Application #	CLIN2-12563 #2
Title (as written by the applicant)	Phase 1/1b study of an immunotherapy cell infusion after HLA-partially matched αβdepleted-Hematopoietic Stem Cell Transplantation (HSCT) in children and young adults with hematologic malignancies.
Therapeutic Candidate (as written by the applicant)	An immunotherapy cell product that is enriched for specialized immune cells called type I regulatory T (Tr1) cells
Indication (as written by the applicant)	Children and young adults with relapse/refractory acute leukemia receiving a specialized stem cell transplant
Unmet Medical Need (as written by the applicant)	Hematologic malignancies are the most common cancer in children and young adults, and current treatment options do not offer long-term cure. We propose that post-αβdepleted HSCT infusion of an immunotherapy cell product will improve the probability of being alive and disease free, thus addressing an unmet medical need.
Major Proposed Activities (as written by the applicant)	• Determine recommended Phase 2 dose (RP2D) of the cell product for for high risk patients with hematologic malignancies receiving αβdepleted-HSCT • Evaluate the safety, and explore the potential for clinical efficacy of infusion of the cell product at the RP2D (or highest dose) after αβdepleted-HSCT • Perform immune monitoring to establish immune criteria that predict successful patient outcomes.
Funds Requested	$11,996,634
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	15
Votes for Tier 1	15
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 proposal have the necessary significance and potential for impact?
Yes: 13	• Identification of a safe and efficacious method to improve immune reconstitution after myeloablative allogeneic transplantation is highly needed for patients with high-risk leukemia and lymphoma. Post-transplant relapse and infections top the list of transplant failures. • This proposal provides and unmet need and a significant value proposition for patients with high-risk leukemias/lymphomas requiring transplantation for cure. • The applicant has done an excellent job of addressing the CIRM grants working group comments. This application is much stronger than the initial application and has the potential to generate significant and impactful clinical data. • The applicant was diligent at addressing all previous reviewer comments and providing explanation of those comments/suggestions that were not easily addressable. • The project combines two interesting approaches that may be synergistic. • The applicants are doing pioneering work on Tr1 cells. Should learn something from this project. • Although the value estimate may be overstated, it is worth pursuing as knowledge gained is likely to drive down future costs.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 13	• The preliminary data and rationale are strong. • Yes, the rationale is sound. • The applicants did an excellent job describing their process of distinguishing significant adverse events and the extensive thought that went into their regulatory process. I no longer have concerns. • They appropriately addressed why they chose the time point for the cell infusion. • Edits to background including other methods of performing haploidentical HSCT are adequate.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 13	• Concerns were addressed in a thorough and thoughtful response. • Good response to previous comments from reviewers. • Yes, the proposal is well planned and designed. • I am OK with 3+3 design and it is not worth pushing further. And while the reference to the 2008 paper was useful they should note this was followed by a paper in 2014 by the same author indicating model based adaptive designs are preferable.
No: 0	*none*
GWG Votes	**Is the proposal feasible?**
Yes: 13	• Yes, the proposal is feasible. • Excellent team with resources to carry out the project. • Project appears feasible. Significant expertise, facilities, and leadership to make this project successful. • Expert Data and Safety Monitoring Committee and excellent letters of support. • Multiple correlative studies proposed to provide potential mechanisms to support efficacy. • The protocol itself is feasible, however I'm not sure how this ultimately reaches a significant number of patients due to cost, complexity, and an unclear path to marketing approval and

	commercialization. The study will add to our understanding in the field, but much more thinking will be needed to turn this therapy into a product.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• Yes, the project serves the needs of underserved communities. • Well-addressed in the section on the study population. • Application of this prophylactic intervention after alternative donor transplantation increases access to underserved populations impacted by fewer donor options. No concerns.
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: 9

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.

Score	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?
9-10: Outstanding response	2	• Applicant stated that 70% of patients are non-White. 38% of the patients are projected to be female which is consistent with the cancer type under investigation. • They have improved their outreach from the previous review.
6-8: Responsive	2	• Strong outreach, mentor training, across School of Medicine Inclusion programs, first in their families to attend college team members.
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*