CLINICAL

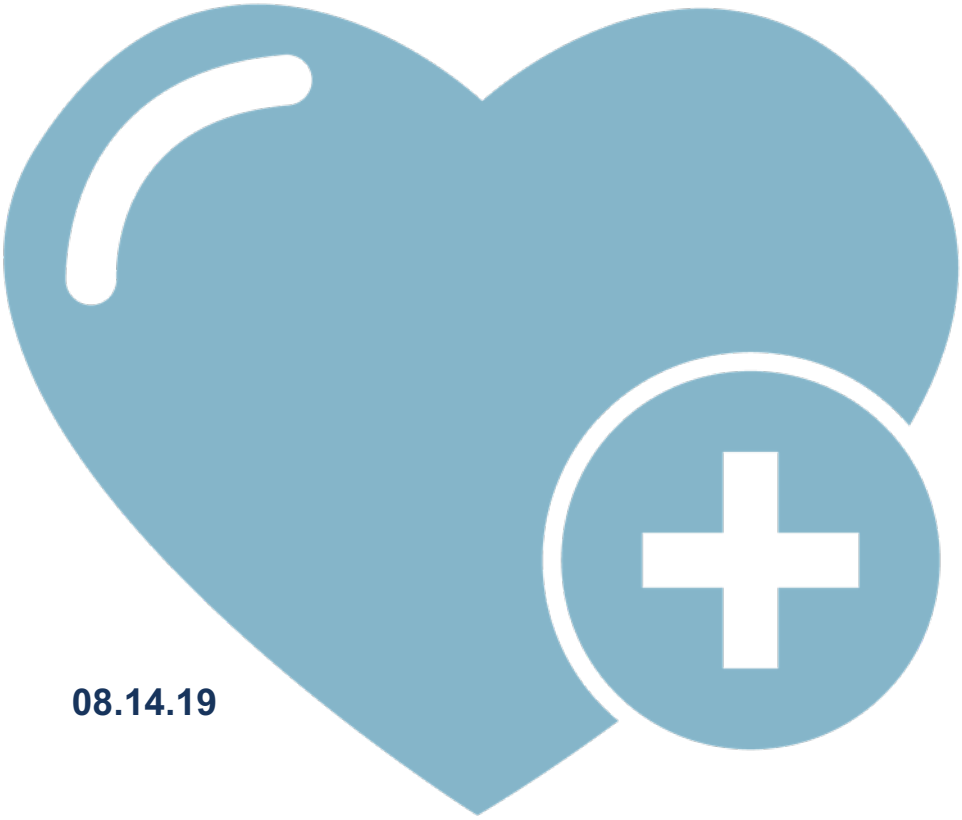
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Clinical Study to Assess Safety and Efficacy of Subretinal Injection of Human Neural Progenitor Cells for Treatment of Retinitis Pigmentosa

Application Number: CLIN2-11620 (Revised Application)	Review Date: 30 July 2019

Clinical Trial Stage Project Proposal (CLIN2)



08.14.19

Clinical Study to Assess Safety and Efficacy of Subretinal Injection of Human Neural Progenitor Cells for Treatment of Retinitis Pigmentosa

APPLICATION NUMBER: CLIN2-11620 (Revised application)

REVIEW DATE: 30 July 2019

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

CNS10-NPC - a human neural progenitor cell line

Indication

Retinitis Pigmentosa

Therapeutic Mechanism

1. Phagocytosis of photoreceptor outer segment debris.
2. The release of pro-survival factors that have localized diffusion to inhibit retinal photoreceptor cell death.
3. Immunomodulation resulting in markedly fewer host inflammatory cells at the site of CNS10-NPC engraftment.

Unmet Medical Need

Retinitis pigmentosa represents an unmet clinical need in ophthalmology. Despite growing understanding of the underlying molecular mechanisms, there remains little in the way of available treatment.

Project Objective

Phase 1/2a Completed.

Major Proposed Activities

Assess clinical safety of the clinical product (CNS10-NPC).

Obtain clinical data based on secondary outcome measures of vision loss.

Manufacture additional clinical product for a subsequent Phase 2 trial.

Funds Requested

$10,494,682 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 15 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 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." Retinitis Pigmentosa (RP) remains an unmet medical need. Gene therapy such as the recently approved Luxturna can only address specific genetic variants of RP. On the other hand, cell therapies such as CNS10-NPC have the potential to improve vision, or at least slow down vision loss, in a broader RP patient population.

In the initial review of the application, reviewers thought that the cell therapy approach was based on sound scientific rationale but wanted to see additional preclinical data that better modeled both the human disease and the proposed clinical surgery procedure. They also made several recommendations to better address patient safety and consent in the clinical protocol.

Reviewers thought that the revised submission provided compelling arguments justifying the intent of the completed preclinical studies and why the studies support clinical evaluation of CNS10-NPC. They also noted that the applicant satisfactorily incorporated the most critical protocol recommendations. Despite having reservations about the mechanism of action and specifying several additional protocol recommendations, reviewers unanimously recommended the application for funding.

Review Summary

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

YES	**14**	**NO**	**0**

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:

- There is an unmet medical need for therapies that treat and slow down visual function loss in RP patients. Luxturna, a recently approved gene therapy, is narrowly indicated for correcting a mutation in RPE65 and thus only addresses 1% of RP patients.
- The proposed cell therapy, CNS10-NPC, has the potential to stabilize or improve vision in a broader RP patient population than gene therapy.
- If the proposed cell therapy has an acceptable safety profile, then a benefit even in slowing down vision loss will have significant impact. However, the therapy may require complex surgery and immunosuppression both of which may impact adoption by both healthcare providers and patients.

2. Is the rationale sound?

YES	13	NO	1

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 cell therapy approach is based on sound scientific rationale and the applicant presented compelling data from rodent and minipig studies to support continued development of the CNS10-NPC therapy.
- There was initial concern that the most comprehensive preclinical data provided used the RCS rat model. This model may not be representative of the clinical manifestation of the disease and it also did not represent the surgical approach that would be used in the clinic. In the revised resubmission, the applicant included clarification on intent for each of the animal models utilized to date, additional data, and assurances from surgeons regarding the surgical approach. Reviewers thought this response adequate to support clinical evaluation of CNS10-NPC therapy.
- Reviewers thought that the mechanism of action for this cell therapy is still unclear but acknowledged that it is a common unknown element for cell therapies at this stage of development.
- In the initial review of the application some reviewers questioned the statistical methods applied in the various preclinical studies. Reviewers thought that the applicant's thorough response detailing statistical methodology for the various preclinical studies had adequately addressed their concerns.

3. Is the project well planned and designed?

YES	14	NO	0

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:

- In the initial review of the application, reviewers raised questions regarding safety of the surgical procedure, risk of inflammation and, based on clinical studies in a different indication with a related cell product, potential risk of tumor formation.
    - In the revised submission the applicant addressed these questions with additional information and clarification, as well as data from other clinical studies.
- In the initial review of the application, reviewers made several recommendations for revisions to the clinical protocol that were incorporated by the applicant in the revised submission:
    - Include an independent data safety monitoring committee for the trial.
    - Trial endpoints should assess change in rate of visual field loss.
    - The heightened risks of cataract surgery in RP patients should be clearly defined in informed consent forms.
    - Risks associated with the proposed immunosuppression regimen must be clearly defined in the informed consent forms.
- In the initial review of the application, the visual acuity inclusion criteria seemed aggressive and reviewers recommended starting with a more advanced RP disease cohort. Reviewers thought that the applicant's justification for the proposed patient cohorts in the revised submission was adequate.
- Reviewers made recommendations for minor modifications to the clinical protocol to help further improve the study design.

4. Is the project feasible?

YES	14	NO	0

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 clinical trial is likely to be achieved in the proposed timeline.
- The applicant has thoroughly identified risks and has good contingency plans in place.
- The team is highly qualified and adequately resourced to perform the clinical trial.

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).