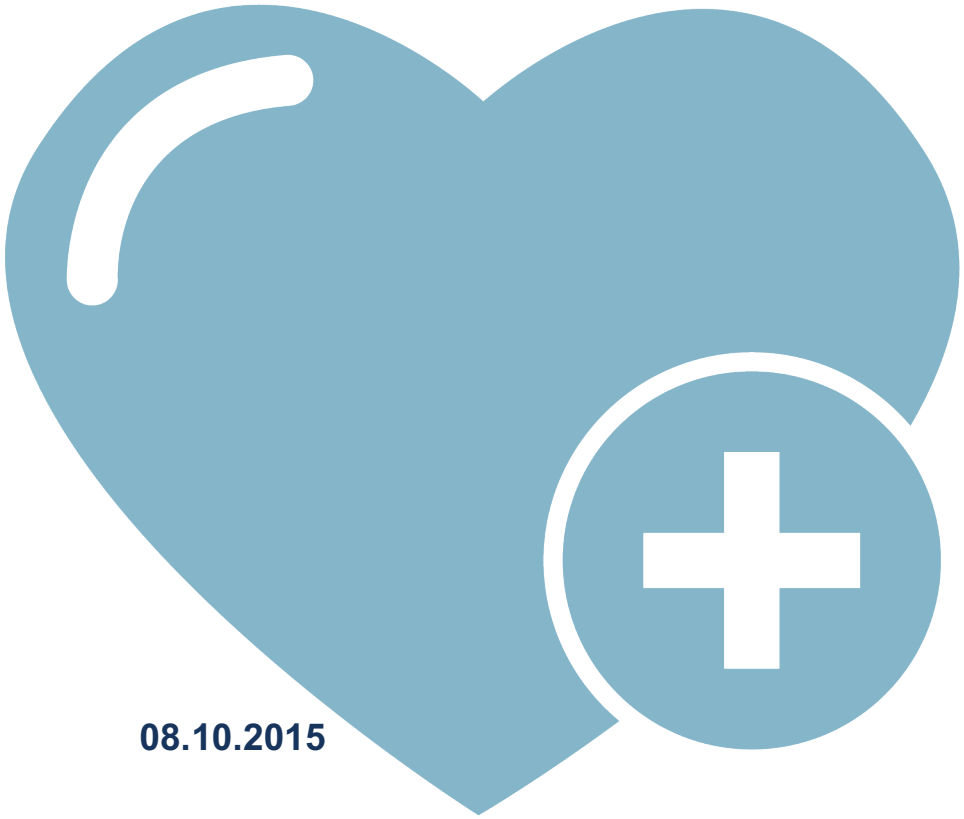
CLINICAL

Grants Working Group Public Review Summary

Development of a Chondrogenic Drug Candidate Targeting Resident Mesenchymal Stem Cells for the Treatment of Osteoarthritis

Application Number: LSP1-08309	Review Date: July 28, 2015

15-01: Late Stage Preclinical Project Proposal



08.10.2015

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Development of a Chondrogenic Drug Candidate Targeting Resident Mesenchymal Stem Cells for the Treatment of Osteoarthritis

APPLICATION NUMBER: LSP1-08309

REVIEW DATE: July 28, 2015

PROGRAM ANNOUNCEMENT: Late Stage Preclinical Projects (15-01)

Therapeutic Candidate

The therapeutic candidate is a small molecule that promotes cartilage resident mesenchymal stem cell differentiation into chondrocytes.

Indication

Osteoarthritis and cartilage injury

Unmet Medical Need

Current therapeutic options for Osteoarthritis (OA) are limited to pain or symptom-modifying drugs and joint replacement surgery; no disease-modifying drugs are approved for clinical use. The therapeutic candidate, if successful, will be the first-in-class regenerative medicine for OA and cartilage injury.

Major Proposed Activities

IND document preparation and filing

GLP toxicology and safety profiling of the therapeutic candidate

Non-GLP determination of maximum tolerated doses upon local administration

Funds Requested

1,667,832 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 12 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.

CIRM 2.0

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Review Overview

The therapeutic candidate is disease-modifying drug with potential to improve the standard of care for a serious unmet medical need, osteoarthritis (OA). Sound preclinical data generated under CIRM funding supports moving the candidate forward through late stage preclinical studies and into clinical trials. The applicant is likely to file an Investigational New Drug (IND) application with the FDA that supports a robust and well-designed Phase 1 clinical trial provided the applicant incorporates input from their Pre-IND meeting with the FDA and adequately addresses the concerns of this panel.

Review Summary

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

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

- The proposed therapy targets one of the leading causes of disability, OA, which does not have disease-modifying treatments available, and the proposed therapeutic is a drug entity that intends to modify the disease state rather than just treat pain.
- A subset of reviewers considered OA to be an urgent unmet medical need, but less urgent than other disease states since other treatment option outcomes are generally good and are improving.

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

- If the drug is demonstrated to be disease-modifying it will significantly improve the standard of care for patients with OA.
- The duration of effect will be a strong determinant in the improvement to standard of care offered by this drug.

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

- This approach is generally low cost, well-accepted, and practical.
- The value proposition depends upon the magnitude and durability of the effect, the number of injections required and time between injections (dosing). There is no strong preclinical data to predict these variables at this time. Therefore, reviewers noted a strong potential for a sufficient and impactful value proposition but could not predict the likelihood of this drug achieving it.

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.

- There is sound preclinical data in the rodent to support the safety of the proposed therapeutic, and it is exciting to see a drug with evidence of potential to modify the OA disease state.
- Although the preclinical efficacy studies may be sufficient, properly designed non-rodent studies would provide more confidence that efficacy in humans is possible and would improve the design of the Phase 1 study.

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

- There is reasonable preclinical data to support moving into the clinic.
- The applicant does not propose measuring biomarkers for bone - only for cartilage. Though some data suggests this drug protects bone, direct evidence of this is desirable to support continued development, although not strictly necessary for moving to the clinic.
- The Target Product Profile (TPP) is vague and needs more detail supported by preclinical data. The efficacy endpoints envisioned by the TPP lack specificity. The applicant needs to align the human program described by the TPP with the preclinical efficacy data.

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 achieves meaningful outcomes to support further development of the therapeutic candidate.

- The project is well-planned and designed to minimize risks and demonstrate safety of the proposed candidate for exploratory use in humans.
- A Pre-IND meeting supported under a CIRM award is proposed for later this year. However, reviewers thought the team has sufficient data for a Pre-IND meeting now and strongly recommended it be conducted as soon as possible and prior to the initiation of the proposed studies.
- There are concerns with the design of the preclinical efficacy studies (outlined in the following bullet points). As safety studies are not in question and these concerns center around durability, dosing, and selection of clinical endpoints, reviewers debated as to whether these matters are best addressed with preclinical or clinical data. Ultimately, reviewers agreed that FDA comment on the preclinical plan is imperative.
  - The non-rodent animal model study utilizes a weight-bearing model accepted by the FDA. However, the time of intervention and length of study does not mimic the proposed human indication – moderate to severe OA. The preclinical package will, therefore, lack evidence of efficacy in this model to support the proposed clinical endpoint. The team should consider a study design that allows them to test the durability of the effect in a chronic model where, given the proposed mechanism of action (MOA), it may even be more likely that efficacy is observed than in the acute setting. FDA may in fact require this, and it should be discussed with FDA in the Pre-IND meeting prior to study initiation.
  - Preclinical dosing is not well-understood, and the non-rodent study could be designed to provide data that would allow refinement of the dosing in the Phase 1 trial. It is not unusual to lack understanding of dose prior to clinical testing, but the team will need to carefully consider justification of the proposed Phase 1 dosing scheme in the IND filing. This should be discussed with FDA in the Pre-IND meeting prior to study initiation.
  - There is little preclinical evidence to support the proposed number of injections required for efficacy. It may be appropriate to collect this data in the clinic, but the team should carefully consider this issue and discuss with FDA in the Pre-IND meeting.
  - There were minor concerns regarding the difference in milieu in the animal models verses that of a typical aged OA patient. Reviewers thought that the proposed MOA can support use in the proposed patient population but recommended the applicant address this issue when discussing MOA in the IND filling.
  - Reviewers noted that most patients in the clinical trial will be on drugs for

OA and none of the preclinical studies consider drug-drug interactions. The applicant should be mindful of this in their IND filing and in designing and conducting the Phase 1 study.

- The CMC section is excellent. It includes desirable features such as production and use of GMP grade material for the pivotal toxicology studies and piloting and exploration of new pathways, which show reasonable yield.
- The draft clinical protocol describes a large Phase 1 that includes randomization and combines assessment of single and multiple doses. The randomization scheme was appreciated by reviewers, and the trial design supports collection of a robust data set, could allow collection of longer term data, and could allow the team to determine an initial sense of efficacy.
- The inclusion of biomarker studies in the preclinical and clinical program is excellent.

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

- Overall, the program is of high quality.
- There is significant reliance on a Contract Research Organization (CRO). There is no indication of any issue with this partnership but it should be managed closely and actively.

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

- The timeline is appropriately aggressive and reflective of the urgency of CIRM's mission.
- The team is focused on filing of the IND and progression to clinical study.
- The proposed project plan has been redesigned from an existing CIRM award to accelerate the program.

Is the project feasible?

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

- The proposed timelines are aggressive but reasonable, and objectives are achievable.
- The lack of input from the FDA could significantly impact the study design and timelines, and, therefore, the feasibility achieving objectives within the proposed timeline.

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 excellent and well-qualified, and includes drug development and project management experience.
- The team should name an appropriately experienced Head of Quality Assurance.

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

- There are viable contingency plans, but they are not well articulated.
- There are not sufficient contingency plans to manage unexpected outcomes.

CIRM Recommendation

The CIRM team met after the GWG to consider its recommendation to the Application Review Subcommittee. This section will be posted publicly.

RECOMMENDATION: Fund (CIRM concurs with the GWG recommendation).