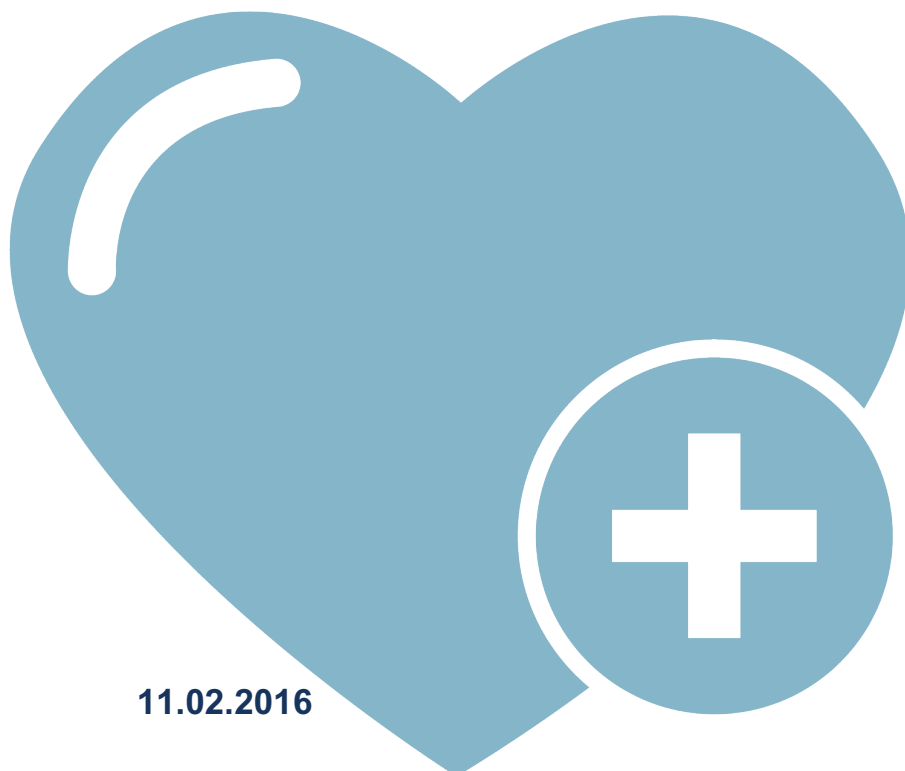


Grants Working Group Public Review Summary

Efficacy and Safety of Cryopreserved Autologous CD34+ HSC
Transduced with EFS Lentiviral Vector Encoding for Human ADA
Gene in ADA-SCID Subjects

Application Number: CLIN2-09339	Review Date: October 25, 2016
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Clinical Trial Stage Project Proposal (CLIN2)



11.02.2016

CLINICAL



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Public Review
Summary

Efficacy and Safety of Cryopreserved Autologous CD34+ HSC Transduced with EFS Lentiviral Vector Encoding for Human ADA Gene in ADA-SCID Subjects

APPLICATION NUMBER: CLIN2-09339

REVIEW DATE: October 25, 2016

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate

Autologous CD34+ hematopoietic stem cells (HSCs) transduced with a lentiviral vector encoding the human ADA gene (OTL-101)

Indication

Adenosine Deaminase - Severe Combined Immunodeficiency (ADA-SCID)

Unmet Medical Need

In ADA-SCID, allogeneic HSCTs from non-HLA matched sibling donors are a high-risk procedure (29-67% survival; source: Hassan, 2012), and the efficacy of chronic ERT is uncertain in the long-term. Preliminary data indicates that OTL-101 may significantly improve outcomes verses available therapies.

Major Proposed Activities

Perform GMP manufacture of 10 patient-specific lots of EFS-ADA LV CD34+ HSPC (OTL-101) and transplant 10 subjects with ADA-SCID

Submit a biologics license application (BLA) to FDA for OLT-101

Complete the 2-year follow-up in patients treated with OTL-101

Funds Requested

\$20,000,000 (\$18,151,530 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 10 GWG members

Votes for Score 2 = 1 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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Public Review
Summary

Review Overview

Reviewers were highly enthusiastic regarding this proposal to conduct a registration trial in an orphan indication (ADA-SCID) with a stem cell and gene therapy product (OTL-101). Additionally, reviewers applauded the move to a cryopreserved product that will allow improved patient access to the therapy. Reviewers recommended this proposal for funding; however, they also noted that costs for the proposed activities are exceedingly high and should be carefully reviewed by CIRM.

Review Summary

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

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

- Current ADA-SCID treatments are suboptimal, and the proposed treatment holds great potential to fulfill this unmet medical need.

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

- The proposed approach represents a potentially curative treatment for the intended patient population.
- The proposed approach is a significant improvement to the current standard of care as allogeneic hematopoietic stem cell transplantation (HSCT) holds a considerable risk of morbidity and mortality and enzyme replacement therapy has a tremendous lifelong cost.

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

- This could be the first stem cell and gene therapy commercial product available in the US for correcting hematopoietic/immune disorders, and, as such, would be highly significant with regards to scientific and medical impact.
- Gene therapy treatments for ADA-SCID patients are available only at a few, large academic medical centers. This project supports commercialization of a cryopreserved product that will greatly expand the availability of this therapy to ADA-SCID patients around the world and at smaller transplant centers. There is a substantial value proposition in making this treatment widely available, standardizing treatments, and improved safety and efficacy of treatment.

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 and clinical rationale is strong.
- The clinical data from the previous trials are strong. This is the first time that someone can credibly say they have cured patients with a gene therapy approach. To do so with one treatment that remains effective for as long as has been measured in patients thus far (up to 4 years) is clinically significant.

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

- The clinical data is compelling and supports a marketing application.

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AGENCY

Public Review
Summary

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.**
- Overall, the project is well planned and designed.
 - The frequent and high quality interactions with FDA support the plan and design of the study.
 - Shipping validation studies were not adequately described in the plan but will need to be undertaken.
 - Plans for comparability studies were not described in detail in the application but are in place and were discussed with FDA.
- b) **Consider whether this is a well-constructed, quality program.**
- This is a well-constructed and high quality program.
 - The use of the proposed lentiviral vectors with subablative busulfan and a cryopreserved product is cutting edge for applying this technology to a commercial setting.
- 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.
 - The applicant has a breakthrough therapy designation with FDA, which should accelerate registration.

Is the project feasible?

- a) **Consider whether the intended objectives are likely to be achieved within the proposed timeline.**
- The proposed trial is feasible and the trial is likely to be completed within proposed timelines.
 - It is possible that it may take more time than envisioned to file the BLA.
 - The most challenging aspect of the project plan is to develop the comparator database that will serve as the control group for statistical analysis of outcomes. Reviewers noted that the database is not yet in place and is essential for the BLA. However, reviewers were confident the applicant would be successful in establishing the database.
- 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 academic team is excellent and highly qualified to carry out the proposed study.
 - The commercial partner is a relatively new entity that does not have an established track record.
- c) **Consider whether the team has a viable contingency plan to manage risks and delays.**
- The contingency plan is sufficient and outlines the major obstacles that may be

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Public Review
Summary

encountered, with reasonable plans to deal with them should they occur.

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)