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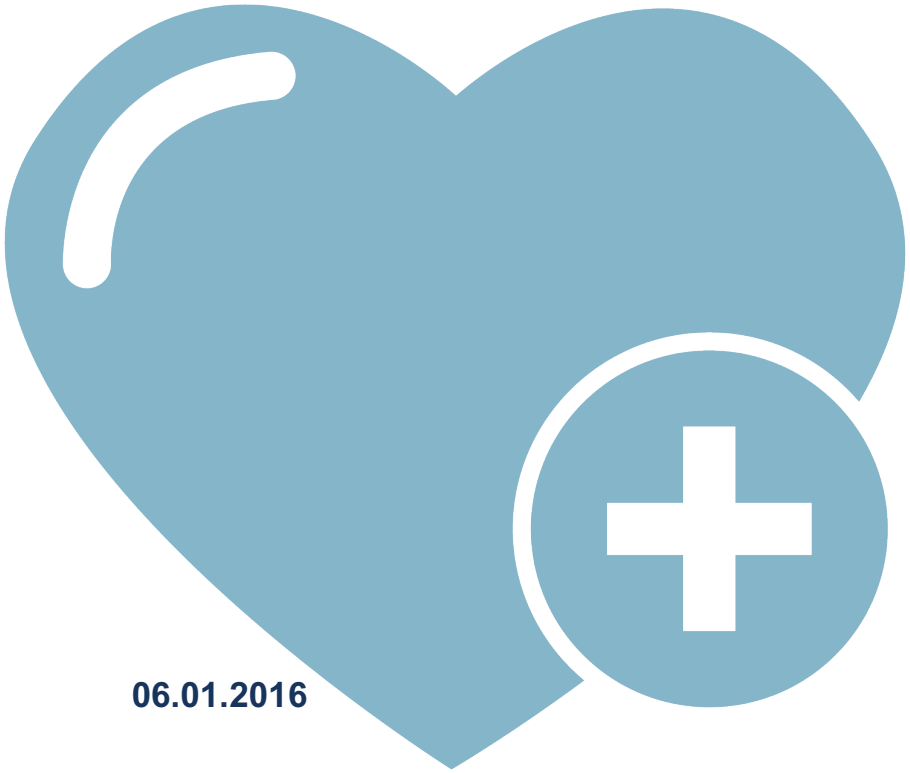
Grants Working Group Public Review Summary

Submission of an Investigational New Drug (IND) Application from the FDA for a Cellular Therapy to Treat Chronic Wounds in Diabetics

Application Number: CLIN1-09187	Review Date: May 23, 2016

Late Stage Preclinical Project Proposal (CLIN1)



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Submission of an Investigational New Drug (IND) Application from the FDA for a Cellular Therapy to Treat Chronic Wounds in Diabetics

APPLICATION NUMBER: CLIN1-09187

REVIEW DATE: May 23, 2016

PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate

Autologous Stromal Vascular Fraction Cells isolated at the point of care

Indication

Ulcers and chronic wounds associated with diabetes

Unmet Medical Need

Chronic wounds place undue burden on the healthcare system nationwide. The current standard of care only has a marginal success rate and chronic wounds continue to debilitate both patients and healthcare providers. We hope to develop a better treatment alternative for chronic wounds and ulcers.

Major Proposed Activities

Prepare IND and Investigator's Brochure

Conduct additional product characterization study per FDA request

Institute endotoxin testing into clinical workflow

Funds Requested

$75,800 ($0 Co-funding)

Recommendation

Score: 3

Votes for Score 1 = 0 GWG members

Votes for Score 2 = 2 GWG members

Votes for Score 3 = 9 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

While the proposed treatment is an economical and practical approach to fulfill an unmet medical need, there is insufficient product characterization and preliminary data with the intended product to support this proposal. In addition, the project plan is not adequate to achieve the intended objective, and the team is not appropriately experienced in product and clinical development.

Review Summary

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

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

- If successfully developed, the proposed treatment could fulfill an unmet medical need.
- The project plan is not structured appropriately to test whether the proposed product will fulfill an unmet medical need.

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

- It is possible that this approach could provide an improvement to the standard of care for this patient population, but the proposal needs significant modification in order to demonstrate a likelihood of success.

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

- If successfully developed, this approach has economy and could offer a sufficient and practical value proposition, but only if the demonstrated therapeutic benefit is sufficient to support adoption.
- There are currently options for similar treatments available to plastic surgeons if they wanted to attempt such treatments, but these are not currently being adopted, presumably because sufficient benefit has not been demonstrated.

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.

- Much of the preclinical data is cited from the literature, not data generated with the proposed clinical product.
- There is not adequate product characterization of the stromal vascular fraction despite access to stromal vascular fractions from a large number of patients.
- There is not adequate measurement of product activity.
- The ability to rinse reagents from the product prior to infusion back into the patient has not been adequately demonstrated.
- There is a demonstrated capacity to perform the described procedure in the operating room.
- Based on preclinical data, this approach has been attempted in similar indications and has been safe but not yet demonstrated clinical efficacy. The applicant has not provided adequate rationale or preclinical data to convince

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reviewers that the outcome would be different here.

- The majority of the cited literature supporting scientific rationale is not from the proposed indication.
- The literature suggests that fat preparations from diabetic individuals are not as effective those from non-diabetic individuals, and the applicant did not adequately address this concern.

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

- Additional characterization of the product is necessary before advancing to IND-enabling studies.

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 applicant includes a competent regulatory consultant on the project team, but the application does not reflect involvement of the consultant. While the applicant clearly intends to utilize this award to gain further access to the regulatory consultant, it is critical that the regulatory consultant be involved in generating an IND-enabling project plan that could be considered adequate for receipt of CIRM funding.
- The patient selection criteria are not well chosen for the proposed patient population and do not allow adequate distinction between selection of patients with diabetic ulcers verses critical limb ischemia.
- The plan to biopsy patients to study mechanism of action (MOA) is not well justified in terms of risk-benefit to the patient, and there are other ways to study MOA.
- Due to the lack of information of the characteristics of the product, it is unlikely that comparability analysis or release assays will be developed any time soon. Demonstration of comparability will be critical to leverage existing clinical data in the IND application.
- There is not a well-constructed plan for product development and expansion to clinical trials.
- The specifics of cell isolation are not adequately described.

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

- There is little information on the characteristics of the product, making evaluation of the quality of the project difficult.
- Details necessary to properly evaluate the quality of the project are missing from the proposal.

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

- The timeline demonstrates an urgency commensurate with CIRM's mission, but the project plan is not sufficiently developed.

Is the project feasible?

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

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the proposed timeline.

- While the proposal could be completed within the proposed timelines, there are too many variables that are uncontrolled in the proposed study to reach the intended objective.

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 seems inexperienced with FDA interactions, regulatory process, clinical development, and product development and needs much assistance in these areas to develop an appropriate and competitive proposal.
- There is a lack of infrastructure to support IND-enabling and clinical research. For example, there is no labeling system for the product that is appropriate for clinical trial product, which is reflective of the lack of appropriate infrastructure.
- The regulatory consultant is very competent though not well utilized in developing the IND-enabling plan.
- There is only one junior level team member named on the manufacturing team. This is not adequate to generate confidence that the manufacturing plan can be executed as proposed.

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

- The applicant has articulated several risks and an adequate contingency plan for those risks, but the major potential risk is not mentioned: delay in meeting FDA requirements for product characterization.

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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: Do Not Fund and Do Not Allow Reapplication for 6 Months (CIRM concurs with the GWG recommendation).