Application #	CLIN2-14024
Title (as written by the applicant)	Sequential same donor αβdepleted-hematopoietic stem cell transplantation (HSCT) from a Human leukocyte antigen-partially matched donor allowing immunosuppression free kidney transplant
Therapeutic Candidate (as written by the applicant)	Mobilized peripheral blood stem cells from allogeneic donors depleted of TCRαβ+ T cells/CD19+ B cells
Indication (as written by the applicant)	Renal failure due to one of four genetic and/or immunological diseases
Unmet Medical Need (as written by the applicant)	Our same donor sequential αβdepleted-HSCT kidney transplantation strategy addresses the urgent unmet medical need to abrogate the need for post-kidney transplant lifelong immunosuppression, the risk of chronic rejection, and, ultimately, the need for repeated transplantation.
Major Proposed Activities (as written by the applicant)	• Perform αβdepleted-HSCT and achieve complete donor engraftment without severe graft versus host disease • Perform post-αβdepleted-HSCT kidney transplantation and discontinuation of the immune suppression within 90 days post-kidney transplant • Develop a closed system for production of αβdepleted-HSC to expand the number of facilities able to provide αβdepleted-HSC manufacturing
Funds Requested	$11,998,188
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 project hold the necessary significance and potential for impact?
Yes: 14	• Tolerance in pediatric kidney transplantation is a relevant clinical goal that represents an unmet need. • The approach is based on existing and published experience in pediatric kidney transplant recipients that are currently off immunosuppression. • This treatment could provide a relatively easy way of improving outcomes of kidney transplant in pediatric and young adolescents, by essentially eliminating the adverse effects of graft rejection, lifelong immune suppression, and the requirement for subsequent kidney transplants. This could improve the current median graft survival of 19.2 years for organs obtained from living donors. The use of a stem cell transplant could also cure the immune condition associated with rare kidney diseases. • Strong unmet need that has the potential for big impact in kidney transplant. • The applicants present a tremendous potential cost savings over existing treatments e.g., savings of over $222M in California in a single year. • An interesting idea and would have a major potential for improving the patient's quality of life and reduce health care costs. • A major strength is tolerance demonstrated in a few patients and a critical unmet need. • A concern is 25% severe graft versus host disease (GvHD) and historically 40% with non-malignant disorders. • Despite the applicants stating that the graft manipulation could be easily performed in other centers using a closed system device, I doubt whether it would be likely to be performed outside a Good Manufacturing Practice (GMP) facility.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 14	• They have treated several patients already with success. This study will expand on these trials and include additional indications. • The project is based on a sound rationale. Request for a support of a phase 1b study builds logically on existing data. • Data from ongoing work is supportive of outcome. • The applicants cite a study involving a few patients in which pre-kidney transplant of an alpha beta/CD19 depleted apheresis product resulted in normal renal function and withdrawal of immune suppression. They also have re-transplanted a patient who is also off immune suppression but suffered from severe GvHD. This patient is rejection-free with normal renal function at 7-month post kidney transplant. • They cite the superiority of this method of hematopoietic graft manipulation over pan-T cell depletion or CD34 selection with their increased risk of post-transplant infections. Depletion of alpha beta/CD19 cells has resulted in no deaths from acute GvHD in a cohort of 70 patients and 90% overall survival in patients with non-malignant disease. Mention is made of pre-clinical experiments in immune deficient mice which could be engrafted with human depleted apheresis cells without xenograft GvHD. Longer term human studies using alpha beta/CD19-depleted grafts have shown high levels of engraftment (98%) without any acute GvHD and <10% chronic GvHD in the recipients. Results from the applicant's own institution show similar results for chronic GvHD, but a 28% incidence of acute grade II GvHD. One patient with beta thalassemia failed to engraft. • On balance the previous clinical experience of the applicants with the proposed approach in terms of achieving normal renal function and withdrawal of immune suppression seems worthy of further investigation despite a possible risk of increased acute GvHD. There is a known risk for failure to engraft in beta thalassemia, so this risk is likely to be less in patients with kidney disease. • Mortality for Stage III or IV GvHD can reach up to 90% in severe cases; approximately 50% can develop chronic GvHD. The investigators should report results on the number and severity of GvHD for interim review. • There is still concern for GvHD.
No: 0	*none*
GWG Votes	**Is the project well planned and designed?**
Yes: 14	• This proposal is well written and constitutes a logical proposal. It is based on good clinical data using alpha beta/CD19-depleted hematopoietic grafts in other diseases not involving a subsequent solid organ transplant, and on some preliminary studies in a few patients who

	went on to receive kidney transplants. There is no pre-clinical data using animal models for this exact proposal, but this was acceptable to the FDA. The applicants have described the risks of the clinical procedure and proposed good mitigation strategies. • The clinical protocol appears well designed. The team is well experienced, and the facilities are excellent. • There is a manufacturing plan in place and the clinical team has a proven track record. The experiments are focused on a small number of patients that will be carefully evaluated and followed. • Well thought out clinical plan for a few initial patients and potential for a subsequent number of patients. • Well written and logical study.
No: 0	*none*
GWG Votes	**Is the project feasible?**
Yes: 14	• The application has a clear and focused outline and is feasible. The team is highly qualified. • Good evidence to support feasibility. • The manufacturing procedure for the alpha/beta/CD19-depleted graft has been widely used at several institutions and is familiar to many GMP facilities, including that of the applicant. As far as I can determine the IND application describes use of a cell concentrator and a cell separator which are pretty much the standard procedure. • The manufacturing section is well written. The GMP staff are experienced in the method to be used, cryopreservation and thawing, release testing of the product. The facility is FDA registered, state licensed, Foundation for the Accreditation of Cellular Therapy (FACT)-accredited and is of adequate design to perform the studies. The proposals for addition of a second depletion and/or collection of a second apheresis product are appropriate. The quality control/release testing is also appropriate, as are the additional characterization studies. • The details of transportation of the starting material and finished products are well described. The applicants correctly identify a risk as the potential unavailability of the separation products from a supplier. They indicate that this would result in a time delay. They correctly identify possible mitigation strategies. They have also allowed for one failure of manufacturing of the product in their application. • There may be some issues to ablate the immune system and issues with GvHD in some of the expanded disease indications they propose to move in to, but these are risks are known.
No: 0	*none*
GWG Votes	**Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?**
Yes: 14	• There is a comprehensive section on Diversity, Equity and Inclusion that deals with likely recruitment ratios, statistical analysis of the potential patient population by race and gender, gender identity issues, engagement with the community and outreach to various alliances and groups. • Project upholds principles of DEI. • Well considered.
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: 9

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	5	• Convincingly and clearly describes how the success of this project would lead to a therapy that positively impacts underserved or disproportionately affected communities. • Well-characterized patient population and outreach efforts. • Great comprehensive overview of needs, mechanisms to accomplish them and demonstrated performance in past trials. • Good marshalling of data related to demographics of disease and direct experience at the institution for 200 patients and a cohort of under 20 patients even though this initial work is on a few patients where immediate demographic impact will be limited by the small number on the trial. • In general, better than population percentages evidence for pulling in lower socio-economic patients and good acknowledgment of financial resources required to support the study. Included are stays at Ronald McDonald house, child/pet care, transport costs, call center and a patient navigator. • Good catchment area draw, ability to support 40 languages, 5th grade level materials for easier comprehension, Lucille Packard experience. • Excellent community outreach programs including non-profits. • Operating under programs representing Health Equity and Justice Equity Diversity and Inclusion.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*