CLINICAL

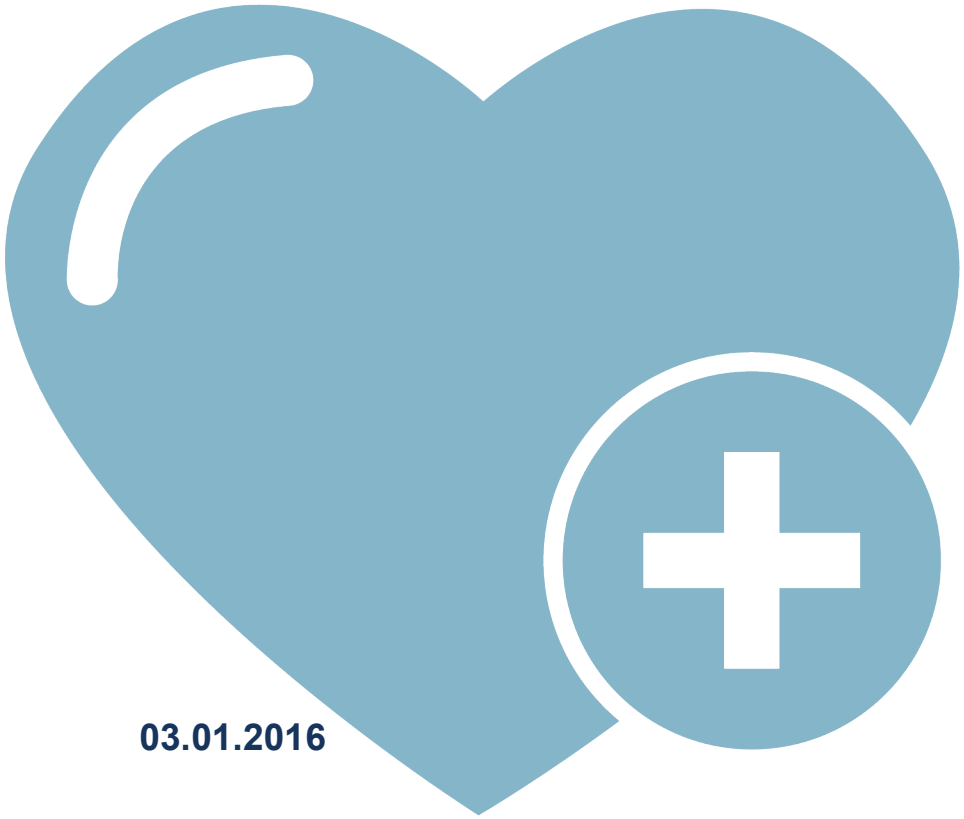
AGENDA ITEM #9
ICOC MEETING
MARCH, 16th, 2016

Grants Working Group Public Review Summary

Allogeneic Cardiosphere-Derived Cells for Duchenne Muscular Dystrophy Cardiomyopathy

Application Number: CLIN2-08334 (Revised Application #2)	Review Date: February 23, 2016

Clinical Trial Stage Project Proposal (CLIN2)



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Allogeneic Cardiosphere-Derived Cells for Duchenne Muscular Dystrophy Cardiomyopathy

APPLICATION NUMBER: CLIN2-08334 (Revised application #2)

REVIEW DATE: February 23, 2016

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate

Allogeneic Cardiosphere-Derived Cells (CDCs, CAP-1002)

Indication

Duchenne Muscular Dystrophy (DMD) Cardiomyopathy

Unmet Medical Need

Heart failure is the leading cause of death among young men with DMD. No specific therapies exist to treat this element of the disease. CAP-1002 is intended to treat the cardiomyopathy associated with DMD.

Major Proposed Activities

Manufacture CAP-1002 in quantities sufficient to treat all subjects enrolled in the trial

Enroll and treat all subjects per the clinical protocol

Funds Requested

$ 3,376,259 ($2,254,032 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 12 GWG members

Votes for Score 2 = 1 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

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

Review Overview

In the review of the original application and the first amendment, reviewers noted the high potential impact of the proposed therapeutic but expressed concerns regarding the risk-benefit profile and questioned the likelihood that the proposed therapeutic would ultimately prove to be efficacious and impact standard of care. In this second amendment to the original application, the applicant depicted its data more clearly and thoroughly, providing sufficient support for reviewers to conclude that CAP-1002 could act as postulated in the DMD cardiomyopathy setting and, ultimately, improve standard of care for DMD cardiomyopathy patients. For this reason, reviewers thought initiating the proposed trial at this time to be warranted and recommended funding of this project.

Review Summary

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

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

- While some stabilizing treatments are available, Duchenne muscular dystrophy (DMD) cardiomyopathy represents a serious unmet medical need and innovative therapies to treat it are needed. The proposed therapy, CAP-1002 has the potential to be such a therapy.

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

- CAP-1002 is intended to stop fibrosis and potentially initiate regeneration following administration to DMD cardiomyopathy patients. If it works as intended, CAP-1002 would represent an improvement to the standard of care.
- Reviewers expressed concerns as to whether or not CAP-1002 would be able to demonstrate significant improvement over the stabilizing treatments currently available, but thought the body of data suggested that clinical trials to test this hypothesis are warranted.

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

- Reviewers noted that DMD is a chronic genetic disorder and it is unlikely that CAP-1002 will address the underlying pathology of the disease. It is, therefore, likely that repeat dosing will be required. Depending on the risk-benefit profile, the frequency of treatment, and the cost per treatment, the value proposition may or may not be sufficient and impactful.
- The inevitable commercial scale up issues will need to be addressed in order for this treatment to provide a practical value proposition. This effort should be initiated fairly soon.

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.

- Clinical data in other cardiac settings supports the safety of intracoronary infusion of CAP-1002.
- Clinical efficacy data in other cardiac settings is intriguing. There are still

questions regarding efficacy, but the balance of data suggests that clinical testing at this time is appropriate.

- While the applicant does not have data in the preferred large animal model of DMD, sufficient preclinical data was provided to support a favorable risk-benefit profile.
- As DMD is a chronic genetic disorder and it is unlikely that CAP-1002 will address the underlying pathology of the disease, repeat dosing is likely needed. In the original review, reviewers were concerned that feasibility of repeat dosing was not adequately demonstrated to justify moving forward with clinical trials in the indication. However, in its revised application, the applicant provided sufficient data to support the feasibility of repeat dosing.

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

- While additional preclinical data might strengthen the risk-benefit profile, there is sufficient data to support clinical trial initiation in the DMD cardiomyopathy patient population.
- Given ongoing drug development to treat the skeletal muscle manifestations of DMD and the possibility that such treatments might soon obtain FDA licensure, development of a complimentary treatment for cardiac conditions associated with DMD is timely.

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.

- While reviewers expressed concerns during the review of the original application and the first amendment that the standard of care may vary between treatment groups, thus making interpretation of results challenging, the second amendment to the application made clear that all patients would receive standard of care medications, including steroids. This information also alleviated concerns regarding deleterious immune responses following treatment administration.
- Concerns that the number of sites would introduce unnecessary variability in the trial were alleviated by assurances that most patients would come from one or two sites, and the other sites were available primarily to ensure enrollment success. The applicant's explanation regarding site training also alleviated concerns.
- Reviewers suggested that the applicant look at the safety and efficacy profile in the adult cohort as a decision point prior to initiating the pediatric cohorts.
- From a manufacturing perspective, the project is well planned.

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

- This is a reasonably well-constructed quality program that will monitor for significant side effects resulting from the delivery of CAP-1002.
- The proposed assay to determine potency will be difficult to quantitate and validate.

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

- The project plan and timeline demonstrate an urgency that is 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 patient population at the proposed centers should support timely enrollment of the proposed clinical trial.

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 has previous experience and can likely carry out the proposed clinical trial.
- The clinical trial sites are excellent, which improves the likelihood that the trial will be successful in demonstrating whether or not this treatment is efficacious in the DMD cardiomyopathy setting.
- The team would benefit from a more defined and experienced manufacturing and quality assurance team.

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

- The contingency plans appear reasonable.
- The failure rate at the master cell bank stage could pose problems moving forward.

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).