Application #	CLIN2-13259
Title (as written by the applicant)	Phase 1 Study of Autologous CD4LVFOXP3 in Participants with IPEX Syndrome
Therapeutic Candidate (as written by the applicant)	CD4+ T cells that have undergone lentiviral-mediated gene transfer of Forkhead Box P3 (FOXP3) and acquired regulatory T cell function
Indication (as written by the applicant)	Immune dysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) syndrome
Unmet Medical Need (as written by the applicant)	IPEX has early severe onset and is a serious clinical challenge. Pharmacological immunosuppression can only partially control autoimmune manifestations and does not prevent organ damage. Allogeneic hematopoietic stem cell transfer (HSCT) can cure the indication, but lack of suitable donors and transplant complications lead to inferior outcomes.
Major Proposed Activities (as written by the applicant)	• Evaluate feasibility and safety of CD4LVFOXP3 infusion (primary objectives) • Explore the potential for clinical efficacy of CD4LVFOXP3 infusion for clinical disease manifestations (secondary objectives) • Perform immune monitoring studies to establish immune criteria that predict successful patient outcomes.
Funds Requested	$11,999,179
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	14
Votes for Tier 1	13
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 proposal have the necessary significance and potential for impact?
Yes: 13	• This proposal aims to use T regulatory (Treg) cells to treat Immune Dysregulation Polyendocrinopathy X-linked (IPEX) syndrome which is caused by the loss-of-function FOXP3 mutations which result in dysfunctional Treg cells. This condition occurs in male patients, is discovered primarily in the first year of life, and is rapidly fatal. Symptoms include development of Type I diabetes, enteropathy, severe eczema, nephritis and severe failure to thrive. It is a rare disease with an estimated 330 patients in the USA. Current treatments are immune suppression (steroids, which do not affect disease progression) and/or allogeneic stem cell transplantation (which may be curative, but may have higher rates of mortality). • The proposed therapy involves the administration of autologous T cells transduced with a lentiviral vector encoding the wild type FOXP3 (CD4LVFOXP3). These are functionally equivalent to normal Treg cells. The therapy would be used to control disease manifestations and as a bridge to allogeneic stem cell transplantation or could even offer an alternative curative treatment. • The proposed treatment offers a promising therapy for IPEX by providing a population of functionally normal Treg cells. It would avoid the complications of lack of donors, graft-versus-host disease and the numbers of infused cells can be controlled in vivo by the administration of basiliximab. The product also contains a marker that can be used to track the cells following infusion. The product can be manufactured using conventional technology and can be stored cryopreserved. It is easy to administer and should be available at a reasonable price. It would, therefore, meet an unmet medical need. • The study addresses an unmet need in a rare population of children and adolescents. However, to optimize impact, the interpretation of severe adverse events (SAE) as disease limiting toxicity (DLT) should include all SAE, especially those related to the listed SAE of special interest. Late DLT should be considered by the data safety monitoring committee (DSMC) with respect to planned dose escalation. • This approach could have a major impact on IPEX. It isn't clear whether this therapy could impact more complex autoimmune disorders. • IPEX is a rare indication but this project is expected to aid in the development of similar technologies for other indications. • Some potential to inform therapeutic approaches in related indications. • A lethal autoimmune disease. Incomplete cure even with BMT. • Area of high unmet need.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 13	• This therapy proposes to replace a dysfunctional Treg cell population with genetically-corrected autologous cells. This avoids the risks associated with immune suppression and allogeneic HSCT. It would also provide a potential treatment for IPEX patients without a matched or partially matched stem cell donor. • The proposal describes a complex enrollment target scheme for a rare clinical indication, but it's likely doable given the expertise and experience of the team. • The proposal is underpinned by robust proof-of-concept data supporting the scientific rationale. • The applicants cite studies showing that IPEX is the direct result of malfunctioning Treg cells and that replacement of 10% of this Treg population is sufficient to control autoimmunity. • The applicants state that the corrected cells contain healthy FOXP3 and and NGFR. The latter marker can be used both for cell selection during manufacturing and for tracking the corrected cells in vivo. This is an attractive feature of the study. • The applicants state that there have been no clinical studies using a genetically-corrected product, but that infusion of CD4+CD25+ cells is both safe and feasible with

	no graft versus host disease (GVHD) in the recipients. There have also been reports of decreased disease relapse in the recipients. Treg cells have been used with some success to treat Type I diabetes.
	• The applicants have used a mouse xeno-GVHD model to show that their cells increased survival of the animals and reduced weight loss due to GVHD. They also demonstrated in this model that the CDLVFOXP3 cells induced a state of tolerance and/or resistance to subsequent re-challenge. A FOXP3 knockout mouse model was used to show that the administration of the cells restored cellular suppressive capacity and that the response was dose-dependent. Importantly, the suppressive function of the therapeutic cells does not interfere with the expected immune responses against infectious agents and malignant cells.
	• The rationale is the delivery of a critical gene; this would be a first in human use of T regulatory cells to treat genetic disease. My concerns are
	  • There are limited data showing that the gene therapy will work in cells of IPEX patients.
	  • The gene will be unregulated after delivery.
	  • Lymphopheresis (the collection of blood cells at the outset of the procedure) is challenging in infants.
	• Excellent preclinical data.

No: 0	*none*
GWG Votes	Is the proposal well planned and designed?

Yes:
13
	• Yes. However, there are potential delays based on low disease prevalence and challenges with recruitment. Applicant could consider broadening inclusion and exclusion criteria as much as possible to support enrollment and in this way prioritize generation of clinical data (even if imperfect) to inform next steps.
	• This proposal contributes to rare disease therapeutics. Unfortunately, plans for data sharing are insufficiently described.
	• The GMP manufacturing plan is satisfactory. It involves (i) collection of patients' autologous cells by apheresis; (ii) selection and cryopreservation of CD4+ T cells; (iii) thawing and activation of the CD4+ cells followed by lentiviral-mediated gene transfer of the wild type FOXP3 gene; (iv) culturing, selection and activation of CD271+ cells; (v) final cryopreservation. The entire manufacturing time is 20 days, with preliminary bacterial and fungal sterility results available on Day 3 and final results on Days 14 and 42.
	• Release assays are documented and meet the usual requirements, including measurement of suppressive potency in a mixed culture system.
	• The applicant will manufacture single lots for 20-36 patients. A concern is that manufacturing has not yet been tested using IPEX cells. The reason for this is evidently due to the scarcity of these patients. IPEX CD4+ cells may prove difficult to collect or handle.
	• There are some gaps in the GMP manufacturing plan.
	  • There is no description to inform whether enough CD4+ T cells can be obtained from IPEX patients by apheresis and immunomagnetic selection.
	  • Reagents are not described for immunomagnetic cell selection, or for selection of CD271+ cells at a later step.
	  • There is little mention of the manufacturing and testing process for the lentiviral vector to be used, nor where or by whom the vector is manufactured. Apparently, this information was provided to the FDA to support the IND.
	  • There is no mention of thawing the transduced cells or an assessment of their stability in vitro during storage and after thawing. This may be necessary in the clinical trial given the scarcity of patients.
	• The study team has an excellent reputation for conducting human clinical studies.
	• The clinical trial will primarily aim to determine (i) the feasibility of GMP manufacturing the product; (ii) the safety and MTD for administration; and (iii) the pharmacokinetics and pharmacodynamics of the infused product.

	• Yes. However, FDA has asked that the applicant review all DLTs and not just those thought to be related to treatment. This seems clear in charter but the protocol is still a bit ambiguous. The plan for sharing individual participant data is not clear. • Good clinical trial design.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 13	• Overall, yes; but recruitment for this trial will be challenging. • The clinical trial will enroll 20-36 patients over four years. The risks of not achieving this goal are discussed under the Risk Mitigation section of the proposal. The applicants propose to offer travel and lodging expenses and to use the Primary Immunodeficiency Therapeutic Consortium (PITC) to optimize enrollment. • A major concern is recruiting the right ages of patients for the specific phases of the study, but this is addressed in the section "Expansive Recruitment Strategy" where a table of current recruitment is provided and mention is again made of using the PITC to aid recruitment. A graph of projected patient enrollment is, however, provided and the Program currently has 17 patients enrolled in its research protocol although all but four of these are >12 y/o at the time of evaluation. • Overall, yes. The extant concerns are about obtaining sufficient total CD4+ T-cell content from IPEX patients, along with subsequent Treg functionality and potential Treg exhaustion. • Given concerns about obtaining enough starting CD4 cells, the applicant might consider not cryopreserving after CD4-enrichment. • I concur with the concerns about obtaining sufficient cells for manufacturing, but the applicants are experienced and are well positioned to respond to potential issues. • The investigators are all named and are experienced. The Principal Investigator (PI) is a world leader in IPEX syndrome and Treg cells. The PI has been involved in dissecting the role of these factors in disease. The role of each investigator is well described and the working environment is excellent. • Clinical trial risks include (i) hypersensitivity reactions to administration of the product and unexpected prolonged immunosuppression - the applicants propose to use dose alteration and basiliximab to counter these risks; (ii) reliability of study data; (iii) product contamination during manufacture - addressed by experience and training of staff; (iv) reagent or supply shortage - addressed by pre-ordering; (v) failure to collect or select sufficient numbers of cells - applicants plan a second apheresis; (vi/vii) lot or equipment failure - they have purchased a second Prodigy, and viii) failure to meet patient dose - addressed by manufacturing multiple lots. Funds for mitigating these risks are described. • The data sharing plan is acceptable.
No: 0	*none*
GWG Votes	Does the project serve the needs of underserved communities?
Yes: 13	• It is not known whether recruiting suitably-aged patients over selected time periods will be truly feasible. The PI has numerous national and international contacts who can help with enrollment. These include a number of foundations in Europe and North and South America. Apart from its exclusive incidence in males, IPEX shows no ethnic or socioeconomic bias. • The currently enrollment trial participants are an ethnically diverse group. The proposal states that no patient will be excluded due to inability to pay or socioeconomic, ethnic or language barriers. • The institution has a number of programs fostering anti-racism, diversity and equity. The laboratories involved in this project employ several first-to-college staff. The applicants also plan to recruit at least one CIRM Bridges scholar. The group has developed an internship-to-career program in the GMP Facility to train students wishing to enter this field of research. This GMP internship-to-career programs aims to recruit up to 6 scholars by its second year.

	• This is a very strong plan.
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: 9.5

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	4	• This is an extremely strong, nearly ideal submission with respect to DEI. The applicants' commitment to the principles of DEI is manifest in the study catchment area, community focus, translation for 40 languages, and plans for mitigation of social economic barriers. The institution offers a Pediatrics Advancing Anti-Racism Coalition; Inclusion, Diversity, Equity in a Learning Environment (IDEAL) program, and training with Health Equity Advanced through Learning (HEAL). • The applicant's inclusion of first-to-college team members, conduct of an anti-racism book club, and teaching of undergraduate and graduate classes on how demographics may influence disease condition, also demonstrate the applicant's clear awareness of DEI. • The proposal references institution's focus on enrolling people who are low-income, uninsured, migrant and seasonal farmworkers, experiencing homelessness, and racial and ethnic minorities. These seem to me to be very forward thinking. I don't think I've ever read a reference to the homeless population as a sub-population needing to be accounted for in trials.
.6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*