicant has provided excellent information on manufacturing as part of their communications with the FDA.
	  ● The facilities and expertise provided through various collaborators and contract groups meet all requirements.
	● The applicants describe and propose strategies to address several risks in the proposal:

	● The major manufacturing risks are insufficient numbers of starting cells which is addressed by performance of a second collection procedure; and the low vector copy number, which is addressed by the proposal to incorporate a new step in the transduction procedure. ● Supply chain issues are addressed satisfactorily within the limits of the collaborating/contracting institutions' ability to do so. ● Vector lot failure is addressed by manufacturing a new lot at no additional cost. ● Failure of a Production Development Run is addressed by having sufficient vector available to perform two additional runs. ● The project seems highly feasible based on the combination of deep experience of the individuals and organizations that have been assembled, the details of the proposal, and the current package of data the applicants have presented to demonstrate feasibility. The assembled team reflects the selection of individuals and organizations with many years of experience in areas required to execute this study, from vector and cell manufacturing, preclinical studies, and clinical study design. ● Based on the data accumulated thus far the proposed activities should be feasible. ● The applicant's strategy for interacting with the FDA is reasonable. However, the applicants indicate that there are several comments from the FDA that they will not be able to address. The applicants indicate that they may request an additional meeting with FDA prior to submission of their IND to discuss why these comments cannot be addressed. The applicant should be aware that it's highly unlikely that such a meeting would be granted because they have already completed a pre-IND meeting. Rather, the applicant should ensure that their IND package has solid data and justifications for any deviation from the FDA requests/comments that were provided in response to their pre-IND package. Based on the review of the proposal, it seems that they do have the necessary data to back up their rationale for not following FDA requests or that they intend to generate these data. ● One reviewer raised a concern regarding retention of DMSO (dimethyl sulfoxide) in the final drug product. Based on another reviewer's experience, the FDA has accepted testing performed on the drug substance in the case of genetically-modified cells that will be frozen before administration as the drug product (except in the case where the cells are to be administered to the brain). While it would be possible to wash the cells to remove DMSO, this would result in a new drug product that would be essentially similar to the original drug substance. The amount of DMSO to be administered would be well within the critical limits for this reagent.
No: 0	● The proposed activities are feasible, though the path to achieve success seems contrived and untested in real world situations.

GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	● Although the disease is very rare, and occurs almost exclusively in White, non-Hispanic individuals, with no gender disparities, the proposal has made a point to do everything they can to reach as widely diverse enrollment as feasible. In addition, they are implementing approaches to reduce barriers to participation, such as limiting in-person clinic visits, providing financial support for travel/housing during treatment, establishing a website to create a sense of community, and providing mental health support services. ● The applicants have assembled a team experienced in working on DEI issues, working with HPP patients, and with sufficient clinical expertise. Cultural sensitivity will be provided to the clinical team as well. ● This is extensively addressed by the application within the limits of the rarity of the disease and that certain unique patient populations (Mennonite Canadians) are more affected by HPP. ● This section of the proposal is detailed and well prepared.
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: 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	5	• The applicants provide a very good data assessment, along with a focus on severity of the disease with clear awareness of financial needs and how to address underserved populations. • The applicants have a good track record in patient diversity to date.
6-8: Responsive	2	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*