Application #	CLIN2SCD-11722 #2
Title (as written by the applicant)	Transplantation of CRISPR-CAS9 Corrected Hematopoietic Stem Cells in Patients with Severe Sickle Cell Disease
Therapeutic Candidate (as written by the applicant)	CRISPR corrected blood stem cells are manufactured from persons with severe sickle cell disease and returned by transplant to the same person
Indication (as written by the applicant)	Persons with sickle cell disease (adults and adolescents) with repeated, severe painful and lung events are eligible for the clinical trial
Unmet Medical Need (as written by the applicant)	Sickle Cell Disease is inherited mostly by persons in under-represented minorities. It has not received enough attention and funding. CIRM is supporting research to discover new cures for sickle cell disease. This proposal could give many more persons with sickle cell disease a chance of cure.
Major Proposed Activities (as written by the applicant)	• Prepare to enroll patients at 2 clinical sites by completing the protocol and readying the clinical and manufacturing teams. • Enroll 3 adults with severe sickle cell disease, staggering the study schedule for a safety assessment before each new patient is treated. • Enroll 3 more adults; if safety and clinical benefit are shown, enroll 3 adolescents on a staggered schedule. If promising, prepare for next study.
Funds Requested (CIRM + NHLBI)	$16,778,814 (Total cost of project is shared equally by CIRM and NHLBI, each contributing $8,389,407)
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	15
Votes for Tier 1: Fund	12
Votes for Tier 2: Needs Improvement	3
Votes for Tier 3: Do not fund	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 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	• Sickle cell disease (SCD) is fairly rare but there are still more than 100,000 people in the US that are affected. Current standard of care does not treat the root cause of the disease - a point mutation in a globin gene. There are other gene correction techniques being developed in parallel and it is not clear which will be the best approach. • The proposed gene editing clinical study addresses an unmet medical need, in particular for SCD patients with an indication for stem cell transplantation. The gene editing approach, as compared to lentiviral-based approaches, preserves spatiotemporal expression of the target gene. • SCD is a devastating disease with known expected shortened life expectancy. • Major strength of this study is an alternative method for gene correction that may prove to have benefits over lentiviral gene correction. • Elegant preclinical models and mouse models. Simple and elegant editing approach. Stable editing using in vitro and in vivo models. • This proposal has the potential of greatly impacting the lives of patients with SCD. • State of the art proposal. There are still concerns with tumorigenesis of this approach but in my opinion only clinical trials will be able to address this definitively. • Responsive to previous reviews. • Potential significant improvement over standard of care - hydroxyurea, unclear how would relate to other lentiviral based gene therapies. • I am concerned about the mutations that specifically disrupt the reading frame that promote a beta thalassemia phenotype. The ramifications of this are unclear. For example, the degree of red blood cell dependence leading to iron overload. How will this issue impact long-term survival? How will the benefit of potential SCD cure outweigh this likely complication? How will patients be advised and educated about this complication?
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 14	• The proposed study is based on sound scientific and preclinical data. The rationale is well supported by a multitude of preclinical and clinical results. • There are no concerns regarding the rationale presented. This was an excellent proposal with a high expertise team. • Yes, the rationale is sound, and they have good pre-clinical data although there are unexplained differences between male and female mice in these studies. While it is quite a different approach, recent data on gene editing in humans make it clear that the approach of gene correction can work stunningly well - another group just showed great data for a rare disease, so I am excited in general about gene correction approaches. • The rationale is sound, minor concerns about possibility of beta-thalassemia phenotype and possibility of malignant transformation cannot be excluded.

	• The applicants responded well to the comments from the prior review, and I believe overall, it is worthwhile to proceed. • No concerns or recommendations. • The presented preclinical in vitro and in vivo data of the applicants are convincing. The genotoxicity analyses are exhaustive: one off-target site was identified, with no evidence of genotoxicity based on genomic risk assessment as well as in vivo toxicology studies. • The applicants responded to a critique regarding the decrease in gene edited cells after transplantation in mice. They note that the decrement in editing frequency was observed but that this decline was not statistically significant. In the pivotal toxicology study, genotyping was performed in 100 mice, and showed a negligible decline in editing after engraftment. • Some concerns around the robustness of engraftment. • I maintain there is a real risk of treatment failure for this approach given the low engraftment in the mice, loss of CFU, and low HDR rate in CD34 cells. Is the potential failure rate different than that of allogeneic transplant which also has a failure rate due to the unique physiology of SCD? This is hard to discern.
No: 1	• Some explanation of the decreased engraftment in male mice was provided with a plan to increase cell dose to address this concern. It is still unclear if this could play a role in study participants and contribute to lower than desired engraftment of gene modified cells in some participants. • Increased myelodysplastic syndrome and/or myeloid leukemia (AML/MDS) risk is acknowledged with a plan to remediate with very limited data to support how best to do this. • Still concerned about the large proportion of indels and possibility of beta-thalassemia phenotype. This is addressed by a guidance to stop the study if this occurs.
GWG Votes	Is the proposal well planned and designed?
Yes: 15	• The study is well planned and is likely to achieve meaningful outcomes that enable further development of clinical gene editing strategies for treating SCD. • Timelines are aggressive but potentially achievable and the studies are well planned. • Well planned proposal and design. • Very good and experienced team. • No concerns or recommendations. • Efficiency of gene correction is on the low side, but they convinced me that those edited stem cells will be selected for. • There will remain a risk of damage to the edited stem cells and consequences thereof, but the testing of this approach is very important to advance this area of medicine. • Still some concern about risk for post-transplant AML/MDS based on the data from other clinical trials (2/47 with additional case of refractory anemia).

	• Secondary outcome comparing number of vaso-occlusive events before and after infusion of modified HPSC would benefit from adjudication of events and possible use of non-parametric statistical test as the population distribution of vaso-occlusive events is usually not normal.
	• They did not address my comments from the previous review: Primary endpoint is stated in three different ways. I realize it is for safety, but this needs to be cleaned up:
	  • Incidence of adverse events including failure of engraftment, malignant clonal expansion related to genomic editing or death. (I assume they mean SAEs but still too broad)
	  • The primary endpoint is the incidence of adverse events including failure of engraftment, malignant clonal expansion related to genomic editing or death, and the rate of Grade 3 or higher serious adverse events attributed to the treatment (not busulfan conditioning). (This seems most reasonable)
	  • Primary safety endpoint: one- and two-years overall survival rate will be estimated using the Kaplan-Meier curves (this really makes no sense in a study this size) The probabilities in table 6: How were they calculated?
	• While the team has outlined and described their need for resources, this application proposes a hefty budget to treat a small number of patients.
	• This study needs to be updated to the new harmonized busulfan targeting for pharmacokinetics.
	• There is no useful data sharing plan.

No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 15	• In my mind this is an excellent proposal. There is potential for malignancies to develop but additional pre-screening and clonal expansion of hematopoietic cells abrogates that to a certain extent. Whether that will lead to regulatory delays is unknown but of course that could affect the timelines. • Applicants take into account that a busulfan based conditioning regime increases the risk of myeloid leukemia. Surveillance for AML/MDS will now be conducted at baseline and after infusion. • The applicants are seasoned professionals and well qualified to conduct the proposed study. The proposed contingency plan is adequate. • They have clearly outlined their plans for outreach and implementation amongst the SCD community. • The team has deep connections with the community they serve. • They should not have problems in enrolling subjects in this trial. • No concerns or recommendations. • The facilities and expertise to conduct this trial are present.

	• It appears feasible but the effects of gene editing on the stem cells to be engrafted remain somewhat unclear. That is, they showed 20% or less engraftment and persistence in the animal models. It may require human testing to determine this. • Elegant and simple approach, though concerns remain using busulfan as conditioning. • Limited description of role of hematologists in the process. This could be particularly challenging at one clinical site with limited availability of adult SCD expertise. Key personnel include a medicine/pediatric trained pediatric hematologist at one clinical site, pediatric hematologist at the other.
No: 0	*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: 8

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.

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?
Score	**Count**	**Comments**
9-10: Outstanding	0	*none*
6-8: Responsive	4	• The applicant convincingly expresses intent, with examples, to be a strong advocate for diversity, equity, inclusion. • This proposal demonstrates an understanding of the challenges faced by individuals who are underrepresented, and an acknowledgement of the need to work to create an environment that promotes greater participation (i.e. enrollment in curative therapy trials for SCD can be slowed by barriers that include a lack of information, lack of strong connections to patients from under-represented populations and their providers that foster trust in the investigative team, inadequate outreach directed at patients and their families). • Describes multiple activities in depth, with detailed information about both their role in the activities and the outcomes. • 2018 and 2020 applicant participated in workshops or other events aimed at increasing participation in SCD trials (i.e. engaged historic faith-based institutions focused on health and social justice, local school districts, and community networks, where these partners disseminate information about SCD care and research to their clientele). • Lastly, the applicant's approach to family engagement – representation (reflecting the diversity of communities served); transparency (providing relevant knowledge and practicing partnerships that span the various phases of our projects); impact (utilizing the input of affected individuals/families in program development); and commitment (promoting

		engagement as a core value) as guiding principles – are very congruent with CIRM's strategic objectives.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*