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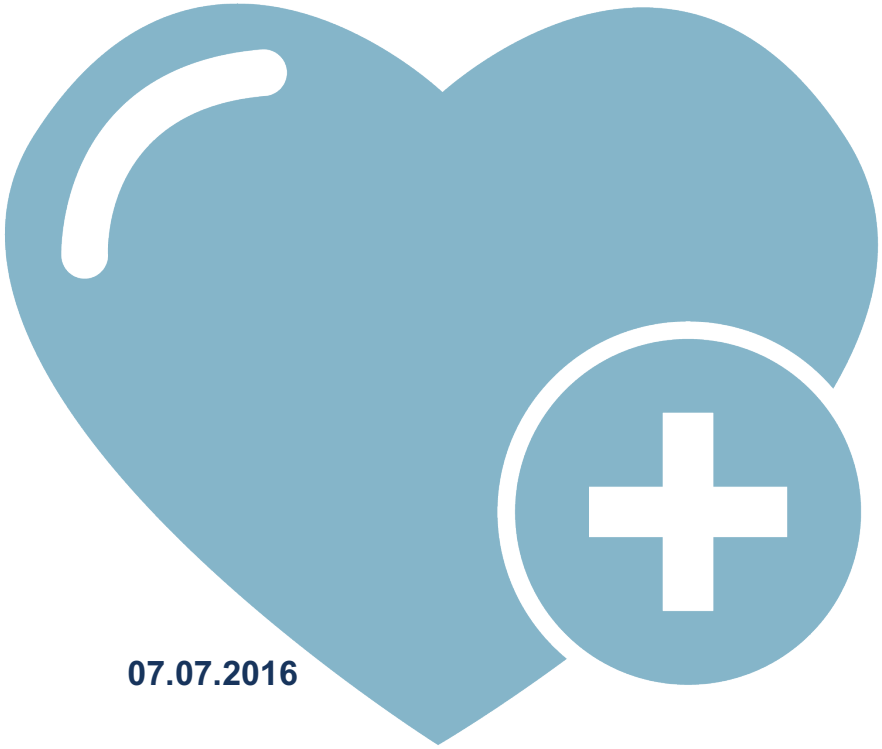
Grants Working Group Public Review Summary

A Human Acellular Vessel in Patients Needing Renal Replacement Therapy: A Comparison with ePTFE Grafts as Conduits for Hemodialysis (HUMANITY)

Application Number: CLIN2-08938 (Revised Application)	Review Date: June 28, 2016

Clinical Trial Stage Project Proposal (CLIN2)



07.07.2016

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CALIFORNIA'S STEM CELL AGENCY

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A Human Acellular Vessel in Patients Needing Renal Replacement Therapy: A Comparison with ePTFE Grafts as Conduits for Hemodialysis (HUMANITY)

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate

Human Acellular Vessel (HAV)

Indication

Conduit for Vascular Access for Hemodialysis

Unmet Medical Need

Current vascular access technologies for hemodialysis are fraught with complications associated with thrombosis, infection, and abandonment. Compared to conventional vascular access treatments for dialysis the HAV has the potential for less frequent clotting, abandonment and infection.

Major Proposed Activities

Manufacturing & distribution of the HAV for clinical testing in dialysis patients

Enrollment in Phase 3 clinical trial and implantation of HAV into patients requiring vascular access for hemodialysis

Longitudinal test subject follow-up, data collection and analysis, and regulatory approval of HAV for widespread clinical use

Funds Requested

$9,999,528 ($9,999,528 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 10 GWG members

Votes for Score 2 = 1 GWG members

Votes for Score 3 = 3 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

This application to conduct a Phase 3 clinical trial to support marketing approval of a human acellular vessel (HAV) conduit to provide vascular access for patients requiring hemodialysis was reviewed three times by the CIRM Grants Working Group (GWG). A number of concerns were expressed during the review of the originally submitted application. The applicant provided thoughtful and thorough responses in the revised applications that alleviated most of the reviewer concerns. Some reviewers remained concerned that a small subset of highly sensitized patients might develop donor specific antibodies to the graft that could put them at higher risk for complications following kidney transplant, and thought this population should be excluded from the trial. Other reviewers did not share this concern, noting that FDA allowed inclusion of the patient population in the proposed trial. Ultimately, reviewers recommended this highly meritorious project for funding by CIRM.

Review Summary

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

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

- While there are other conduits available to provide vascular access for hemodialysis, there are complications associated with their use, and some patients are not eligible for treatment with those conduits. The proposed conduit holds the potential to fulfill this unmet need.
- There was a difference in opinion amongst the reviewers regarding the impact. Some reviewers felt strongly that there is an important unmet medical need that could be fulfilled by this conduit while others thought this to be an imperfectly met rather than unmet medical need and that this conduit would offer only an incremental improvement.

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

- Reviewers thought it likely that this approach would provide an improvement over the standard of care for the intended patient population.

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

- The product could offer an impactful and practical value proposition based on the risk-benefit profile suggested by the existing clinical data.
- Reviewers noted that the cost of goods (COGs) is high and needs to be brought down as manufacturing is scaled in order to allow the commercial product to be offered at a cost that provides a sufficient value proposition.
- During the review of the originally submitted application, due to uncertainties in the manufacturing plan reviewers were concerned that the applicant might have difficulty meeting market demand should marketing approval be obtained. The applicant alleviated these concerns with their responses to reviewer questions in the revised applications.

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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.

- Existing clinical data suggests little deterioration and good patency of the graft, which supports product efficacy.
- The primary concern expressed by some reviewers centered on kidney rejection or shortening of the lifespan of a transplanted kidney in patients who receive the HAV conduit, develop anti-donor antibodies, and subsequently receive a kidney transplant. However, not all reviewers agreed that this is a major concern.
    - Some reviewers thought the immunologic data regarding anti-donor antibody formation did not support a favorable risk-benefit profile in highly sensitized patients and suggested excluding such patients from the study or including a specific warning in the informed consent document.
    - Other reviewers were not concerned by the immunologic data and noted that FDA has allowed the inclusion of the patient population in the clinical protocol. Further, these reviewers noted that the field does not fully understand what level of sensitization leads to greater risk of complications following kidney transplantation. These reviewers thought it more appropriate that this issue continue to be monitored during the proposed clinical trial rather than excluding the patient population or including a warning.
    - Reviewers also noted that the vast majority of patients receiving dialysis will not receive a kidney transplant. Therefore, anti-donor antibody formation will not negatively impact these patients.

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

- The existing data is promising and supports continued development of the product.

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 of the application, reviewers expressed a number of concerns regarding CMC elements (process validation, analytic methods, technology transfer, scaling of manufacturing, etc.), the potency assay, statistical analysis, and product manufacture and comparability. These concerns were fully addressed in the review of the revised applications, such that the project plan and design is considered to be appropriate and likely to support meaningful outcomes.
- Though a single Phase 3 trial in this indication is acceptable to gain marketing approval, reviewers observed that the commercial facility will not be fully online until after the completion of the Phase 3 clinical trial. While acceptable, this is not preferable and is a risk to gaining marketing approval that should be monitored and mitigated. Demonstration of comparability of the product produced at the commercial facility to that used in the Phase 3 clinical trial will be critical.

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

- Overall, this is a well-constructed, quality project.
- Additional monitoring for development of donor-specific antibodies would improve the quality of this project.

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 to CIRM's mission.

Is the project feasible?

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

- Reviewers expressed concerns with the feasibility of timelines during the first review of this application. However, these concern were fully addressed during the review of the revised applications, and reviewers consider the project to be feasible and objectives achievable.

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 well-qualified and appropriately staffed and has access to all the necessary resources to achieve the project objectives.

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

- Team has a viable contingency plan to manage risks and delays.

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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).