

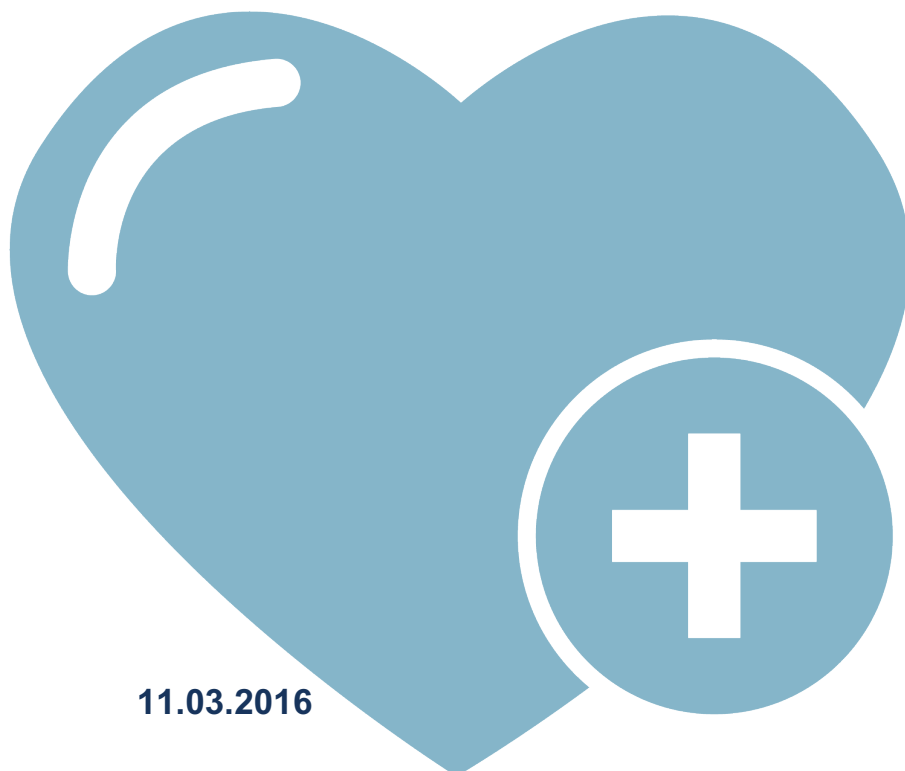


# Grants Working Group Public Review Summary

Pulmonary Arterial Hypertension Treated with Cardiosphere-Derived  
Allogeneic Stem Cells

Application Number: CLIN2-09444	Review Date: October 25, 2016
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Clinical Trial Stage Project Proposal (CLIN2)



11.03.2016

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# Pulmonary Arterial Hypertension Treated with Cardiosphere-Derived Allogeneic Stem Cells

**APPLICATION NUMBER:** CLIN2-09444

**REVIEW DATE:** October 25, 2016

**PROGRAM ANNOUNCEMENT:** CLIN2 Clinical Trial Stage Projects

## Therapeutic Candidate

Allogeneic cardiosphere-derived stem cells (CAP-1002)

## Indication

Pulmonary Arterial Hypertension (PAH)

## Unmet Medical Need

PAH is a progressive condition for which there is no cure. Even with substantial pharmacologic advances in the modern treatment era, survival still remains unacceptably poor. The administration of CDCs has the potential to reduce adverse arteriolar remodeling in PAH.

## Major Proposed Activities

To assess the maximum feasible dose and safety of CAP-1002 through a Phase 1a clinical trial in patients with PAH.

To assess long term safety and exploratory efficacy outcomes of CAP-1002 through a randomized Phase 1b clinical trial in patients with PAH

## Funds Requested

\$ 7,354,772 (\$0 Co-funding)

## Recommendation

Score: 1

Votes for Score 1 = 7 GWG members

Votes for Score 2 = 5 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 for at least six months after the date of the GWG's recommendation.

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## Review Overview

Reviewers noted the great interest from physicians and patients and the high potential for impact in utilizing stem cell treatments to improve the standard of care in PAH. While some reviewers expressed concerns that the preclinical and clinical rationale for use of this product is not sufficient, other reviewers thought the preclinical and clinical evidence supports moving to clinical testing of the safety and efficacy of CAP-1002 in this patient population. All reviewers agreed that the proposed clinical trial is well-designed and feasible. Ultimately, the Grants Working Group recommended this proposal for funding.

## Review Summary

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

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

- PAH is a devastating disease that lacks curative therapies and is a clear unmet medical need.
- The preclinical data suggest that the proposed treatment could potentially impact the unmet medical need, but it remains highly exploratory.

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

- If effective, the proposed treatment approach would provide an improvement to the standard of care.
- As the proposed study is designed to assess safety, not efficacy, it is not adequately powered to assess an improvement over the current standard of care. However, if the treatment reduces alveolar remodeling as expected, it would likely be an improvement over standard of care.

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

- If safe and effective, a stem cell treatment for PAH would offer a sufficient and impactful value proposition for patients and health care providers. There are not sufficient data at this time to assess the likelihood that this particular treatment will be effective, though it is likely to be safe.
- Reviewers noted that there is considerable interest from physicians and patients in this therapeutic 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 preclinical rat model is not a very good model of the human disease. However, the applicant argued that because the applicant is interested in assessing reduction of inflammation as a potential mechanism of action (MOA), the model is appropriate for preclinical testing. Reviewers agreed that the model is appropriate for such an assessment, and that the preclinical data for reduction of inflammation is compelling.
- Reviewers didn't fully understand the rationale for using cardiac-derived cells to treat a pulmonary condition. However, the applicant's proposed MOA involves

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reduction of inflammation, not tissue regeneration, and there are data to suggest this may occur, thus tempering this concern.

- Clinical data from trials in other indications and preclinical data using the proposed route of administration for PAH support a favorable safety profile for this product.
- Reviewers were uncertain whether a one-time infusion of these cells would have durable therapeutic effects.

**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 at this time.
- Reviewers noted that clinical data in other indications is not negative, but it is also not overwhelmingly positive, which curtailed enthusiasm somewhat.

**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.**

- This trial is well designed to assess safety in the patient population and to meet the objectives of the program announcement.
- The clinical protocol includes a standard battery of tests and assesses clinically relevant endpoints.
- The clinical protocol is well designed from an operational point of view.
- The applicant suggests that the MOA might involve reduction of inflammation following treatment, yet the proposed study does not include secondary endpoints to assess inflammation. The applicant should consider including endpoints to assess inflammation at preselected time points.
- Given the time to decline in this patient population, reviewers were not convinced the study is sufficiently powered to make a conclusion about the secondary efficacy endpoint of "time to clinical worsening". Further trials would be needed to confirm any signals for this endpoint.
- Reviewers noted that the tool selected to assess quality of life is expensive, and there is another freely available and validated tool that could be utilized. This could be a more economic and powerful way to assess the impact of the treatment on the patient's quality of life.

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

- This is a well-constructed, high quality program with the right people undertaking the right study.

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

- The project plan is commensurate with CIRM's mission and the timeline demonstrates an adequate urgency that is commensurate with CIRM's mission.

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**Is the project feasible?**

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

- It is likely that the applicant will be able to operationalize the clinical trial and achieve the intended objectives.
- Given the strong track record of this team in clinical trial enrollment, reviewers thought it likely this trial could be enrolled as projected, especially given the availability of patients.

**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 appropriately qualified and strong and has all the necessary resources in place to conduct the proposed activities.

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

- There is an extensive contingency plan to manage risks and delays, especially regarding enrollment risks, that is backed by a strong institutional commitment.

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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).