CLINICAL

AGENDA ITEM #9
ICOC MEETING
MARCH, 16th, 2016

# Grants Working Group Public Review Summary

## Ex Vivo Transduction of the Human Artemis (DCLRE1C) cDNA by Lentiviral Vector AProArt into CD34+ Hematopoietic Cells for Artemis (ART)-Deficient Severe Combined Immunodeficiency (SCID)

| Application Number: CLIN1-08363 (Revised Application) | Review Date: February 23, 2016 |
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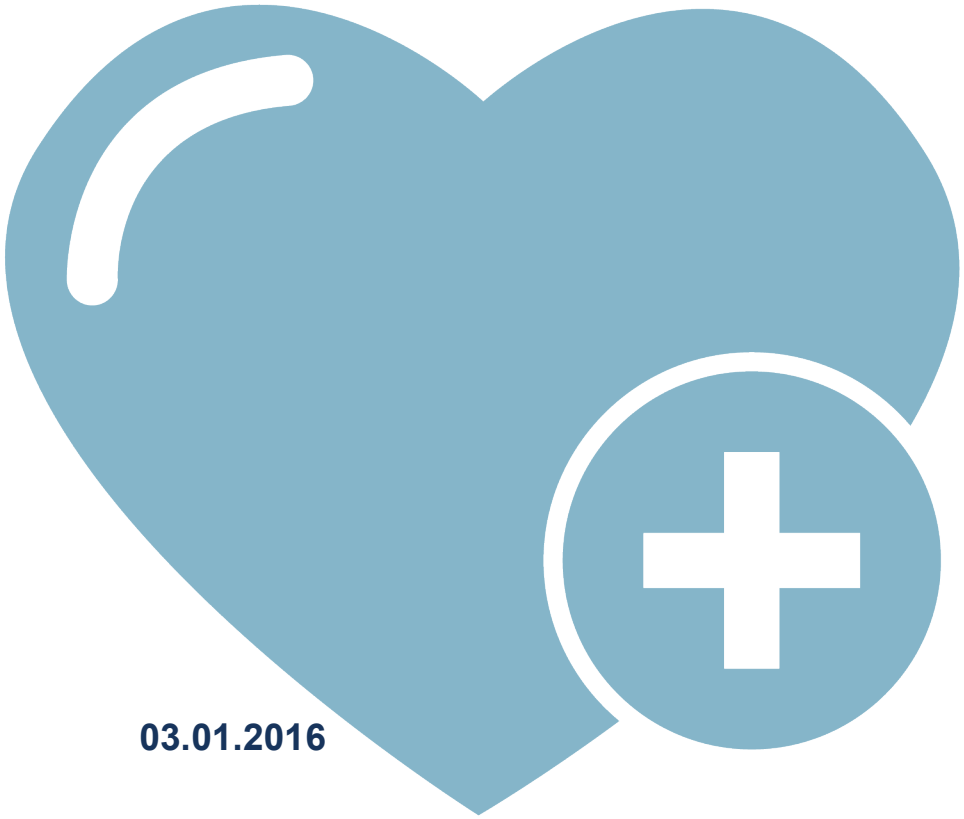
Late Stage Preclinical Project Proposal (CLIN1)



**03.01.2016**

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# Ex Vivo Transduction of the Human Artemis (DCLRE1C) cDNA by Lentiviral Vector AProArt into CD34+ Hematopoietic Cells for Artemis (ART)-Deficient Severe Combined Immunodeficiency (SCID)

**APPLICATION NUMBER: CLIN1-08363 (Revised application)**

**REVIEW DATE: February 23, 2016**

**PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects**

## Therapeutic Candidate

Blood-forming stem cells harboring a severe combined immunodeficiency (SCID) gene defect, modified to become normal by addition of a correct copy of the Artemis/DCLRE1C DNA repair gene (Art).

## Indication

Treatment of SCID due to defects in the Art gene.

## Unmet Medical Need

Current standard bone marrow transplants for SCID require chemotherapy that is harmful to Art-SCID patients and can lead to graft rejection and graft vs host disease. Patients are tolerant to their own blood-forming stem cells, so correcting and returning them could lead to a lasting cure.

## Major Proposed Activities

Manufacture sufficient preclinical vector (AProArt) for toxicity and efficacy studies and clinical grade vector for the clinical trial

Complete nonclinical toxicity studies and demonstrate ability to manufacture transduced human cells at clinical scale

Complete nonclinical efficacy studies

## Funds Requested

$4,268,865 ($0 Co-funding)

## Recommendation

Score: 1

Votes for Score 1 = 8 GWG members

Votes for Score 2 = 6 GWG members

Votes for Score 3 = 1* 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.

*Indicates that this score was recorded after the vote to forward the recommendation to the Board.



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Public Review Summary

# Review Overview

The applicant provided thoughtful point-by-point responses to the concerns reviewers expressed in the original review. Some reviewers thought that the ensuing clinical trial may not be feasible and wanted to see these issues resolved prior to funding this late stage preclinical award. However, a majority of reviewers were impressed by the quality of the revised application; thought the clinical trial issue could be resolved during the term of this award; and recommended funding of this project based on the serious unmet medical need, strong preliminary data, and overall high quality.

# Review Summary

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

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

- In the absence of a matched sibling donor, severe combined immunodeficiency (SCID) due to defects in the Artemis/DCLRE1C gene (ART) is more difficult to treat than many other forms of SCID and patients are in need of treatment options.

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

- A successful gene corrected autologous stem cell treatment for ART-SCID would improve the standard of care for the many patients without a matched sibling donor.
- This approach would improve upon the current standard of care because it would avoid the requirement for immune suppression or high dose alkylating agent conditioning and their associated morbidities.

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

- It appears that this strategy offers an impactful value proposition for patients as it holds the potential to have a major impact on quality of life and survival compared to what is currently achieved.

**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 scientific rationale for replacement of a defective gene product (Artemis protein) in the affected population of cells (T-cell and B-cell derivatives of autologous hematopoietic stem cells) is sound.
- Strong preclinical data support that gene correction and differentiation of transplanted cells into needed cell types is feasible.
- The gene is well characterized and early proof of concept is provided.
- This approach is similar to that used in ADA-SCID (adenosine deaminase deficiency SCID), which provides support for the clinical rationale.
- The current vector construct appears to avoid genotoxicity issues and exhibits the desired activity at non-toxic doses.
- Initial data supports feasibility of the proposed conditioning regimens.

- Data collected in animal models that are more permissive of T cell reconstitution would strengthen the proposal.
- Data demonstrating transduction of long-term reconstituting stem cells is critical. Therefore, reviewers would have appreciated longer term studies than those presented in the proposal.

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

- Strong data supports the continued development of this treatment and initiation of IND-enabling studies.

**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.**

- The design and feasibility of the ensuing clinical trial needs significant improvement. It is unclear that sufficient patients will be available to enroll the trial. Detailed information on the number of patients that meet eligibility criteria at each proposed site is required alongside a reasonable assessment of competing trials that may reduce availability of those patients. While this proposal does not include the conduct of the trial, this project has no impact without the ability to ultimately conduct a successful clinical trial.
- The applicant should conduct serial transplants or limiting dilution assays to see gene modified long-term reconstituting cells in sufficient numbers, given that dose limiting transplants may occur.
- The application suggests that product will be manufactured 6 months ahead of the study, but there is no mention of a stability study. This needs to be addressed.
- Using CFUs as a determinate of transduction is questionable and likely results in overestimation of the number of stem cells transduced. The applicant should develop a more direct method to assess transduction.
- The plan to validate cryopreservation is not well described, and acceptable outcomes are not defined.
- The inclusion/exclusion criteria describing how and when busulfan will be utilized in the clinical trial and how busulfan affects eligibility is confusing as written. This should be carefully and clearly described in the clinical protocol.
- The backup plan in the event busulfan does not perform as expected depends upon a drug that is difficult to acquire in the United States. The relationship that allows access to this drug should be better described. Additionally, how and when the backup drug will be used is poorly described.
- The quality systems plan is either not adequate or is not adequately described. This should be addressed moving forward.
- Risk assessments are inadequate for cytokines and other reagents with regard to human and animal sourced materials. This should be addressed moving forward.

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

- This is a well-designed quality program.
- The applicant has been responsive to concerns expressed by the Food & Drug Administration (FDA), a mark of a quality project.

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

- The project plan demonstrates an urgency that is commensurate with CIRM's mission and proposes completion of preclinical studies and preparation for a clinical trial in 18 months.
- Though timelines are aggressive, they are not inappropriately aggressive given CIRM's policy of operational milestone-based payments.

**Is the project feasible?**

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

- Timelines are aggressive. While this may pose a challenge to the team, the timelines are feasible.
- The applicant needs to carefully quantitate step-by-step yields in order to determine the minimum number of cells necessary (given the transduction efficiency) per kilogram of body weight of the patient to support transplant. Harvesting sufficient number of cells to achieve the required dose will be immensely challenging.
- It is not certain that enough hematopoietic stem cells can be transduced to engraft patients receiving low dose busulfan.
- Despite some concerns, most reviewers thought it likely that the intended project objectives will be achieved.

**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 investigators are well-qualified and this is a strong team.
- The vector facility is competent and should be able to perform as expected.
- This ensuing clinical trial may require a consortium of centers to fully enroll, and the applicant should consider building such a consortium.
- There is an experienced project manager devoting 100% time to the project.

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

- Although a contingency plan was provided, the team has not adequately planned for contingencies related to generating an adequate dose of transduced hematopoietic stem cells.
- It is unclear whether contingency plans to assess alternatives to busulfan are sufficient.

# 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).