CLINICAL

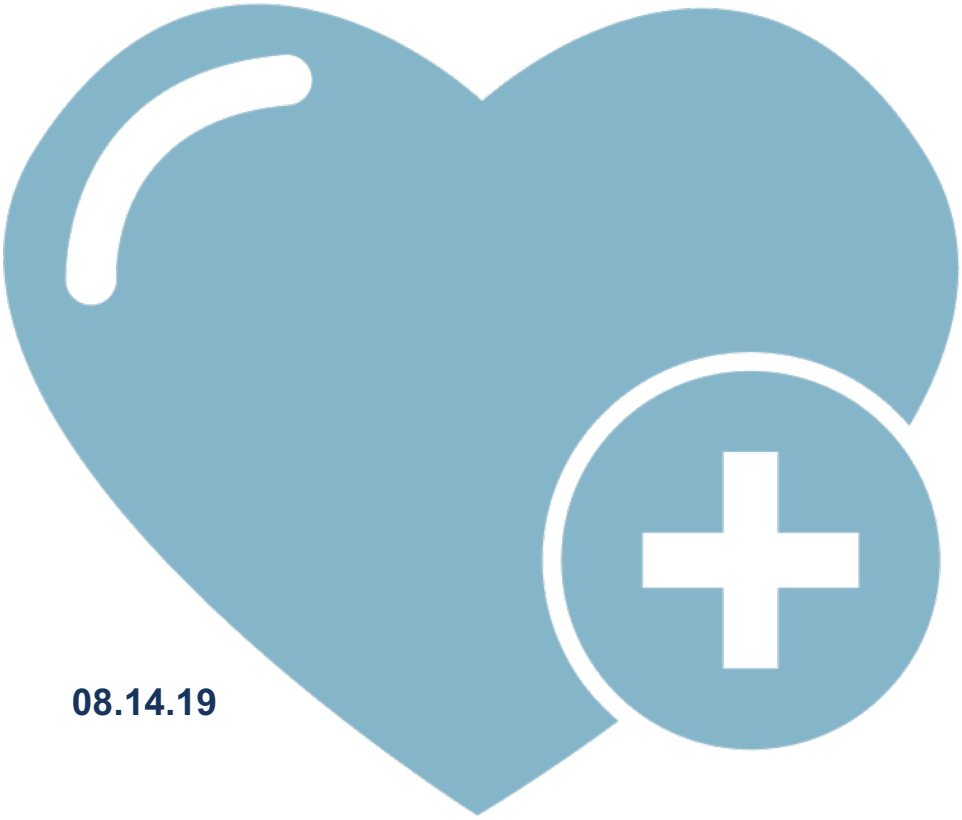
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

A Phase 1b Safety Study for MRI guided delivery of AAV2-GDNF for the treatment of Parkinson's disease

Application Number: CLIN2-11661	Review Date: 25 July 2019

Clinical Trial Stage Project Proposal (CLIN2)



08.14.19

A Phase 1b Safety Study for MRI guided delivery of AAV2-GDNF for the treatment of Parkinson's disease

APPLICATION NUMBER: CLIN2-11661

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

AAV2-GDNF is a gene therapy product encoding Glial cell line-Derived Neurotrophic Factor (GDNF).

Indication

Parkinson's disease

Therapeutic Mechanism

AAV2-GDNF will be delivered into the putamen. GDNF is a growth factor expected to act by stimulating regeneration of the terminals of dopamine producing neurons that are progressively lost in PD. This is expected to result in an increase in dopamine production leading to improved motor and non-motor functions.

Unmet Medical Need

Current therapies such as L-DOPA and Deep Brain Stimulation help to alleviate the symptoms, but the loss of dopamine producing neurons continues, so they are progressively less effective. AAV2-GDNF is a disease-modifying approach, expected to slow and/or halt the progression of PD.

Project Objective

Phase 1b trial completed

Major Proposed Activities

Activation of California clinical site for recruitment and treatment of study subjects.

Patient enrollment, randomization, dosing and completion of 18-month primary follow-up post-surgery.

Manufacturing of AAV2-GDNF for Phase 2/3 clinical studies, and drug comparability studies.

Funds Requested

$7,998,962 ($3,500,000 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 13 GWG members

Votes for Score 2 = 2 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

Parkinson's Disease (PD) is a critical unmet medical need. Reviewers thought that the proposed AAV2-GDNF gene therapy has potential as a one-time treatment for durable motor symptom control and delayed disease progression. While reviewers agreed that there is strong preclinical evidence supporting GDNF therapy in PD, prior clinical trials studying GDNF protein infusion as well as the phase 1 trial for the proposed AAV2-GDNF therapy have not shown clear signs of clinical efficacy. Despite these concerns, they thought that the applicant provided a compelling rationale for studying improved AAV2-GDNF dosing, delivery and brain coverage in both early and late-stage patients in this follow-up trial.

Reviewers commended the clinical trial design and strong qualifications of the team. However, they thought that the proposed manufacturing activities for supplying follow-on trials were expensive and potentially outside the scope of this project. A number of reviewers recommended that CIRM fund this project with the exception of the manufacturing activities.

As part of the review, the GWG must assess whether this gene therapy project is eligible for CIRM funding as a vital research opportunity. The GWG unanimously voted this project as a vital research opportunity for CIRM; they then recommended that CIRM fund this project.

Assessment of Vital Research Opportunity

For projects that are not stem cell-based, the GWG must determine by a 2/3 majority vote whether they believe the project represents a vital research opportunity to permit funding. The vote tally is presented below.

GWG Vital Research Opportunity Vote

YES	**21**	**NO**	**0**

Review Summary

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

YES	**15**	**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:

- Parkinson's Disease (PD) remains a critical unmet medical need. There are no disease modifying or restorative treatments for PD patients.
- The proposed gene therapy has the potential to slow disease progression and provide amelioration of motor symptoms. While it may not improve non-motor symptoms, it still has the potential to be a significant advance in patient care beyond currently available oral medications, deep brain stimulation and lesion therapies.
- The proposed single administration gene therapy would be of significant value to patients and healthcare providers if it is shown to have durable effect on motor symptoms and disease progression.

2. Is the rationale sound?

YES	15	NO	0

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 scientific rationale for using GDNF in PD to regenerate dopaminergic terminals and protect dopaminergic neurons is strongly supported by 25 years of preclinical data from *in vitro* and animal modeling studies.
- Single and repeated infusion of GDNF has been studied in several clinical trials and has failed to show efficacy. Reviewers agreed that inadequate dosing may have been a weakness of those approaches and gene therapy has potential to overcome that limitation.
- The previous phase 1 study with AAV2-GDNF showed safety and tolerability but no evidence of clinical efficacy. Reviewers agreed that limited coverage of the putamen with AAV2-GDNF may have been a major limiting factor.
    - They thought that the proposed surgical approach aimed at improving coverage of the putamen with AAV2-GDNF in this trial is reasonable.
    - Some reviewers noted that there are no preclinical data to support the proposed threshold amount of GDNF coverage in the putamen.
- Despite concerns regarding prior clinical failures with GDNF infusions reviewers thought that AAV2-GDNF merited continued clinical development.

3. Is the project well planned and designed?

YES	15	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:

- The proposed phase 1b clinical trial is clearly laid out, addresses key questions, measures relevant outcome parameters and has robust mitigation plans for risks to study participants.
    - The inclusion of imaging studies in the clinical protocol will enhance the knowledge to be gained from this trial.
    - Reviewers appreciated the inclusion of both early and late-stage patients but thought that earlier stage patients are more likely to benefit from this therapy.
    - Reviewers noted that the imaging-guided infusion procedure has several criteria for stopping infusion but these are inconsistently and loosely described in the protocol. Reviewers recommended that the criteria be more clearly defined to ensure consistent decision-making during the surgical procedure.
- A number of reviewers thought that the proposed manufacturing activities for supplying the follow-on phase 2/3 studies were outside the scope of this project. They strongly recommended that CIRM not fund the manufacturing activities as part of this award.

4. Is the project feasible?

YES	15	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 completed in the proposed timeline.
- The proposed team is outstanding and has a strong track record in surgical care of PD patients and in PD research.
- The applicant should make all possible efforts to ensure that the California clinical site enrolls at the same rate as the non-CA site.
- There was a minor concern that it may be difficult to enroll early-stage PD patients for this risky intervention.

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).