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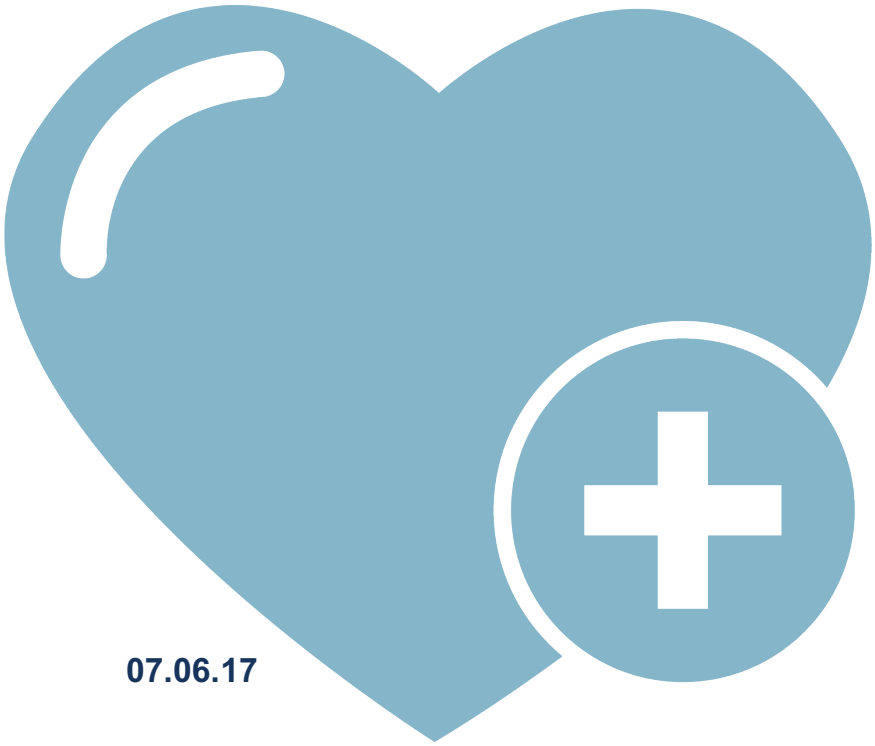
Grants Working Group Public Review Summary

A Phase 3, Randomized, Placebo-controlled Multicenter Study to Evaluate Efficacy & Safety of Repeated Administrations of Modified MSCs in Patients with ALS

Application Number: CLIN2-09894 (Revised Application)	Review Date: 27 June 2017

Clinical Trial Stage Project Proposal (CLIN2)



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A Phase 3, Randomized, Placebo-controlled Multicenter Study to Evaluate Efficacy & Safety of Repeated Administrations of Modified MSCs in Patients with ALS

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

A cell therapy that delivers high levels of neurotrophic factors to the CNS

Indication

Amyotrophic lateral sclerosis (ALS) or Lou Gehrig Disease

Therapeutic Mechanism

The cell therapy is aimed at providing high levels of neurotrophic factors directly to the CNS, to support the dying neurons

Unmet Medical Need

Amyotrophic lateral sclerosis (ALS) is a fatal neurological disease in which the degeneration and death of motor neurons (MNs) leads to weakness, paralysis and eventually respiratory failure. There remains a great unmet medical need for safe and effective treatments for people with ALS.

Project Objective

Complete phase 3 clinical trial

Major Proposed Activities

Manufacturing of cell therapy product

Enrollment of 200 patients for the study

Conduct clinical trial

Funds Requested

$15,912,390 ($15,912,390 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 9 GWG members

Votes for Score 2 = 3 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

This is a revised application that previously received a score of "2". In the initial review of this application, the reviewers expressed concerns and raised questions related to the preclinical data to support a mechanism of action (MOA), the inclusion of intramuscular injections, and the design of the trial, which does not include a comparison to MSCs alone and does not allow possible crossover of control patients to the treatment group. The applicants provided additional preclinical data and rationale for their clinical design in the revised submission. Some reviewers expressed continued concern that the proposed study design would not allow a demonstration of superiority of the treatment over MSCs alone. However, most reviewers thought that the applicant had provided adequate additional information to support moving forward with the proposed clinical trial and felt that it is an important study worthy of CIRM funding.

Review Summary

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

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

- ALS is a horrible and devastating human disease without any effective treatment.
- If successful, the proposed treatment would fulfill an unmet medical need.

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

- If successful, the proposed therapy will provide an improvement over the standard of care, and has the potential to become the standard of care.

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

- The proposed therapy clearly will be very attractive for patients and care providers.

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.

- Overall, the rationale is improved from the initial submission with additional details about the MOA and preclinical studies.
- The concept of introducing stem cells to locally produce neurotrophic factors was very attractive when this development program began several years ago. At the current time these concepts seem somewhat outdated. Nevertheless, the applicants provide clinical data showing an increase in trophic factors in the cerebrospinal fluid (CSF) that are supportive of their approach.
- The applicant provided reference to supportive data showing superiority of the

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treatment in a series of preclinical models of Huntington's disease, multiple sclerosis, and autism.

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

- The revised application provides additional data in support of the approach that strengthen the proposal.
- The data support continued development of the product.

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.

- Overall, the proposed phase 3 study is well-designed. If executed successfully, it will provide a very meaningful outcome, generating data to define the overall value of the program and the path to regulatory approval and marketing.
- The investigators have now included slow vital capacity (SVC) as a clinical measure in the revised clinical trial per GWG recommendations.
- The current protocol will still not answer the question of whether the product is better than untreated autologous bone marrow-derived MSCs. However, reviewers felt this is not critical for the current study as a positive outcome in this trial may allow a demonstration of superiority over MSC alone in a future study.

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

- Previous concerns about regulatory interactions and over-aggressive timelines have been answered in a satisfactory way in the revised application.

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

- The proposed plan and timeline demonstrate urgency and are 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 proposed timeline is ambitious but reasonable and achievable.

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 core team is composed of well-trained and experienced individuals. Some concern was expressed about previous industry experience of the individual responsible for cell manufacturing. However, new data provided in the revised application make a strong case that manufacturing is handled and quality controlled in an appropriate way.

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

- The contingency plan accounts for possible risks related to enrollment and manufacturing and the mitigation plan is appropriate.

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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).