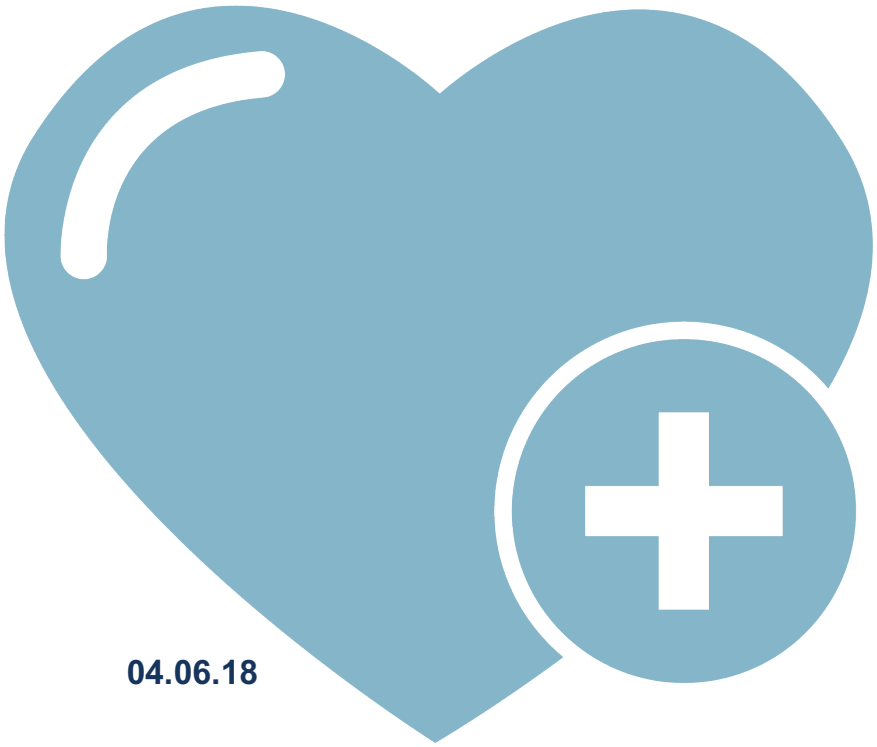
CLINICAL

Grants Working Group Public Review Summary

Gene Transfer for Artemis-Deficient Severe Combined Immunodeficiency Using a Lentiviral Vector to Transduce Autologous CD34 Hematopoietic Stem Cells

Application Number: CLIN2-10830 (Revised Application)	Review Date: 29 March 2018

Clinical Trial Stage Project Proposal (CLIN2)



04.06.18

CLINICAL

Gene Transfer for Artemis-Deficient Severe Combined Immunodeficiency Using a Lentiviral Vector to Transduce Autologous CD34 Hematopoietic Stem Cells

APPLICATION NUMBER: CLIN2-10830 (Revised application)

REVIEW DATE: 29 March 2018

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Bone marrow stem cells that have been treated by inserting a normal Artemis gene into the DNA using a modified virus called a lentivirus.

Indication

Children with severe combined immunodeficiency or "bubble baby disease" due to a defective gene that makes a protein called Artemis

Therapeutic Mechanism

Stem cells from the bone marrow normally generate key components of the immune system including T and B cells. Children with Artemis deficiency do not make T or B cells. Gene therapy for these patients will involve correcting the patient's own bone marrow stem cells by inserting a normal Artemis gene into the DNA so that normal T and B cells can be produced, thus completely correcting this immunodeficiency.

Unmet Medical Need

Artemis deficiency is the most difficult form of SCID to treat with a bone marrow transplant from a healthy donor; serious complications are much more likely than for other forms of SCID. Using gene-corrected stem cells from the patient should eliminate these issues while restoring normal immunity.

Project Objective

Complete a phase 1 trial of toxicity/feasibility.

Major Proposed Activities

Complete a trial to assess the clinical safety of gene-corrected patient's stem cells in babies and older children with Artemis deficient SCID

Determine the feasibility of restoring normal T and B cell immunity with gene-corrected patient's stem cells

Use special research assays to characterize completeness of T, B and NK cells restoration

Funds Requested

$12,000,000 ($0 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;

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

CLINICAL

- 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.

CIRM 2.0

CALIFORNIA’S STEM CELL AGENCY

Public Review Summary

CLINICAL

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

Review Overview

Reviewers agreed that Artemis-deficient severe combined immunodeficiency (ART-SCID) lacks optimal curative therapies and is an unmet medical need. Reviewers were enthusiastic about the proposed gene therapy noting that it has the potential to be curative and to overcome several important limitations of the current standard of care. In the initial review of the application, reviewers were generally supportive of the project but had concerns about feasibility of patient enrollment and whether the applicant had adequately addressed FDA feedback on the trial design.

Reviewers thought that the applicant's responses in the revised application, which included justification for inclusion of identified patients, the plan for additional recruitment and the plan for addressing FDA feedback, were sufficiently detailed and convincing. Therefore, they unanimously recommended the application for funding.

Review Summary

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

a) Consider whether the proposed treatment fulfills an unmet medical need.

- ART-SCID is a rare disease for which there is no optimal therapy.
- The proposed treatment fulfills this unmet medical need by using a curative gene editing approach on the patient's own stem cells.

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

- The current standard of care is allogeneic hematopoietic stem cell transplantation, which has several disadvantages including limited access to therapy, risk of graft-versus-host disease and failure of B cell reconstitution.
- The proposed approach overcomes the limitations of allogeneic hematopoietic stem cell transplantation and increases access to curative therapy by correcting the genetic deficit in the patient's own hematopoietic stem cells.

c) Consider whether the proposed treatment offers a sufficient value proposition that supports its adoption by patients and/or health care providers.

- The patient population is small, and in the United States occurs mainly in minority groups. However, the potential benefits are large for both the individual patients and for the development of effective gene therapies.

c) 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?

- N/A

Is the rationale sound?

a) Consider 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.

CLINICAL

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

- There is sound scientific and clinical rationale for this approach. The scientific rationale is strongly supported by the preclinical data, which was previously funded by CIRM.

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

- The preclinical data gathered to date and the success of gene editing in other SCID indications strongly support clinical development of the proposed treatment.

Is the project well planned and designed?

a) Consider 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.

- The phase 1 clinical trial is appropriately designed to demonstrate safety of the procedure.
- Reviewers noted that the project plan and design were informed by the applicant's experience investigating gene therapy in other SCID indications.
- In the initial review of the application, reviewers had concerns about the safety and efficacy of the proposed conditioning regimen to open up a bone marrow niche for the gene edited autologous stem cells.
    - Reviewers thought that the applicant's response, which noted that the conditioning regimen was informed by their clinical experience investigating gene therapy in other SCID indications, was adequate and appropriate.
- In the initial review of the application, it was unclear whether the applicant had an adequate plan to address the FDA's requirement for staggering the first 3 enrolled patients.
    - The applicant's response in the revised submission described the staggering plan in greater detail and allayed reviewer concerns.

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

- The phase 1 trial is well-designed and will create value.
- Reviewers had a minor concern that the proposed number of manufacturing training runs may be excessive.

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

- The project timeline is appropriate and demonstrates adequate urgency.

Is the project feasible?

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

CLINICAL

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

- In the initial review of the application, reviewers had concerns about feasibility of patient enrollment. They noted that the applicant had already identified a number of potential patients to enroll for the trial. However, reviewers were concerned whether the prior treatment history of these patients would exclude them from participating in this trial or would impact the safety and efficacy of the proposed procedure.
    - Reviewers thought that the applicant's response, which justified inclusion of these patients based on prior literature and their own prior clinical experience, was thorough and convincing.

b) Consider 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.

- The team is highly qualified and has the necessary expertise and resources to conduct the manufacturing and phase 1 trial activities.

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

- The team has a viable contingency plan to address the identified project risks.

CLINICAL

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

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).