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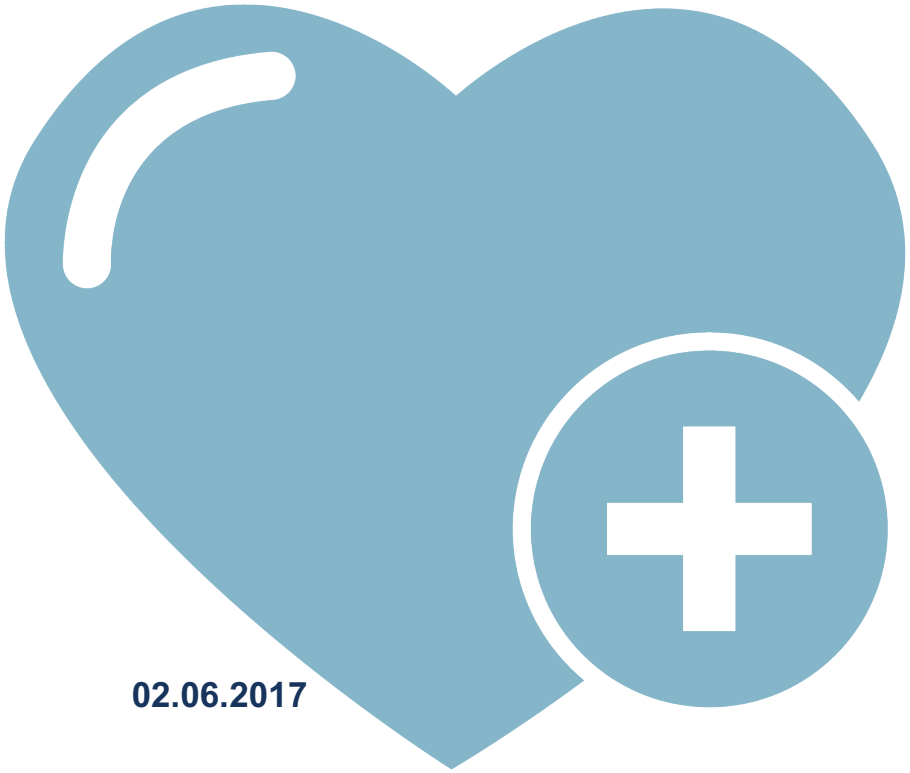
Grants Working Group Public Review Summary

Allogenic Human Adipose-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis

Application Number: CLIN1-09472 (Revised Application)	Review Date: 31 January 2017

Late Stage Preclinical Project Proposal (CLIN1)



02.06.2017

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Public Review Summary

Allogenic Human Adipose-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis

APPLICATION NUMBER: CLIN1-09472 (Revised application)

REVIEW DATE: 31 January 2017

PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

Intra-articularly injected allogeneic culture-expanded human adipose derived mesenchymal progenitor cells

Indication

Knee osteoarthritis (OA)

Therapeutic Mechanism

Cartilage regeneration (as determined by cartilage volume increase) and immunomodulatory effects

Unmet Medical Need

There is no approved disease modification therapy for OA, and OA is a leading cause of both hospitalization and joint replacement surgery. Our product provides symptom relief and structure modification benefits.

Project Objective

File IND

Major Proposed Activities

Manufacture product to supply the proposed trial

Complete non-clinical safety study requested by the FDA

File IND

Funds Requested

$2,291,976 ($572,994 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 10 GWG members

Votes for Score 2 = 1 GWG members

Votes for Score 3 = 1 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

Reviewers agreed that the proposed product holds potential to provide a disease-modifying benefit to patients with knee osteoarthritis (OA) and addresses an unmet medical need for a huge health burden in California. The reviewers also agreed that the team leading this project is excellent. However, during previous reviews of this application, reviewers were concerned whether the applicant would be able to leverage existing data from preclinical and clinical studies conducted in China for the eventual IND filing. Data provided by the applicant in the revised application alleviated these reviewer concerns, and reviewers were confident that the applicant will be able to execute the proposed project plan and file a well-prepared IND with the FDA. Reviewers, therefore, recommended this project 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.

- Knee OA is an unmet medical need, particularly in California where more is spent on OA management than any other state.

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

- Other than knee replacement, there are few effective therapies available. If the proposed treatment results in structural modification benefits and prevents or improves cartilage damage, this would be a significant improvement to the standard of care.
- If the proposed treatment exerts analgesic effects, this would be an improvement to the standard of care.

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

- If the proposed product successfully alleviates symptoms, this would provide a sufficient value proposition to patients. If the product results in disease-modifying benefits, as suggested by existing clinical data, the value proposition for patients and health care providers is substantial.
- Development of the proposed allogeneic product provides a substantial value proposition as compared to that of the autologous product.

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 proposed project is based on a sound scientific rationale supported by substantial preclinical and clinical data with both an autologous version of the product and the proposed allogeneic product.
- Early outcomes of clinical research with the autologous product in China suggest that the product is safe and has potential to provide both symptomatic relief and disease-modifying benefits.
- Data with the allogeneic product from trials conducted in China is not yet available, but will be available to support the eventual IND filing. Establishing

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comparability of the product manufactured in China with that manufactured in California is critical, and the subject of the proposed project. While reviewers were concerned about product consistency during the first review, lot manufacturing data provided in the revised application supports the ability of the applicant to demonstrate comparability and gives reviewers confidence that the technology transfer will be successful.

- Certain key IND-enabling studies had not yet been completed by the time of the previous review of this application. However, the completed preclinical study reports submitted with the revised application support the proposed project.

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

- The preclinical and clinical data support continued development of this therapeutic candidate.

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 initially expressed concerns regarding the draft clinical plan, but the revised application alleviated many of these concerns. Reviewers encouraged the applicant to continue to develop a strong clinical plan during the course of this award.
- The plan to build upon work conducted in China and transfer this technology to California is solid and based upon good communication with the FDA.

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

- This is a well-constructed, quality program.

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

- The timelines and project plan demonstrate an urgency commensurate with CIRM's mission and move this product quickly toward initiation of a phase 1 clinical trial.

Is the project feasible?

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

- The team has executed on FDA requests in a timely manner and should be able to achieve an IND submission in the outlined time frame.
- The manufacturing capabilities in China and at the California partner institution support successful execution of the proposed project plan.

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 teams in China and the US are excellent, experienced, and focused on moving into clinical development of this product in the US.
- Some reviewers raised concern that the newly appointed PI is less experienced and has not demonstrated the skills to lead clinical trial.

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- All resources are in place to conduct the proposed activities.
- Reviewers suggested the addition of a statistician to the team to aid in clinical trial planning activities.

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

- The contingency plan is carefully considered and is based upon experiences of the project team in China, which is an advantage.

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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).