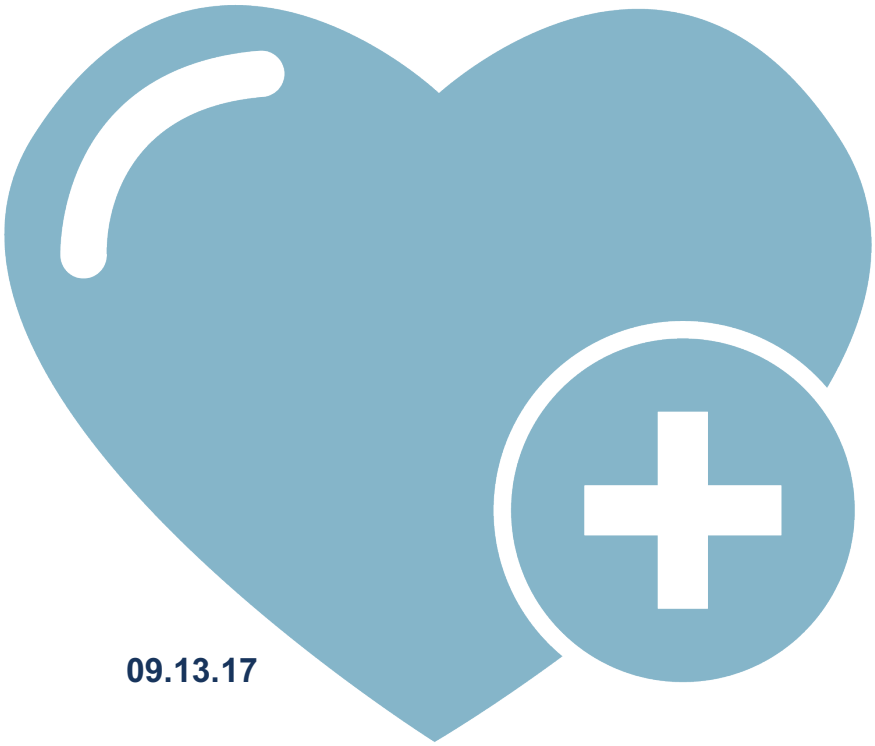
CLINICAL

Grants Working Group Public Review Summary

Clinical trial of directly vascularized islet cell replacement therapy for high-risk type 1 diabetes

Application Number: CLIN2-09672 (Revised Application)	Review Date: 29 August 2017

Clinical Trial Stage Project Proposal (CLIN2)



09.13.17

CLINICAL

Clinical trial of directly vascularized islet cell replacement therapy for high-risk type 1 diabetes

APPLICATION NUMBER: CLIN2-09672 (Revised application)

REVIEW DATE: 29 August 2017

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Pancreatic progenitor cells in a delivery device that allows direct vascularization

Indication

High-risk type 1 diabetes including "brittle" diabetes and hypoglycemia unawareness

Therapeutic Mechanism

People with type 1 diabetes have lost their pancreatic cells that make insulin, and therefore have to self-administer insulin. It is very difficult to manage blood sugar to safe levels by this method. Chronically too high can lead to blindness, kidney failure, nerve damage, and heart problems, and too low can cause coma or death. This product will replace the lost pancreatic cells and provide a natural biological ability to maintain stable healthy blood sugar levels.

Unmet Medical Need

There are over 100,000 people in the US with type 1 diabetes so severe that they are at constant risk of hospitalization and/or death. Within months after administration, this product could naturally restore those patients' blood sugar to normal healthy levels and save their lives.

Project Objective

Phase 1/2 trial completed

Major Proposed Activities

Manufacture and quality control of the test article for clinical trial

Launch and run clinical trial

Assay development

Funds Requested

$20,000,000 ($8,571,429 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 15 GWG members

Votes for Score 2 = 0 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.

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

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 thought that there was adequate rationale to support clinical investigation of the proposed islet replacement product and that the study was appropriately designed to inform on the safety and efficacy of this approach. However, reviewers had concerns about the sustained functionality of implanted cells and about the long-term foreign body response to the encapsulation device. The revised application provided additional data and information on the preclinical studies performed to date with the proposed islet replacement product. Reviewers thought that the wealth of preclinical data generated to date supported clinical investigation of the islet replacement product and unanimously 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.

- The product is being developed for a subset of type 1 diabetics defined as having hypoglycemia unawareness, extreme glycemic lability, and/or severe hypoglycemic episodes. There is a clear unmet medical need to serve this high-risk patient population.

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

- The approach has the potential to provide an improvement over standard of care, at least in the short term.
- The approach relies on an unlimited cell source thereby increasing patient access to islet transplantation.

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

- This product addresses the unmet need for accessibility to islet transplants by providing a potential limitless source of islets derived from embryonic stem cells.
- Reducing the incidence of severe hypoglycemic episodes should result in less hospitalizations as well as improved quality of life for patients. The true cost savings to the healthcare system will depend on the ultimate cost of the product as well as durability of the treatment.

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 applicant has demonstrated improved vascularization of the new device design and long-term functionality of the implanted cells in relevant preclinical animal models.
- In the initial review of the application, reviewers thought that the applicant provided inadequate detail on the preclinical studies performed with the therapeutic candidate. Reviewers thought that the applicant's response, which included updated datasets and clarifications on the functional outcomes in the animal models, was satisfactory and further supported the scientific rationale.
- There is sound clinical rationale for the proposed project based on positive patient outcomes experienced in experimental cadaveric islet transplantation procedures.

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

- The preclinical data gathered to date strongly support clinical investigation of the proposed 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.

- Reviewers noted that the clinical study is carefully and conservatively planned to allow investigation of device performance and cell viability in a small initial patient cohort before moving on to dose-response studies in a larger cohort.
- The study design involves close monitoring of patients and appropriate time points for evaluation in the early and midpoint stages of the study, which will enable detection of product failure relatively early.
- Some reviewers expressed concern that long-term GLP safety studies and potency assay development for product release will be done concurrently to patient enrollment for the phase 1 study.
- Some reviewers thought it was premature at this early stage in the project to start activities toward eventual breakthrough therapy designation filing.

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

- This is a well-organized program.
- There are experienced personnel on the team to ensure appropriate quality

CLINICAL

systems.

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

- The project plan and timeline demonstrate urgency.

Is the project feasible?

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

- The intended objectives are likely to be achieved in the proposed timeline.
- The product shelf-life may be a bottleneck during the phase 2 portion of the study but the applicant has appropriate plans to address this issue.
- Some reviewers thought that the proposed plan to submit an IND amendment may be riskier than the applicant anticipates.

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 proposed team is well qualified to execute the proposed clinical trial, manufacturing and potency assay development activities.
- The regulatory budget is not commensurate with the proposed regulatory activities.
- It was unclear why the study would need clinical consultants in addition to the PIs.
- The number of institutional personnel involved in the project appeared to be high given the scope of activities being performed by the applicant institution.

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

- In the initial review of the application, reviewers thought that the applicant hadn't identified and accounted for risks associated with encapsulation device failure in patients. Reviewers thought that the applicant's response, which noted a contingency plan to make minor modifications to the device, was likely the only reasonable approach for the project.

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

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).