Application #	CLIN1-13988
Title (as written by the applicant)	Genome Editing of Autologous Hematopoietic Stem Cells to Treat Severe Mucopolysaccharidosis type 1 (Hurler Syndrome)
Therapeutic Candidate (as written by the applicant)	Autologous blood stem cells edited to restore iduronidase expression
Indication (as written by the applicant)	Severe Mucopolysaccharidosis type 1 (MPS1/ Hurler syndrome)
Unmet Medical Need (as written by the applicant)	Severe MPS1 is a progressive disease without effective treatment. Allogeneic hematopoietic stem cell transplantation is used, but it is limited by the need for matched donors (causing delay/progression), insufficient disease correction, and the risks for graft-versus-host disease and graft failure
Major Proposed Activities (as written by the applicant)	• Develop process for Patient Scale Manufacturing Runs and Complete three that meet release specifications • Completion of nonclinical safety studies • Submit clinical protocol to the Institutional Review Board and file an Investigational New Drug (IND) with the FDA
Funds Requested	$5,999,919
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	13
Votes for Tier 1	13
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 project hold the necessary significance and potential for impact?
Yes: 12	• Yes, a gene-modified cell therapy for MPS1, and potentially other lysosomal storage diseases, would address an unmet need and a potentially vast improvement over current standard of care.

	• There is a clear unmet need for this disorder. The current standard of care is allogeneic blood stem cell transplantation which is associated with significant morbidity and mortality, and the amount of enzyme that can be delivered is limited. • The currently available therapeutic options are not curative. More importantly, the current options show limited efficacy and have safety concerns. The proposed treatment is likely to provide better efficacy as well as better safety. • Current treatments have limited efficacy, so a new treatment is significant. • The applicant further argues that there is little safety concern for achieving too high a dose of the enzyme. • With 40 or so patients born with Hurler's per year, this is a very small segment of the population to be impacted.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• The rationale is sound and is supported not only by the in vivo proof of concept data with the proposed construct in an animal model of disease but also the reported data in an ongoing clinical trial transplanting autologous cells with a different gene therapy approach showing positive results, including long-term engraftment in MPS1 disease. • This is a novel gene editing approach. There is reasonable data regarding this in the murine MPS1 models. • A platform study for the gene editing is significant. • Yes, the rationale from a manufacturing perspective is scientifically sound. The approach is currently being used for other diseases
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**

Yes:
12
	• The project plan benefits from a successful pre-IND meeting which outlined specific recommendations for enabling translation to the first in human trial.
	• The agency recommendations were addressed in the current proposal for the most expeditious route to the clinic i.e., executing additional studies vs. further rationalization of adequacy of available data.
	• The applicant proposes to leverage the toxicology and genotoxicity data obtained from this program for future lysosomal storage disease programs utilizing genome editing consistent with platform approaches that have recently been encouraged by both NIH and FDA.
	• The applicant has proposed further rationalization with support for optimizing potential benefit in a reconsideration of the recommended initial first in human clinical population.
	• The manufacturing portion of the program is fairly well designed. Just a few minor comments for consideration:
	  ○ For large scale manufacturing, ensure that the critical raw materials and ancillary raw materials are of the highest grade available.
	  ○ Table 3 is missing appearance, cell count, and mycoplasma testing; a later table does indicate appearance and mycoplasma. However, you will also need a total cell count (not just % viability or % CD34+ cells).
	  ○ Stability testing should include nearly all of your lot release tests, not just a select subset.
	  ○ The potency acceptance criterion will need to be quantitative, not just a fold increase. Establish a criterion based on your manufacturing data.
	• If all FDA comments are adequately addressed, the IND submission should be successful.
	• While the scientific rationale is sound, the clinical outcomes that will be assessed will likely need additional work, and the possibility of enrolling patients at the anticipated rate may be difficult.

No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 12	• The program objectives are likely to be achieved within the proposed timeline which carefully lays out interdependencies. • Successful meeting with FDA; timelines reasonable. • Internal and external resources are sufficient to execute the proposed preclinical and manufacturing plans. • Contracted vendors established.

	• The procedural basis of this, and the ability to perform the manufacturing, appears well in hand. • There will be close cooperation between the research, manufacturing and clinical teams during development and the facilities and staff are suitable to perform the proposed studies. Some of the manufacturing tasks are also similar to those in an ongoing IND study. • The manufacturing procedure is relatively straightforward and can be accomplished by an experienced team. • The tech transfer should benefit from the organization's manufacturing experience with modifying hematopoietic stem cells for other diseases. • The FDA review largely focused on the adequacy of potency assays and the applicants have agreed to add some of those suggested and to investigate the use of others, with the proviso that additional tests may be needed. The other comments on the CMC section can be easily addressed. • They do not specify the type of colony-forming unit (CFU) assays that will be used for release, nor do they specifically mention the risk that insufficient cells will be available at various stages in the manufacturing procedure. • Lot failure is cited as a risk and the current rate is 5% resulting in a 3-month delay. Scale-up is also cited as a potential risk and although additional runs are proposed in the mitigation plan, they do not state what measures they would investigate to correct the problem(s). • As there are several competing therapies in trials, recruitment of subjects will be challenging.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 12	• The applicant has presented a very comprehensive understanding and proposed plan addressing DEI. • Demographic populations were well specified in terms of DEI • They do check all the boxes, but with a limited population of patients to fulfill this directive, extensive recruitment will be necessary. • I have no concerns.
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	0	*none*
6-8: Responsive	4	• Planned activities reflect a good faith effort and have the potential to be effective in outreach and engagement. • Well characterized patient population and outreach efforts.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*