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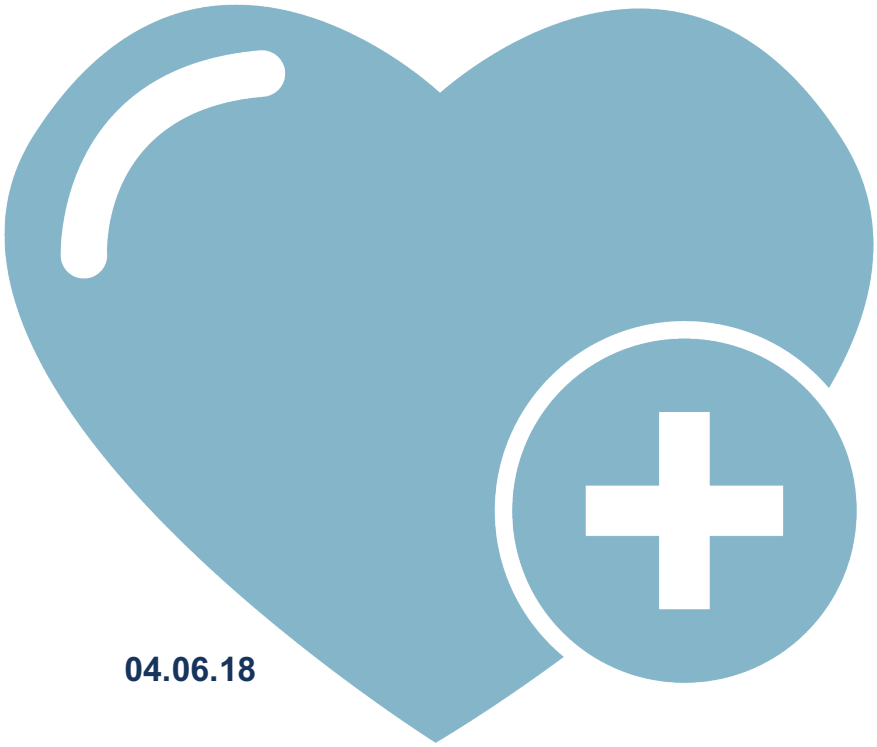
Grants Working Group Public Review Summary

A Phase 1/2 Study to Assess the Safety, Tolerability, and Efficacy of an Autologous HSPC Transplant in Transfusion-dependent β-Thalassemia

Application Number: CLIN2-11031	Review Date: 29 March 2018

Clinical Trial Stage Project Proposal (CLIN2)



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A Phase 1/2 Study to Assess the Safety, Tolerability, and Efficacy of an Autologous HSPC Transplant in Transfusion-dependent β-Thalassemia

APPLICATION NUMBER: CLIN2-11031

REVIEW DATE: 29 March 2018

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

The candidate is a gene-edited cell therapy candidate for patients with transfusion-dependent beta-thalassemia

Indication

Transfusion-dependent beta-thalassemia

Therapeutic Mechanism

The candidate is intended to disrupt BCL11A erythroid enhancer in CD34+ HSPC resulting in an increase in fetal hemoglobin which can substitute for reduced or absent adult Hb. Therefore, treatment with the candidate may potentially reduce or eliminate need for chronic blood transfusions and likely improve quality of life of patients.

Unmet Medical Need

Beta-thalassemia patients require life-long blood transfusions which result in iron overload in many organs. Consequently, patients require iron chelators to treat iron overload. Overall, thalassemia patients have lower quality of life and shorter lifespan compared to overall US population.

Project Objective

Safety established, efficacy/activity observed

Major Proposed Activities

Manufacture product for each subject in the proposed phase 1 / 2 clinical study

Assess safety, tolerability, biological activity, and clinical efficacy over a 52-week period

Decision to continue development; plan phase 3 study

Funds Requested

$8,000,000 ($14,993,120 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 12 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;

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- 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.

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Review Overview

Reviewers agreed that, given the significant drawbacks of current treatment options for transfusion-dependent beta-thalassemia (TDT) patients, this is a significant unmet medical need. Reviewers were generally enthusiastic about the proposal. They agreed that there is strong scientific rationale for using a targeted gene editing strategy in the patient's own hematopoietic stem cells to enable continued expression of fetal hemoglobin in erythroid cells. Reviewers thought that the *in vitro* and preclinical *in vivo* data supported the scientific rationale of targeting BCL11A. Reviewers thought that the phase 1/2 trial was carefully designed to assess safety and efficacy of the gene therapy approach. They had minor concerns about the lack of detail regarding the off-target analysis but strongly supported clinical development of the project. Therefore, they unanimously recommended the project 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.

- The proposed treatment, which would involve autologous gene-edited hematopoietic stem cell transplantation, fulfills the unmet medical need in TDT by offering a one-time curative treatment.

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

- The gene therapy approach is likely to provide a major improvement over the current standard of care, which relies on regular blood transfusions throughout the patient's lifetime.
- The gene therapy approach is also likely to provide a major improvement over curative allogeneic bone marrow transplantation, which has associated problems of donor shortage and risk of graft-vs-host disease.

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

- The proposed gene therapy treatment has the potential to offer a strong value proposition if it is shown to be successful as a one-time curative treatment. It is also likely to increase patient access to curative therapy.

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.

- The scientific rationale of targeting the BCL11A erythroid enhancer is strong. It is a targeted gene editing approach that would result in therapeutic levels of

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fetal hemoglobin expression.

- The scientific rationale is supported by *in vitro* data showing successful gene editing in patient-derived human cells and by *in vivo* data in mouse models.
- There is extensive preclinical data demonstrating safety of the approach with very low off-target effects. Some reviewers would have preferred to see detailed results of the off-target analysis.

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

- The preclinical data gathered to date strongly support clinical development of the 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 1/2 clinical trial is carefully designed to assess safety and preliminary efficacy.
- It was unclear to the reviewers why both of the proposed agents would be needed to mobilize HSC.
- Since it is unclear what percentage of modified bone marrow cells would need to engraft for therapeutic effect, some reviewers recommended that the applicant assess this via bone marrow harvest in the clinical study.

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

- The proposed experiments are essential and the results of the phase 1/2 trial will inform on the curative potential of gene-modified stem cells.

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 demonstrates urgency that is commensurate with CIRM's mission.

Is the project feasible?

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

- This is a well-designed project that is likely to achieve the intended objectives within the proposed timeline.

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 proposed team is highly qualified and the project involves appropriately

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qualified manufacturing and clinical partners to execute the clinical trial.

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

- The applicant has identified appropriate risks and proposed adequate contingency plans.

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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).