Application #	CLIN1-14006 #2
Title (as written by the applicant)	Hematopoetic stem cell gene therapy for the treatment of Tay-Sachs disease
Therapeutic Candidate (as written by the applicant)	Autologous hematopoietic stem cells transduced with a HexA/HexB expressing lentiviral vector
Indication (as written by the applicant)	Tay-Sachs disease
Unmet Medical Need (as written by the applicant)	Currently there is no cure for Tay-Sachs disease. Only palliative care is available. If successful, our therapeutic candidate will restore beta-hexosaminidase activity in the central nervous system (CNS) of affected patients and halt disease progression.
Major Proposed Activities (as written by the applicant)	• Evaluate the in vivo toxicity of HexA/HexB vector transduced cells in NRG mice including pathology, tumorigenesis, and vector copy number • Manufacture and certify a clinical lot of HexA/HexB lentiviral vector for use in a future Phase I clinical trial • Perform a manufacturing dry run for a mock drug product • Submit an IND to the FDA for a future Phase I clinical trial
Funds Requested	$4,048,253
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	14
Votes for Tier 1	14
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: 13	• A therapy that could prevent or reverse clinical symptoms would be an important improvement over standard of care.

	• Yes, the proposed drug product would address an unmet medical need and be an improvement over the current standard of care. • I was enthusiastic about this proposal initially and remain so. I think this is an important body of work and could be extremely beneficial for Tay Sachs patients.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The rationale is sound and validated by both in vitro (including patient fibroblasts and B cells) and in vivo proof of concept studies (showing phenotypic improvement) conducted to date. • There are clinical precedents of similar "cross-corrections" in the treatment of other monogenic diseases, e.g., MLD, ALD, MPS1 and AS. • Yes, the proposal is based on sound rationale. From a chemistry, manufacturing, and controls (CMC) perspective, the applicant has a proven track record using a similar process, which is scientifically sound. • Yes, the information provided in the proposal justifies continued product development.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 13	• I still continue to think this will be challenging as a single site trial but the Alpha Clinics can help with recruitment. • The assay for function of HexA is now ready to go and so I'm even more pleased with the proposal now than previously. • The project benefits from a successful pre-IND meeting with FDA and a clarifying follow-up to meeting that provides a very clear roadmap to support a successful IND. • The proposal includes a specific discussion on the value added of the secondary transplantation study in NRG mice to assess tumorigenicity. While the final recommendation was that the investigator 'could provide a justification for not doing the study' there is some risk in what would be 'acceptable preclinical data to address their concerns' as arguments were previously made. As such the study will be conducted as requested in the original meeting minutes. The study as designed will allow for two assessments of VCN at 4 and 6 months. • From a CMC perspective, the project is well planned. The manufacturing design, including timeline and budget, appear acceptable. I recommend that the new CliniMACS instrument should be purchased early in Year 1, in order to receive, install, qualify, and train personnel prior to use for cell manufacturing.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 13	• The trial appears feasible, although I do have doubts about the enrollment timeline and whether the recruitment strategy is sufficient. • The objectives and milestones should be achievable. • The applicant has a demonstrated performance record based on previous CIRM grants. • Yes, the project appears highly feasible from a CMC perspective. The applicant has experience in the manufacture of lentiviral vector and gene-modified cell therapy product, which bolsters the feasibility of a successful project. The FDA written requests for CMC appear to be manageable at the IND stage, and there are no deal-breakers. I encourage the applicant to ensure that all CMC responses are addressed. In addition, while the current program can proceed with a 3-plasmid system, I encourage the applicant to move to a 4-plasmid system in the future. • This proposal will use autologous, genetically corrected, hematopoietic progenitor cells (HPC) to correct the deficiencies in the HexA gene that cause Tay-Sachs disease. They will use a HexA/HexB-expressing lentiviral vector to transduce autologous CD34-enriched HPC, based on previous promising CIRM-funded pre-clinical studies in mice. • The lentiviral vector will be produced at the institution's GMP Facility using a 3-plasmid system. I was unable to find much information about the production method and testing of the vector, apart from single paragraphs on pages 30, 55 and 84 of the redlined version of the proposal, which states the facility's experience in making vectors and some of the testing. This is in contrast to other CIRM applications from this institution, where this information was well presented. • The FDA recommended a 4-plasmid manufacturing approach, but the applicants appear to have convinced them that a 3-plasmid system is acceptable.

	• There were very few other questions from the Agency regarding vector manufacturing and release. This will start after completion of the in vivo toxicity studies and is expected to take 3-4 months including testing. This seems short for production and testing of a clinical vector lot. The applicant states that they have not encountered any problems with previous manufacturing runs of clinical vectors. I am, therefore, assuming that vector production is in good hands. • The manufacturing of the drug product is well described and employs a widely used protocol for CD34-positive cell enrichment and for transduction. The release testing is described and expected ranges are provided. • Their experience with previous manufacturing of transduced CD34-positive cells also predicts no problems (1% failure rate) that could not be addressed by performing a second apheresis. • They state that there is a 48-hour window after receipt for product administration, but I do not see any stability data for the frozen or thawed products. • They also do not foresee problems with the supply chain, although several critical supplies are available from only one vendor. • I could not find a discussion of quality review during manufacturing, testing and release. • Failure of a GMP manufacturing run is mentioned as a potential risk but it is not clear if this applies to the vector or the drug product. Both are, however, discussed in later sections. • Although I would have liked to see some additional information on the vector manufacturing and testing, I (and for the most part the FDA) feel comfortable that this facility has the experience to manufacture the lentivirus. • They are also experienced in producing transduced CD34-positive cells, so I feel that the manufacturing section is adequate.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 13	• Given the genetic predispositions of this disease, the group described the DEI challenges and potential outreach opportunities quite well. • On this presentation the team described quite fully the extensive outreach and DEI activities undertaken by the institution. Quite impressive. • Improved from the initial submission. • The DEI section has been strengthened. • Much improved. • Excellent improvements.
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: 7.5

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	• Yes, in this submission, the group described the special genetic challenges presented for Tay-Sachs and how they would approach these. I was impressed by the careful detailing of the sub-categories of effected populations such as French Canadiens and Cajuns.

		• The outreach and DEI activities undertaken by the institution are extensive and impressive. • Addresses the DEI components and the potential to impact other neurological conditions that impact the broader community.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*