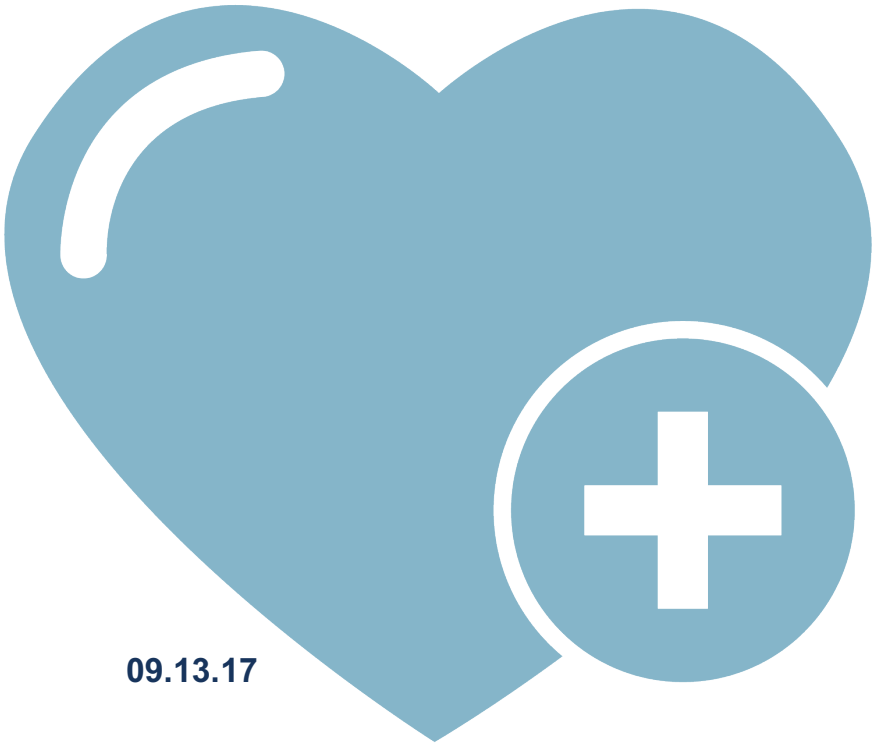
CLINICAL

Grants Working Group Public Review Summary

A Phase 3 Study Comparing the Utility of Human Acellular Vessels to Arteriovenous Fistula in Subjects with End-Stage Renal Disease (California Sites)

Application Number: CLIN2-09688 (Revised Application)	Review Date: 29 August 2017

Clinical Trial Stage Project Proposal (CLIN2)



09.13.17

CLINICAL

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

A Phase 3 Study Comparing the Utility of Human Acellular Vessels to Arteriovenous Fistula in Subjects with End-Stage Renal Disease (California Sites)

APPLICATION NUMBER: CLIN2-09688 (Revised application)

REVIEW DATE: 29 August 2017

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Human Acellular Vessel (HAV)

Indication

Conduit for Vascular Access for Hemodialysis

Therapeutic Mechanism

Mechanism of action: the HAV is comprised of intact extracellular matrix constructed by human smooth muscle cells (SMC) in a biomimetic bioreactor system. The manufacturing process is designed to create a biologic matrix similar in protein composition and 3 dimensional structure with biomechanical properties that are observed with native tissue. Once implanted, the HAV is remodeled by the host resulting in a vascular structure more similar in histological appearance to native vascular tissue.

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.

Project Objective

Completion of Phase III Clinical Program

Major Proposed Activities

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

Enrollment in Phase III Clinical Trial and Implantation of HAV into patients requiring vascular access for hemodialysis

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

Funds Requested

$14,082,865 ($26,425,033 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 8 GWG members

Votes for Score 2 = 2 GWG members

Votes for Score 3 = 5 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.

CLINICAL

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

Review Overview

This is a revised application that previously received a score of "2". In the initial review of the application, reviewers noted that the proposed HAV product could be a safer alternative to arteriovenous (AV) fistulae for vascular access in end stage renal disease patients. They noted that the applicant had agreement from the FDA on the phase 3 trial design to compare HAV with AV fistulae. However, they had concerns about recommending funding for a new phase 3 trial without having data from the ongoing phase 3 trial comparing HAV to synthetic grafts and about the overall value proposition of the HAV product. Most reviewers thought that the safety data from the ongoing phase 3 trial and value proposition information provided in the revised application were adequate. Reviewers determined that the HAV product has the potential to reduce central catheter usage and thereby reduce the risks of infection and morbidity in hemodialysis patients. Reviewers also noted that the both the proposed and ongoing phase 3 trials are necessary for product approval and most reviewers thought that the two trials may be conducted in parallel. Therefore, reviewers recommended the application 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.

- Safe and reliable vascular access for hemodialysis is an unmet medical need for patients with end-stage renal disease.

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

- The standard of care AV fistulae suffer from long maturation lead times and high maturation failure rates. This results in the patient being on central catheter for prolonged periods of time and thus at higher risk for infection. The proposed off-the-shelf HAV is an alternative treatment approach to AV fistulae and would reduce lead time to AV access and reduce the risk for infection.

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

- The HAV could reduce healthcare costs and burden on patients by eliminating surgical procedures associated with AV fistulae.
- The HAV could reduce healthcare costs and increase patient safety by reducing central catheter time and the associated risks of infection and site morbidity.
- Some reviewers thought that the value proposition was unclear given the high manufacturing costs of the product and that the durability of treatment is unknown.

CLINICAL

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

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 for the use of HAV for vascular access in hemodialysis are strongly supported by the pre-clinical and clinical studies performed to date.

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

- The safety and efficacy data from previous clinical studies supports continued development of the therapeutic candidate.
- Some reviewers questioned whether another phase 3 study should be supported without having reviewable efficacy data from the current ongoing phase 3 study. However, other reviewers noted that it would not be reasonable to conduct the two phase 3 trials in a sequential manner.

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 pathway to the clinic is appropriately planned and has agreement from the FDA. The proposed phase 3 trial, in conjunction with the ongoing phase 3 trial, would enable FDA registration for HAV as an alternative treatment option to AV fistulae.
- The clinical trial is well designed and has been agreed upon by the FDA in a special protocol assessment.

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

- This is a well-constructed program that is structured similarly to the ongoing phase 3 study that has been successfully enrolling patients.

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

- The project plan and timeline are designed to enable product registration with the FDA upon completion of the proposed and currently ongoing phase 3 trials.

CLINICAL

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

Is the project feasible?

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

- The applicant has already demonstrated the ability to enroll, treat and monitor patients in its ongoing phase 3 trial.

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.

- This is an exceptionally well-qualified and experience team.

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

- The team has identified appropriate risks and has a reasonable contingency plan.
- The ongoing phase 3 study demonstrates that the team has the capacity to manage risks and delays.

CLINICAL

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

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).