CLINICAL

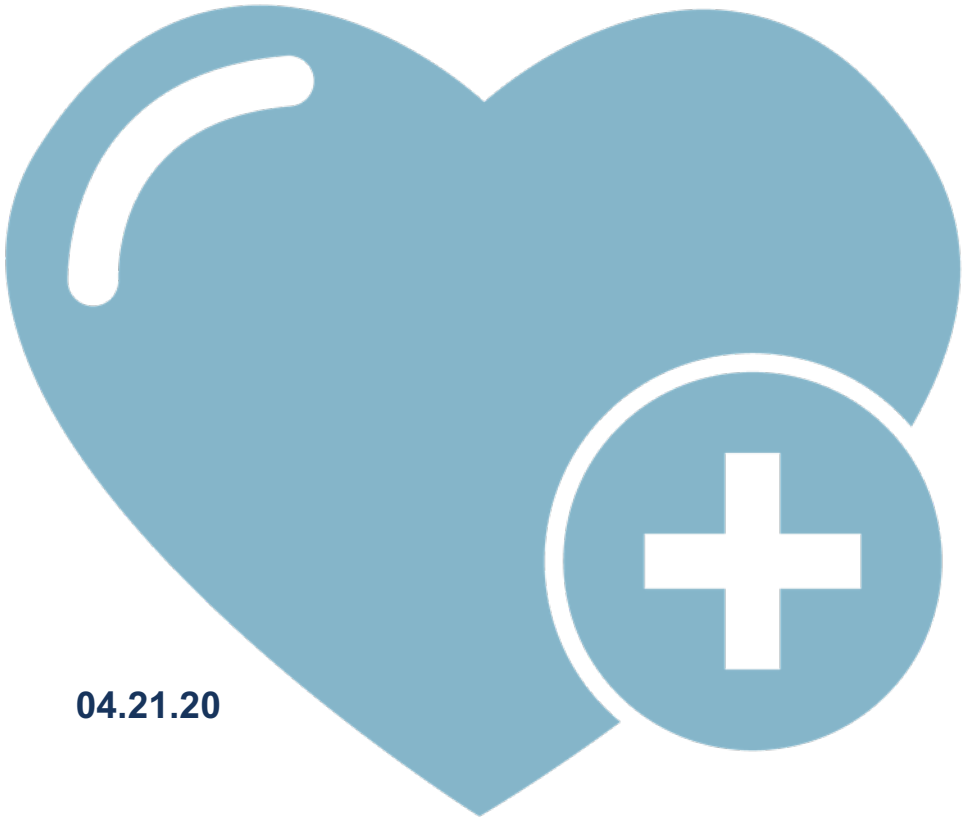
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

A Phase 1 Study of ECT-001 Expanded Cord Blood and Myeloablative Regimen with Reduced Toxicity in Patients with Severe Sickle Cell Disease.

Application Number: CLIN2SCD-11674 (Revised Application)	Review Date: 13 April 2020

Clinical Trial Stage Project Proposal (CLIN2)



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A Phase 1 Study of ECT-001 Expanded Cord Blood and Myeloablative Regimen with Reduced Toxicity in Patients with Severe Sickle Cell Disease.

APPLICATION NUMBER: CLIN2SCD-11674 (Revised application)

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

ECT-001 graft contains more stem and immune cells than conventional cord blood graft, leading to prompt recovery and better outcomes for patients.

Indication

Severe Sickle Cell Disease

Therapeutic Mechanism

Hematopoietic stem cell transplantation is the only cure for severe sickle cell disease. The ECT-001 expanded cord blood cells will replace the patient's sickle red blood cells with healthy cells.

Unmet Medical Need

African-Americans are the most affected by sickle cell disease. Unfortunately, donor availability for this specific population is very limited for standard bone marrow transplantation. The usage of cord blood unit with sufficent cell doses would eliminate the donor availability problem.

Project Objective

Complete a Phase 1 Trial

Major Proposed Activities

- Manufacture product to supply the proposed trial
- Assess clinical safety and efficacy

Funds Requested

$2,000,000 ($857,143 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 15 GWG members

Votes for Score 2 = 0 GWG members

Votes for Score 3 = 0 GWG members

- 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.

Review Overview

This application proposes the utilization of expanded cord blood as a treatment for sickle cell disease (SCD). As donor-matched cell transplantation for SCD is limited by donor availability, the use of this product could expand the use of hematopoietic stem cell transplantation (HSCT) as a treatment option for SCD patients. This proposal was a resubmission that had undergone two prior reviews. In prior reviews, concerns were raised regarding the data presented in support of the proposed product, safety concerns regarding the inclusion criteria, as well as adequacy of the T cell dose. The applicant responded in subsequent resubmissions with additional data from the scientific and clinical literature, a publication using the product in prior trials, modifications to the protocol as requested, as well as IRB approval of the protocol from their institution. Overall, the reviewers thought the applicant responded well to prior concerns, and thus the GWG voted unanimously to recommend the application for funding.

Review Summary

1. Does the project hold the necessary significance and potential for impact?

YES	**15**	**NO**	**0**

Reviewers considered the following:

a) Whether the proposed treatment fulfills an unmet medical need.

b) Whether the approach is likely to provide an improvement over the standard of care for the intended patient population.

c) Whether the proposed treatment offers a sufficient value proposition such that the value created by it supports its adoption by patients and/or health care providers.

d) If a Phase 3 Trial is proposed is the therapy for a pediatric or rare indication or, if not, is the project unlikely to receive funding from other sources?

Summary of Reviewers' Comments:

- The project has clinical significance and a potential for impact. Sickle cell disease carries a very high burden throughout the lifetime of the patient.
- The proposed treatment addresses an unmet medical need. The current standard of care is either drug based or hematopoietic stem cell transplantation (HSCT) based. Transplantation outcomes are not optimal due to preexisting conditions specifically affecting sickle cell disease patients.
- This treatment has the potential to broaden donor availability for patients with sickle cell disease seeking HSCT.
- Reviewers disagreed on the clinical competitiveness of the proposed therapy. Some thought that the potential for curative gene therapy approaches, while likely to be costly, would obviate the need for transplantation-based therapies. Others thought that the proposed therapy, due to its presumed lower cost, could be an alternative to gene therapy options.

2. Is the rationale sound?

YES	15	NO	0

Reviewers considered the following:

a) Whether the proposed project is based on a sound scientific and/or clinical rationale, and whether the project plan is supported by the body of available data.

b) Whether the data supports the continued development of the treatment at this stage.

Summary of Reviewers' Comments:

- Overall, reviewers agreed that the applicant has responded to each of the concerns raised in prior reviews, and that the rationale is sound based on scientific and clinical literature.
- In response to prior concerns regarding the conditioning regimen, the applicant provided clarification and data in support of the proposed regimen.
- In response to prior concerns regarding the data presented in support of the proposed therapeutic product, the applicant clarified previously presented data, and provided additional data from a previous trial, including a recent publication.

3. Is the project well planned and designed?

YES	15	NO	0

Reviewers considered the following:

a) Whether the project is appropriately planned and designed to meet the objective of the program announcement and to achieve meaningful outcomes to support further development of the therapeutic candidate.

b) Whether the proposed experiments are essential and whether they create value that advances CIRM's mission.

c) Whether the project timeline is appropriate to complete the essential work and whether it demonstrates an urgency that is commensurate with CIRM's mission.

Summary of Reviewers' Comments:

- Overall, reviewers agreed the project is appropriately planned and has meaningful outcomes that support further development of the therapeutic candidate.
- In the previous reviews, there were concerns about the age range and stopping rules in the protocol. In the resubmission, there are now staggered entry of the proposed age cohorts, adjustment of the minimum age of patients to be included, and the role of the DSMB has been clarified with explicit review criteria. In addition, institutional IRB approval was sought and

obtained as suggested by the reviewers in the prior review.

- There was concern that the proposed T cell dose would not be adequate to facilitate engraftment and prevent graft rejection. Reviewers have some remaining concerns regarding the T cell dose, however, there was agreement that clinical testing of the treatment would be the only way to resolve this question.
- A few reviewers recommended the following further adjustments to the protocol:
    - Consider exclusion of patients with severe vasculopathy, moyamoya, or known CNS aneurysms, or consider adding CNS hemorrhage to the stopping rules.
    - Consider excluding patients with type SC and SB+thalassemia or consider making the criteria for disease severity in this subset of children more stringent, as these patients typically have higher life expectancy and relative lower risk for severe complications.
    - Auto-immune problems (anemia, thrombocytopenia, neutropenia) can occur in non-malignant transplants at much higher incidence than malignant transplants. Please include monitoring for these.
    - The definition for hydroxyurea failure should be defined more clearly. Two episodes of pain while receiving hydroxyurea over a lifetime is likely; there should be a time frame defined for these events.

4. Is the project feasible?

YES	15	NO	0

Reviewers considered the following:

a) Whether the intended objectives are likely to be achieved within the proposed timeline.

b) Whether the proposed team is appropriately qualified and staffed and whether the team has access to all the necessary resources to conduct the proposed activities.

c) Whether the team has a viable contingency plan to manage risks and delays.

Summary of Reviewers' Comments:

- The project is feasible, and the intended objectives are likely to be achieved in the proposed timeline.
- The proposed teams are qualified and staffed to meet the objectives.
- It is recommended that the applicant include a pediatric or adult-care focused sickle cell expert on the DSMB.

CIRM Recommendation to Application Review Subcommittee

The CIRM recommendation to the Application Review Subcommittee is considered after the GWG review and did not affect the GWG outcome or summary. This section will be posted publicly.

RECOMMENDATION: Fund (CIRM concurs with the GWG recommendation).