CLINICAL

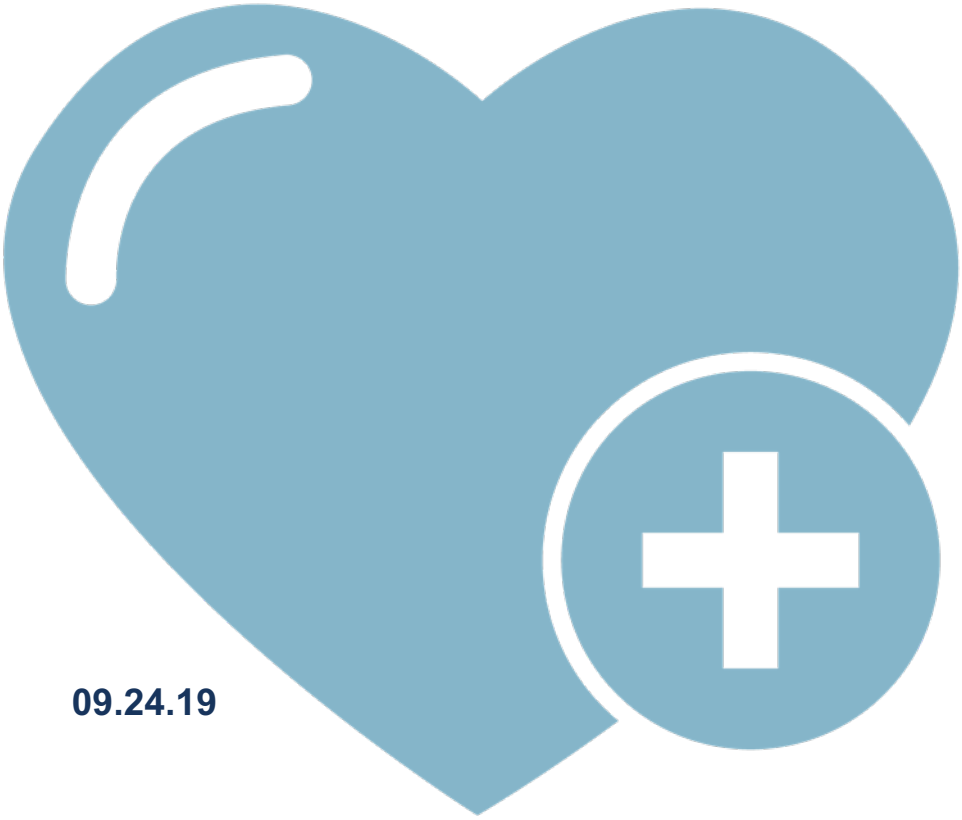
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

A Phase 2 Study of the Safety of Repeat Intravitreal Injection of Human Retinal Progenitor Cells in Adult Subjects with Retinitis Pigmentosa

Application Number: CLIN2-11472 (Revised Application)	Review Date: 16 September 2019

Clinical Trial Stage Project Proposal (CLIN2)



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A Phase 2 Study of the Safety of Repeat Intravitreal Injection of Human Retinal Progenitor Cells in Adult Subjects with Retinitis Pigmentosa

APPLICATION NUMBER: CLIN2-11472 (Revised application)

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Allogeneic human retinal progenitor cells (hRPC)

Indication

Retinitis Pigmentosa (RP)

Therapeutic Mechanism

The cells are intended to remain suspended in the vitreous cavity of the eye and exert a beneficial neurotrophic effect on the degenerating retina.

Unmet Medical Need

RP is an incurable orphan disease. There are no treatments currently available other than a retinal chip for very end stage patients. To date, there is nothing that will restore sight or slow the progression of vision loss in RP. Achieving any measurable benefits would be groundbreaking.

Project Objective

CMC readiness & re-dosing

Major Proposed Activities

Perform critical path manufacturing activities and conduct an in vitro comparability study of clinical versus commercial processes.

Validate endpoints to ensure that changes in patients' vision function and functional vision are captured by appropriate and meaningful endpoints.

Assess the safety of a repeated injection of the product in proposed Phase 2 study.

Funds Requested

$6,608,592 ($4,405,728 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 12 GWG members

Votes for Score 2 = 1 GWG members

Votes for Score 3 = 2 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.

Review Overview

This is a revised application that previously received a score of "2" on two prior submissions. The application proposes a phase 2 clinical trial to study the safety of a second treatment of allogeneic retinal progenitor cells for patients with retinitis pigmentosa (RP), a genetic disease in which patients progressively lose their vision. Reviewers agree that this is an unmet medical need, with no currently approved treatments that would be applicable to RP patients with different underlying genetic mutations.

In the prior reviews of the application, reviewers had significant concerns with the safety of the proposed treatment of both eyes, safety of repeat dosing in the same eye, and with the timing of the proposed study beginning prior to data readout of the currently in-progress phase 2b study. These concerns have been addressed in the current proposal, which has removed the treatment of both eyes, extended the time between repeat dosing of the same eye, and postponed start of the proposed study until data from the in-progress phase 2b can be utilized to inform the proposed study. Reviewers agree that the current proposal prioritizes rate-limiting and essential CMC work that will be necessary for commercialization and further development of the product. Prior concerns remain with regard to the overall efficacy of the product, the lack of a clear mechanism of action and its potential impact on potency assays, as well as potential comparability issues that may arise during the process of commercializing the product. For a few reviewers, the project did not warrant funding because of these remaining concerns, together with the incremental nature of the proposed trial, and the limited impact and value of the proposed activities. However, most reviewers generally agreed that the applicant was responsive to prior critiques and the current proposal minimizes the overall risk of the project, while still moving it forward. Thus, the reviewers recommended the application for funding.

Review Summary

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

YES	**13**	**NO**	**2**

Reviewers considered the following:

a) Whether the proposed treatment fulfills an unmet medical need.

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

c) Whether the proposed treatment offers a sufficient value proposition such that the value created by it supports its adoption by patients and/or health care providers.

d) If a Phase 3 Trial is proposed is the therapy for a pediatric or rare indication or, if not, is the project unlikely to receive funding from other sources?

Summary of Reviewers' Comments:

- This project meets an unmet need. RP is an inherited disease that ultimately results in blindness. Aside from Luxturna, which is only applicable for a small number of RP patients with a specific mutation, there is currently no treatment for the majority of RP patients.
- The approach is reasonable and has an acceptable risk to benefit ratio. It has the ability to make a significant difference in a patient's visual function and quality of life if it is effective.
- The critical issue that will determine impact will be whether the results from the current phase 2b trial at the higher dose will be effective, and whether repeat dosing will provide a sustained impact on functional vision.

2. Is the rationale sound?

YES	13	NO	2

Reviewers considered the following:

a) Whether the proposed project is based on a sound scientific and/or clinical rationale, and whether the project plan is supported by the body of available data.

b) Whether the data supports the continued development of the treatment at this stage.

Summary of Reviewers' Comments:

- The applicant has made revisions to their proposal, clinical protocol, budget, and timeline based on recommendations from prior reviews. The proposed project and next steps both for clinical and CMC are sound and make sense.
    - In the prior review of the proposed clinical protocol, reviewers thought that the inclusion of bilateral injections in the treatment plan was unacceptable for patients enrolled in the trial because of safety concerns as well as limitations for future treatment options. Reviewers commended the applicant team for following the GWG recommendation and removing bilateral injections from the clinical protocol.
    - In the prior review of the proposed clinical protocol, reviewers recommended a minimum time period between repeat injections in the same eye given that the safety of repeat injections in the same eye and the immune response is still unclear. Reviewers noted that the revised submission proposes repeat injections timed further apart as requested.
    - In the initial review of the application, reviewers were concerned that they were was limited scientific rationale for the proposed dose. In the revised submission, the applicant proposed that the proposed clinical study will take into account the ongoing phase 2b. Reviewers agreed that the ongoing phase 2b data will help define and inform the doses, endpoints, patient selection, contingency plan, and overall design.
- The mechanism of action is still not fully understood. It is unclear whether the cells need to be alive or if this effect is mediated by soluble substances.

3. Is the project well planned and designed?

YES	14	NO	1

Reviewers considered the following:

a) Whether the project is appropriately planned and designed to meet the objective of the program announcement and to achieve meaningful outcomes to support further development of the therapeutic candidate.

b) Whether the proposed experiments are essential and whether they create value that advances CIRM's mission.

c) Whether the project timeline is appropriate to complete the essential work and whether it demonstrates an urgency that is commensurate with CIRM's mission.

Summary of Reviewers' Comments:

- Based on feedback from the prior review, the current proposal now has a revised, safer study starting after the database lock for the phase 2b trial which will occur Q4 2019. This revision was made to account for the possibility that the treatment effect might be small, which would preclude moving forward with the proposed trial.
- Reviewers recognized that the applicant team needs to develop a commercial grade product and that it could be a rate-limiting step for clinical progress and development. Based on reviewer recommendations the project activities were modified to enable conduct of the critical CMC work. Reviewers noted that this work is being conducted at risk to CIRM pending outcome of the ongoing phase 2b trial.
- The reviewers' initial comments and concerns on the container closure system were adequately addressed in the revised submission.
- The reviewers' previous concerns on the critical nature of the proposed process changes remain. Given that the overall process is significantly changed, there is a strong possibility that the product will change in moving to phase 3 clinical trials. The meeting with the FDA to discuss the proposed process changes and studies required to demonstrate acceptable comparability will be critical. The timing for this meeting should be provided and results from this meeting should be shared with CIRM as it may significantly impact the cost/risk/timeline for the program.
- A cell therapy approach that is not limited to a single type of mutation is clearly a potentially valuable option for the RP patient population given the large number of different mutations resulting in RP. However, there may be differences in responses for each type of mutation in the RP population. It would be helpful to address this issue in the clinical trial design - evaluating patient responses with respect to specific mutations.

4. Is the project feasible?

YES	14	NO	1

Reviewers considered the following:

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

b) 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.

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

Summary of Reviewers' Comments:

- The intended objectives are likely to be achieved as long as the ongoing phase 2b randomized clinical trial shows some efficacy. The applicant team has redefined the objectives to match the reviewer recommended changes in timeline and work. The budget has been reworked to take into account the shift in timing, study design and scope of work.
- The current timeline indicates that the comparability studies will be initiated in Q4 of 2019. Based on this timeline, FDA feedback on the proposed plan should be available now or very soon. CIRM should review the plan to determine the potential risk of additional *in vivo* testing requirements that have not been anticipated in the current proposal.
- The team has the internal expertise and knowledge and has engaged the appropriate consultant expertise to execute the project.
- The revised proposal will allow for review of the data from the phase 2b clinical trial prior to advancing into phase 3. This is a significant reduction in risk, given that data on safety and efficacy from the higher dose will be available.
- It is unclear what the contingency plan is if the ongoing phase 2b trial does not demonstrate the expected efficacy profile for the product.

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).