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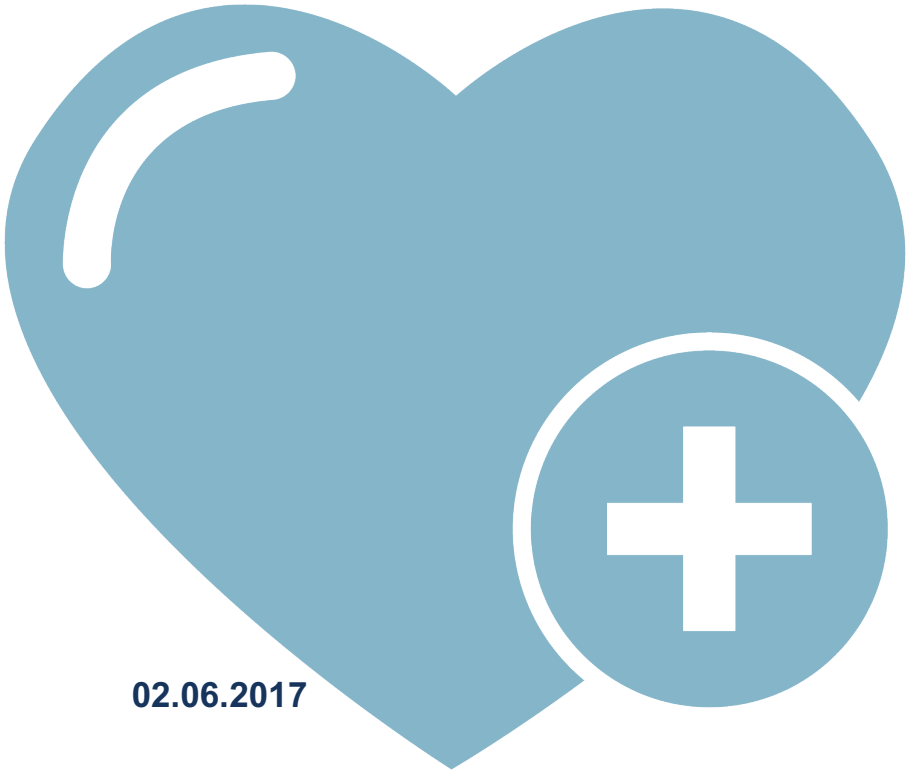
Grants Working Group Public Review Summary

Lentiviral Gene Therapy for Infants with X-linked Severe Combined Immunodeficiency using Autologous Bone Marrow Stem Cells and Busulfan Conditioning

Application Number: CLIN2-09504 (Revised Application)	Review Date: 31 January 2017

Clinical Trial Stage Project Proposal (CLIN2)



02.06.2017

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Lentiviral Gene Therapy for Infants with X-linked Severe Combined Immunodeficiency using Autologous Bone Marrow Stem Cells and Busulfan Conditioning

APPLICATION NUMBER: CLIN2-09504 (revised application)

REVIEW DATE: 31 January 2017

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Bone marrow stem cells will be transduced with a lentiviral vector to deliver a normal copy of the gamma-chain gene

Indication

X-linked severe combined immunodeficiency (XSCID)

Therapeutic Mechanism

The gene therapy will correct the patient's own bone marrow stem cells. Transplantation with corrected cells will lead to restored production of immune cells resulting in correction of the underlying immunoeficiency disorder.

Unmet Medical Need

XSCID is a catastrophic disease of childhood. Children with matched sibling donors do well with bone marrow transplant, but most cases lack a matched sibling donor. Outcomes with an alternate donor are significantly inferior and are more prone to complications. Using the patient's own bone marrow stem cells for transplantation after lentiviral transduction, as proposed with this therapeutic, could spare the patient life-long treatments.

Project Objective

Phase I/II trial completed.

Major Proposed Activities

Open LVXSCID-ND trial at the California partner institution

Enroll at least 6 patients from California at the California performance site

Analyze immune reconstitution and safety in XSCID gene therapy patients.

Funds Requested

$11,924,780 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 10 GWG members

Votes for Score 2 = 2 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.

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Review Overview

During the first review of this application, reviewers expressed some concerns with the existing clinical data; with the proposed plan to transfer production of the product to the second, California-based site; and with the ability to enroll the trial within the proposed timelines. Based upon the revised application, reviewers were satisfied that the clinical data supports moving forward with the proposed clinical trial, and that the applicant should be able to enroll the trial as projected. While a subset of reviewers remained unconvinced that manufacturing at the California-based site is necessary, most reviewers were convinced by the applicant's response that the technology transfer and manufacturing of the product at the California site is both necessary and feasible. Therefore, this application is recommended 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.

- There is a need to develop curative therapies for x-linked severe combined immunodeficiency (XSCID), and the proposed therapeutic has such promise.

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 an HLA-matched allogeneic bone marrow transplant. The proposed therapy, if successfully developed, would improve this standard of care by reducing the significant toxicities.

c) Consider whether the proposed treatment offers a sufficient, impactful, and practical value proposition for patients and/or health care providers.

- The value proposition of the proposed treatment depends on its ability to reduce toxicities and improve the safety profile as compared to the standard of care, on the proposed improved conditioning regimen, and on the ability to move to a cryopreserved product. If these are realized, the product will offer a sufficient, impactful, and practical value proposition.
- Reviewers noted that other gene and cell therapy products for this disease are in development. The value proposition of the proposed product will also depend on its ability to provide a safety, efficacy, or practical advantage over these competing products.

Is the rationale sound?

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

- The proposed project is based on a sound scientific rationale.
- The clinical rationale is sound and based on reasonable clinical data.
- Reviewers expressed concerns in the first review of this application regarding specific aspects of the efficacy data from previous patients, but the current patient data provided with the revised application supports the clinical rationale.

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

- The preclinical and clinical data support the continued development of the therapeutic candidate.

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 achieve meaningful outcomes to support further development of the therapeutic candidate.

- During the first review, some reviewers questioned the need for the second clinical trial site in California. However, the applicant addressed this concern, and reviewers were convinced that adding the California trial site is necessary for enrollment and improves the likelihood of success of the clinical trial.
- Some reviewers were supportive of the plan to transfer GMP production of the product to the California partner organization, noting that the applicant organization has successfully completed this type of technology transfer in the past and has limited capacity to produce the product for the external trial site. Other reviewers did not think the technology transfer to be necessary given both the cost of the technology transfer and the variability that could be introduced between the two trial sites.
- During the first review, reviewers expressed concern regarding how manufacturing at the California site would be validated. The applicant's response alleviated these concerns.

b) Consider whether this is a well-constructed, quality program.

- This is a well-constructed, quality program.

c) Consider whether the project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission.

- The project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission.
- During the first review of this application, reviewers noted that the applicant had not yet begun discussions with the FDA regarding product registration. Given the rarity of patients who have this disease, all clinical trial subjects will be critical for the Biologics License Application (BLA), and it is likely that a historical database will be necessary for marketing approval. To move towards approval expeditiously, early discussions with FDA regarding endpoints and what is needed for registration are essential. Reviewers accepted the applicant's reasons for not yet initiating discussions with FDA, but nevertheless strongly encouraged the applicant to not wait much longer to do so.

Is the project feasible?

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

- During the first review of the application, reviewers were concerned about the slow enrollment and the ability to attract sufficient number of patients to the clinical trial at the California site given the rarity of patients and competing clinical trials.
    - The applicant provided updated enrollment information, and reviewers were satisfied that the applicant trial site is actively

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enrolling patients and has been provided greater institutional support to enable enrollment.

- Reviewers were satisfied that the California trial site is committed to meeting enrollment projections. Though they still had some concerns as to whether sufficient patients would be available to enroll this trial and competing trials, reviewers thought this concern was sufficiently addressed to move forward with the trial as proposed.

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 excellent, appropriately staffed, and has access to all the necessary resources to conduct the proposed activities.

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

- The contingency plan is generally acceptable, but reviewers would have liked to have been provided more data regarding the number of new cases per year at each trail site and the number of patients treated with gene therapy per year at each site.

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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).