APP #	TITLE	BUDGET REQ	FUND	SCORE	1	2	3	Product Type	Approach
SICKLE CELL DISEASE INITIATIVE - CLIN APPLICATIONS									
CLIN2SCD-12031	Phase 2 Study of Hematopoietic Stem Cell Gene Transfer Inducing Fetal Hemoglobin in Sickle Cell Disease	**$8,333,581**	**Y**	**1**	13	2	0	Cell and gene therapy	Gene therapy in autologuous HSC to silence beta-sickle globin and induce anti-sickling fetal hemoglobin

Application #	CLIN2SCD-12031
Title (as written by the applicant)	Phase 2 Study of Hematopoietic Stem Cell Gene Transfer Inducing Fetal Hemoglobin in Sickle Cell Disease
Therapeutic Candidate (as written by the applicant)	Autologous CD34+ cells transduced ex vivo with a lentiviral vector
Indication (as written by the applicant)	Sickle cell disease with severe phenotype.
Unmet Medical Need (as written by the applicant)	Sickle cell is a severe disease with protean manifestations. The only curative therapy is an allogeneic stem cell transplant, optimally with an HLA-identical sibling donor. However, <20% of sickle cell patients have such a donor available.
Major Proposed Activities (as written by the applicant)	• Enrollment of one patient to fill remaining slot of pilot study and enrollment of patients on continuing phase 2 study. • Development and validation of cell manufacturing in CA site to support west coast enrollment, including CA sites. • Clinical and cell manufacturing site monitoring of CA sites.
Funds Requested	$8,333,581
GWG Recommendation	*Tier 1: Exceptional merit and warrants funding, if funds are available*

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.

Score Count	15
Votes for Score 1 (exceptional merit and warrants funding)	13
Votes for Score 2 (needs improvement)	2
Votes for Score 3 (sufficiently flawed and does not warrant funding)	0

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA. Following the panel's discussion and scoring of the application, the scientific 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	• Sickle cell disease affects 100,000 people in the U.S and probably 8,000 in California and causes a great deal of morbidity and early mortality, particularly in those with sickle cell anemia (60 to 65% of SCD at birth) still doesn't have a cure. • There is tremendous unmet medical need for SCD. There is a need for potentially curative therapies.

	• Potential improvement over standard of care and addresses limitations of allogeneic HSCT and limited availability of matched sibling donor. • Yes, given the limitations with finding matched allogeneic transplants. • Excellent construct design. Highly promising pre-clinical and phase 1 clinical data. • The phase 1 trial has shown strong clinical data. If this is seen in phase 2, the trial will have significant potential to make an impact. • Multiple other novel gene therapeutics are under development for sickle cell disease.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• Scientific rationale of increasing fetal hemoglobin and thereby decreasing polymerization of hemoglobin S is supported by 40 years of pre-clinical and clinical data. • There is a strong scientific rationale for the induction of fetal hemoglobin in SCD. • The rationale for increasing fetal hemoglobin in sickle cell disease is good but likely to attenuate rather than cure the disease. • Use of lentiviral vectors to transduce CD34 stem cells is an established successful paradigm for treatment of genetic diseases. • Pre-clinical and phase 1 clinical data supports efficacy of the lentivirus vector and they have demonstrated effective collection of stem cells, preparation of vector, and production of the cellular product. • There is exceptionally strong pre-clinical and phase 1 clinical proof of concept for the therapeutic concept. The rationale is as strong as they come. • Some concerns about toxicity of preparative regimen, residual hemolysis because of incomplete amelioration of sickle cell disease, and long term efficacy and adverse effects of preparative regimen.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• Overall, the study is well planned and is poised to address the aims of the proposal. • Excellent planning of initiation and structure including using an existing clinical trials network to support multicenter clinical research infrastructure. • The phase 2 study is essential for clinical development and would bring this study including manufacturing of the the cellular product to California (and 4 of the 8 sites). • The phase 2 design is appropriate and well thought out. • 75% reduction in vaso-occlusive events (primary outcome) is a clinically meaningful reduction and greater than what is typically seen for hydroxyurea (and similar to that seen for chronic transfusion). • Some suggestions for improvements (or at least answering questions about) clinical trial raised in discussion are worth communicating to investigators and the NHLBI. However, I don't think this should require re-review by CIRM. • Waiting to have the new manufacturing process worked out prior to starting the study would certainly be preferable and result in a much cleaner data set. Every effort should be made to make that happen. • It is unclear why the applicant plans to open another academic GMP manufacturing site in the west coast. This will add greater logistical complexity and may lead to delays in a registration trial.

	• Timeline is appropriate. There was an initial concern about change in methods to manufacture the vector that was addressed in the response from the investigative team.
No: 1	• I feel strongly due to the aggressive nature of the hypothesis there needs to be a futility analysis included. • I also feel the need to suggest a parallel control group to help reduce bias in recruitment.
GWG Votes	**Is the proposal feasible?**
Yes: 14	• The applicant and the collaborators are experts in this space. They have designed a study that is both feasible and poised for success. • Likely to be completed though it may take some additional time even with a highly effective team and motivated local investigators. • The phase 1 data indicate that this therapy should be successful. • Yes, there is planned increase in the number of sites needed to execute the proposed trial. • The 8 clinical sites and central study team as well as CRO are all very experienced with access to essential resources. • Reasonable contingency plan to manage smaller risks and delays and plenty of patient interest in gene therapy to easily enroll 25 participants, so will be able to proceed with fewer sites if needed. • Only major concern is if CRO has difficultly converting vector production to non-adherent cells as this could cause a major delay. Other reviewers thought this was unlikely to be an issue.
No: 0	*none*