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# Grants Working Group Public Review Summary

## A Double-Blind, Controlled Ph 2b Study of the Safety and Efficacy of Modified Stem Cells in Patients with Chronic Motor Deficit from Ischemic Stroke

| Application Number: CLIN2-10344 | Review Date: 30 May 2017 |
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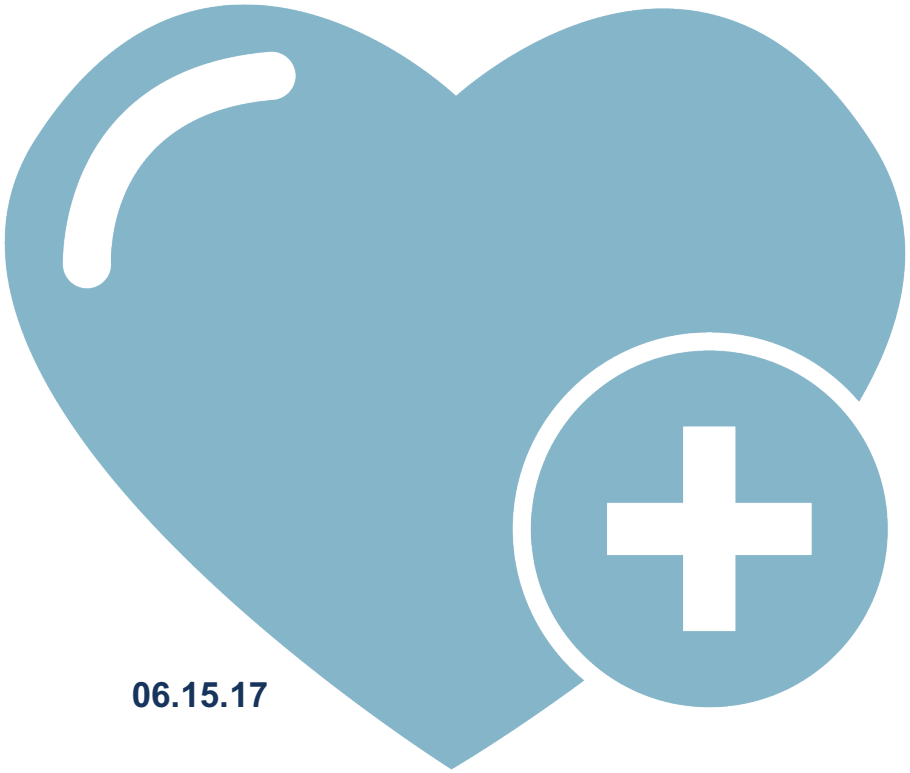
Clinical Trial Stage Project Proposal (CLIN2)



**06.15.17**

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# A Double-Blind, Controlled Ph2b Study of the Safety and Efficacy of Modified Stem Cells in Patients with Chronic Motor Deficit from Ischemic Stroke

**APPLICATION NUMBER: CLIN2-10344**

**REVIEW DATE: 30 May 2017**

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

## Therapeutic Candidate or Device

Modified adult donor bone marrow-derived mesenchymal stem cells (Modified MSC)

## Indication

Chronic motor deficit secondary to ischemic stroke

## Therapeutic Mechanism

Local intracerebral delivery of Modified MSC adjacent to motor pathways stimulate via a paracrine mechanism neuropoiesis & angiogenesis by the release of FGF-2, other trophic factors & ECM proteins. The net effect is alteration of synaptic transmission appearing to improve motor function in a hitherto inhibitory milieu. Collectively, these properties are thought to promote neuroplasticity seen as the basis for improvement in motor function observed in stroke patients treated with Modified MSC.

## Unmet Medical Need

There are no proven medical treatments available for chronic disability secondary to stroke. Results from our Phase 1/2a study suggest that Modified MSC has a favorable safety profile and the potential to improve motor function in these patients.

## Project Objective

Complete Ph2b trial; EOP2 meeting; Enable Phase 3

## Major Proposed Activities

Completion of Ph2b ACTIsSIMA clinical trial.

Manufacture Modified MSC clinical supplies.

Further investigate and validate the mechanisms of action to identify additional measures of potency and validation of associated bioassays.

## Funds Requested

$19,998,580 ($22,465,474 Co-funding)

## Recommendation

Score: 1

Votes for Score 1 = 8 GWG members

Votes for Score 2 = 4 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

Given the suboptimal recovery from stroke, there is a need for therapies that have the potential to improve motor outcome in patients. Reviewers noted that the proposed project was based on 15 years of preclinical and clinical work on the modified MSC product. The proposed project is requesting funds to support completion of an ongoing Phase 2b study, manufacturing optimization and development of potency assays. Reviewers thought that the Phase 1/2a results demonstrated that the product was safe and that there was a trend toward efficacy. Therefore, the reviewers recommended the project for funding to continue development of the product.

## Review Summary

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

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

- Recovery from stroke is often suboptimal and there is much room for improvement over the standard of care.

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

- This product has the potential to improve patient outcomes based on the preliminary clinical data.

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

- The proposed treatment will need to have a durable effect of a magnitude that warrants intracranial surgery, anesthesia, post-surgical care and morbidity from adverse events.

**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.**

- This project is based on 15 years of preclinical and clinical work.
- Results from the Phase 1/2a study demonstrated that the product was safe, there was some suggestion of efficacy and a trend toward dose dependency.
- Some reviewers thought that the mechanism of action was not well understood.
- Some reviewers thought that the therapy would have a greater potential for clinical benefit in an acute stroke setting.

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

- The Phase 1/2a clinical data supports continued development of the therapeutic candidate.

**Is the project well planned and designed?**

**a) Consider whether the project is appropriately planned and designed to**

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**meet the objective of the program announcement and achieve meaningful outcomes to support further development of the therapeutic candidate.**

- Reviewers thought that the project plan to expand study sites, optimize manufacturing and develop potency assays was reasonable.
- Reviewers noted that the investigators had developed safe surgery and sham surgery procedures. However, there was concern that as the sites increased, the complication rate could also increase. In particular, they were concerned that the procedure is performed with sedation and local anesthesia. It was not clear that the subjects will always be in a rigid head frame. Movement during injection could be harmful.
- Some reviewers expressed concern about the primary efficacy endpoint being defined as proportion of responders with ≥10 point improvement on the FMMS scale, which may not meet definition of MCID.
- Some reviewers thought that a thorough statistical analysis could result in a more efficient study design.
- Reviewers were unclear how the results of the manufacturing optimization activities would impact the ongoing trial.

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

- Reviewers thought that this is a well-constructed program with appropriately qualified manufacturing and clinical operations partners and vendors.
- Safety management plans and data and statistical oversight were perceived as a strength of the proposal.

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

- The project plan and timeline demonstrate appropriate urgency commensurate with CIRM's mission.
- CIRM funding would be used to add additional sites to increase enrollment rate.

**Is the project feasible?**

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

- Reviewers were concerned about the slow enrollment rate to date on the ongoing Phase 2 trial. However, they did note that the planned addition of sites could address this concern.

**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 qualified to conduct the proposed activities and has partnered with demonstrated leaders.
- Reviewers were unclear on who would be the responsible neurosurgeon for the study.

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

- The team identified relevant risks and has an appropriate contingency plan to manage them.

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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).