Application #	CLIN2-14338 #2
Title (as written by the applicant)	Autologous T Cells to Treat Refractory/Relapsed Pediatric Liver Cancer
Therapeutic Candidate (as written by the applicant)	Engineered T-cell therapy whereby autologous T cells are modified to target and kill cancer cells positive for specific markers.
Indication (as written by the applicant)	Pediatric subjects aged ≥ 1 year to ≤ 21 years who are positive for specific cancer cell markers and have relapsed/refractory (r/r) hepatoblastoma (HB), Hepatocellular malignant neoplasm not otherwise specified (HCN-NOS), or hepatocellular carcinoma (HCC).
Unmet Medical Need (as written by the applicant)	There is no approved therapy in any line of treatment for any form of pediatric liver cancer. The candidate T-cell therapy has great potential to improve the prognosis and survival outcome of pediatric subjects with r/r HB, HCN-NOS, or HCC and replace chemotherapy which has severe lifelong side effects.
Major Proposed Activities (as written by the applicant)	• Complete Phase 1, assess clinical safety and tolerability of [candidate] T cells and determine the recommended phase 2 dose. • Activate a clinical site at a California Institution. Promote trial awareness, DEI-focused outreach, enrollment, and retention efforts. Support trial operation. • Manufacture the T-cell product to supply the proposed trial. Manufacture a lentiviral vector lot to supply the proposed trial.
Funds Requested	$10,600,072
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	14
Votes for Tier 2	1
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: 14	• Pediatric liver malignancies have poor prognoses, low survival, and no FDA-approved treatments. The resubmission has updated information about the frequency of these malignant liver tumors in children. Overall, the potential market size is ~ 80 children per year in the US. • There is an unmet need for pediatric liver cancer. • Yes, but the impact would be limited to a small number of patients and will be in the setting of multiple other competitors. • Because of the lack of any FDA-approved treatments, the value proposition is clear here. But because these diseases are ultra rare, the commercialization and profitability remain questionable.
No: 0	• If the treatment is safer in children than other therapies, then the project has the potential to be impactful. • There are better options in clinical trials, and with the small number of pediatric patients in the US, commercial success in questionable. • The accrual of participants is a primary concern given the competition with other hepatic carcinoma studies in progress.
GWG Votes	**Is the rationale sound?**
Yes: 13	• The applicants have an FDA-cleared IND with sound scientific rationale. Preliminary data from clinical trials (adult and pediatric) support continued development. No significant adverse events and dose-limiting toxicities have been observed so far. Manufacturing was feasible with a 100% success rate. • The resubmission includes a strong rationale for the pediatric clinical trial and provides detailed data from the first patients treated in the adult clinical trial. • The scientific rationale is sound. • Given the current results presented and the known competition with cell therapy products that are manufactured from allogeneic sources and are off-the-shelf, it is questionable whether the findings are sufficient to support funding at this time. • The commercial rationale is not convincing. • There are concerns that this therapy could lead to off-target toxicity in placental tissue, and other late effects.
No: 1	• There is still no real proof of efficacy in adults. It is challenging to support progressing to children without adult efficacy data, particularly when there are no longer term safety data.
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• The overall project is appropriately planned. • The planning is appropriate to provide the best chance of success. • The applicants did a very good job responding to concerns regarding their patient and dose review governance. • The resubmission provides information about (i) comparability studies and (ii) non-compliance with GLP toxicology. The applicant explains that the plan and results of the comparability study assessing process 1 vs. process 2 were available. The comparability study between sites, which will include process automation, is planned for the future and not written at this time. • The project is feasible but anticipates a long clinical trial duration. This raised the question of whether the time to outcomes should be a factor when considering funding for this program. ◦ On the plus side, the ability to follow participants for the anticipated duration may contribute to understanding this disease. • A GLP toxicology study was not conducted, and the applicants justified that this was due to a lack of a relevant animal model. FDA has accepted this explanation. • Yes, but toxicity studies should be performed. This should have been undertaken in transgenic mice expressing one of the target markers. Alternately, the applicants should have engineered a suicide gene in the T cell therapy, particularly given the tremendous concern for off target toxicity on placental tissue and late effects.
No: 0	*none*
GWG Votes	**Is the project feasible?**

Yes: 13	• The timeline and feasibility are very dependent on the patient accrual rate. A small number of patients have been treated in the trial already. The applicants feel confident that they will able to accrue the remaining patients in the provided time frame. • The team is qualified to perform the work. A contingency plan and risk mitigation are present in the project. • Enrollment will be a challenge and is expected to take several years. Because of this bottleneck, it is advisable to establish milestone payments based on the number of patients successfully enrolled during the funding period, which will also account for the fact that the trial is actively enrolling. • There have been no changes to the manufacturing section in the revised proposal, and it is still acceptable.
No: 1	• It is unclear whether the applicants can feasibly show outcomes in a reasonable amount of time. Because longer studies require more funding, this calls into question the need and ability to raise funds throughout the full clinical development phase. • The feasibility of recruiting is not clear. Based on the patient population, there are 80 possible patients available for recruitment in the timeframe of this grant. It is unclear if the applicants will be able to recruit their target number from this very small population. There are also not enough data available to evaluate how many potential patients might be excluded by the exclusion criteria and requirement to express the markers that this therapy targets.
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• The selected Project Manager demonstrates a greater understanding of how a targeted DEI effort can uphold the principles of DEI. For example, the Project Manager is working on establishing a questionnaire to help the applicant address the social determinants of health and identify variables that burden trial participation. • The Project Manager will also engage the American Society of Clinical Oncology regarding their Trials Participation Initiative to increase the participation of underrepresented populations in clinical trials by providing education and resources to patients and their communities. • Yes. The resubmission provides more information related to DEI. • The applicants have a well defined DEI plan. • The project excellently upholds DEI principles. • It is unclear if applicant will achieve enrollment milestones as identified in the application.
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	6	• The planned activities reflect a good faith effort and have the potential to be effective in outreach and engagement. • The applicants provide a strong DEI response • The applicants have a documented commitment to underserved populations afflicted by this condition. Their partnership plan is an additional DEI strength.

		• The applicant plans to establish a patient advisory board and/or community steering committee to provide input and feedback. The groups should help the applicant identify additional community organizations they could partner with and provide insights into effective outreach strategies. • The applicant plans to deploy a patient-centered website and YouTube channel to ensure it contains diverse imagery, and lay language, and that videos are offered in multiple languages to reach a diverse patient population.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*