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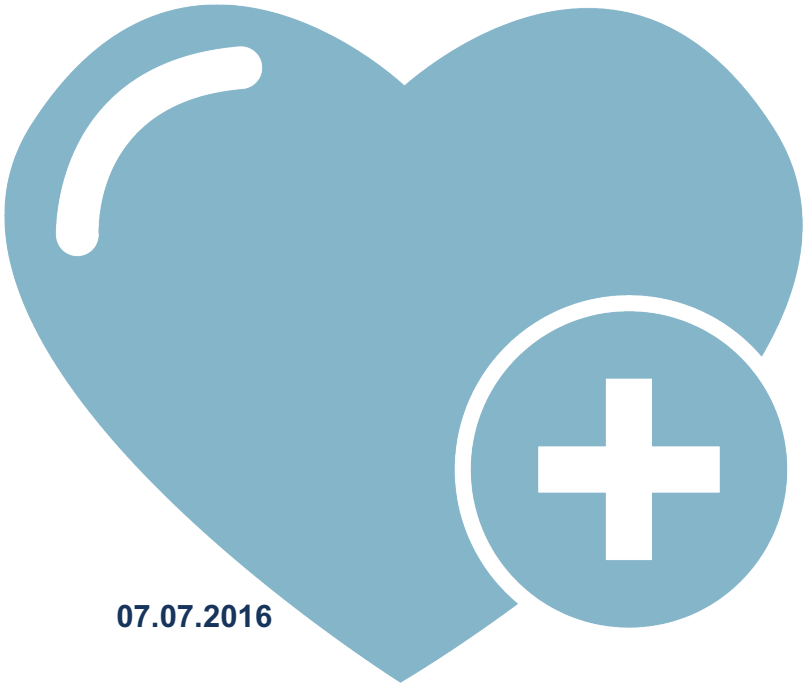
Grants Working Group Public Review Summary

Stem Cell-Derived Islet Cell Replacement Therapy with Immunosuppression for High-Risk Type 1 Diabetes

Application Number: CLIN1-08671 (Revised Application)	Review Date: June 28, 2016

Late Stage Preclinical Project Proposal (CLIN1)



07.07.2016

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Stem Cell-Derived Islet Cell Replacement Therapy with Immunosuppression for High-Risk Type 1 Diabetes

APPLICATION NUMBER: CLIN1-08671 (Revised application)

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PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate

Human embryonic stem cell (hESC)-derived pancreatic progenitor cells delivered in a device that allows direct vascularization of the cell therapy

Indication

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

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.

Major Proposed Activities

Manufacture and quality control assessment of the cells and devices for preclinical and clinical studies

Execute GLP preclinical safety study

Prepare and submit IND application to FDA to allow clinical testing of VC-02

Funds Requested

$3,984,164 ($994,343 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 6 GWG members

Votes for Score 2 = 4 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

During the review of the originally submitted application, reviewers were concerned that the device specifications were not adequate to support this stage of preclinical research and that the scientific rationale was insufficient to support continued development of this product. However, the applicant responses in the revised application sufficiently addressed reviewers concerns such that reviewers recommended this application for funding. While reviewers continue to have some reservations regarding the scientific rationale for use of a perforated encapsulation device, they thought there was sufficient promise to warrant continued development of the proposed product and agreed that clinical trials are the next reasonable step, assuming the safety profile is favorable at the completion of this project.

Review Summary

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

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

- There is significant unmet medical need in the stated patient population, and this treatment could fulfill the unmet medical need in the portion of the population that meet the criteria for islet transplantation.

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

- This treatment could improve the standard of care for patients in that it could provide a more readily available source of progenitor cells for transplantation than is currently available.

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

- It is too early to tell whether the proposed product would offer a sufficient, impactful, and practical value proposition as this will depend on efficacy data not yet available.
- The value proposition is somewhat limited by the need for ongoing immunosuppression with this treatment approach.

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 rationale for the first generation product for use of an encapsulation device was to protect the treatment recipient from the hESC-derived cells and the cells from deleterious immune responses by the recipient. While data supports that introduction of holes into the device does improve engraftment of cells, some reviewers questioned the rationale for use of a device with perforations that could allow cells to travel in and out of the device.
    - Reviewers wondered what will be accomplished using the perforated device that cannot be accomplished by simply delivering cells as this device is likely to allow two-way cellular traffic.
    - Reviewers thought that the tumorigenicity risk with the perforated device is increased as compared to the first generation encapsulated

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combination product, but also noted that tumorigenicity studies are a large component of the proposed project.

- The reviewers were not certain of the clinical relevance of the number of cells studied by the applicant for tumorigenicity and thought the applicant might be overly optimistic that smaller number of cells will not leave the device. However, reviewers also noted that a series of preclinical studies with the hESC-derived cells at different stages of differentiation do support safety.
- Ideally, reviewers would like to see additional safety and engraftment studies in large preclinical animal models to support the rationale and a favorable risk-benefit assessment before moving to human clinical trials. However, they acknowledged the extreme difficulty of doing xenotransplant studies and conceded that clinical trials are likely the next logical step.

- In the original review, a number of CMC concerns were expressed as the device configuration and manufacturing protocol seemed poorly defined. In the review of the revised application, reviewers thought many of these concerns were adequately addressed, and the device sufficiently defined to move forward with the proposed project.

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

- The data supports continued development of this product and movement to clinical trials, provided the IND-enabling safety data is favorable.
- Large animal preclinical model data would provide stronger support but reviewers acknowledged that it might not be possible to collect such data in the xenotransplant setting.

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.

- In the review of the originally submitted application, reviewers were concerned whether comparability could be established such that all described preclinical studies could be used to support the IND application. The applicant clarified in the revised application that the studies would be repeated with devices manufactured under the preclinical and clinical manufacturing protocol, thus alleviating reviewer concerns.
- Reviewers appreciated that the applicant altered aspects of the draft clinical protocol in response to concerns expressed during review of the originally submitted application.
- Reviewers suggested the applicant carefully monitor insulin management in the event insulin independence is not achieved in the clinical trial. Ideally insulin monitoring would begin prior to treatment initiation so that treatment effects on insulin dose can be observed.
- The choice of immunosuppression is based upon islet transplant regimens and a regimen tailored to this product is not adequately investigated in the proposed project plan.

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

- Reviewers thought the overall project to be of high quality and studies to be well-constructed.

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- Reviewers noted that the revised application includes improved medical monitoring and refined clinical endpoints from that proposed in the original application, which adds quality to the overall project.
- Reviewers would have appreciated updated information regarding the ability to manufacture the larger device and would like to see further demonstration of manufacturing capabilities, but they were overall satisfied with the applicant's ability to reproducibly manufacture the device for the proposed preclinical studies.

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

- The project plan and timelines demonstrate an urgency commensurate with CIRM's mission.

Is the project feasible?

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

- The project plan appears appropriate to achieve the intended objectives of the project.
- The timelines proposed in the original application did not seem feasible. However, revised timelines are more likely to be achieved, though they remain ambitious.
- CIRM will need to establish meaningful milestones in order to ensure progress.

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 of high quality with a demonstrated track record of operational success.
- The project is appropriately staffed and has all the necessary resources to conduct the proposed activities.

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

- The team appears to have an adequate 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).