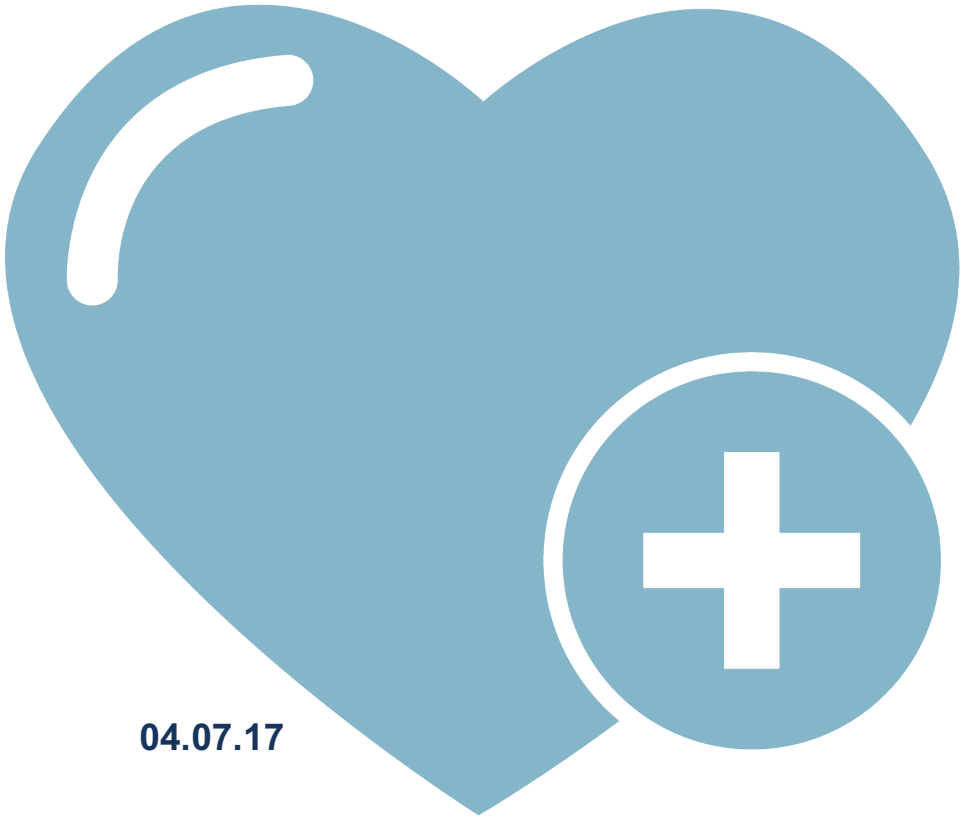
CLINICAL

Grants Working Group Public Review Summary

IND-Enabling Studies for a Trial of IV Allogeneic Mesenchymal Stromal Cells in Patients with Acute Ischemic Stroke

Application Number: CLIN1-09811	Review Date: March 28, 2017

Late Stage Preclinical Project Proposal (CLIN1)



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IND-Enabling Studies for a Trial of IV Allogeneic Mesenchymal Stromal Cells in Patients with Acute Ischemic Stroke

APPLICATION NUMBER: CLIN1-09811

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PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

Mesenchymal stromal cells (MSCs)

Indication

Acute ischemic stroke

Therapeutic Mechanism

Paracrine effects and immune modulation

Unmet Medical Need

Stroke remains a leading cause of human disability for which treatment options are limited. These cells are expected to reduce disability after stroke.

Project Objective

We will submit an IND to the FDA.

Major Proposed Activities

Perform IND enabling activities

Finalize clinical trial details

Funds Requested

$1,381,293 ($0 co-funding)

Recommendation

Score: 3

Votes for Score 1 = 0 GWG members

Votes for Score 2 = 2 GWG members

Votes for Score 3 = 13 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

The reviewers generally agreed that acute ischemic stroke represents a significant unmet clinical need and that successful completion of proposed activities could lead to an IND filing for the proposed product. However, the reviewers were unenthusiastic about the value proposition of the proposed product. The reviewers were not convinced that the cited literature or the applicant's preclinical studies supported a neural repair mechanism of action of the proposed product. Furthermore, the reviewers cited several concerns about the clinical study design, assay development and manufacturing plans. Therefore, the reviewers did not recommend this project for 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.

- One drug has been approved to treat acute stroke (tPA), but only about 5% of patients are eligible to receive it. Acute stroke, therefore, represents an important unmet medical need.

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

- The applicant postulates that other stem cell based approaches for this indication failed because the hypothesis was neuroprotection rather than neural repair. However, the supporting data for the proposed product shows insufficient evidence for neural repair, which is the putative MOA. Therefore, reviewers were not convinced that this approach is likely to improve standard of care.

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

- A stem cell-based treatment would be impactful and would offer a good value for the patients and health care in general. However, reviewers did not think this treatment is the right approach to achieve such value.

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.

- In general, the use of MSCs for stroke and neurological injury has a firm scientific rationale.
- While the applicant presents a meta analysis of preclinical studies with MSCs as their primary justification, reviewers were skeptical about interpretation of the results as there appeared to be a bias in publication of positive data.
- Reviewers thought that the rationale for the use of fresh allogeneic cells is based on outdated thinking in the literature.
- Reviewers thought that the dose range proposed for the clinical study was not consistent with consensus in the field that minimum dose for efficacy is 2M/kg.

- The MSC treatment is proposed to be administered in a therapeutic window after stroke that could be considered subacute rather than acute. But there is insufficient evidence presented to support the proposed subacute therapeutic window. A majority of the studies in the cited meta analysis administered MSC within 24 hours post-stroke. Further, in a published Phase 2 trial, cells similar to MSCs were administered intravenously to patients with acute ischemic stroke; these patients showed insufficient benefit when cells were administered 48 hours post-stroke and posthoc analysis showed benefit in patients when cells were administered within 36 hours post-stroke.
- The proposed therapeutic MOA is neural repair; however insufficient evidence is provided in support of this.

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

- Reviewers did not think that the data supported the development of this approach as designed due to insufficient preclinical data from the applicant and outcomes observed in other similar clinical trials.
- The proposed dosing regimen in the planned clinical study isn't supported by the preclinical data cited in the applicant's meta-analysis.
- There are at least 20 clinical trials currently occurring worldwide using MSC to treat stroke. Based on the number of trials occurring some additional consideration should be given to dose levels, dose timing, and the possibility of repeat dosing.

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.

- The proposed work will prepare the project for an IND filing.
- However, the proposed design of the clinical trial is unlikely to show benefit given both the pre-clinical data and the current experience with bone marrow derived cells and stroke.

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

- There are serious concerns about cell formulation, dose range, and dose timing proposed in the clinical study design.
- The proposal does not present a plan for basic cell characterization, manufacturing process development, or batch-to-batch consistency testing, all of which are critical for an allogeneic cell product.
- The planned biomarker and potency assays are under-developed and are not indicative of the state of the art (imaging and bioactivity). There are serious concerns about the lack of specificity in criteria for these assays.

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

- The timeline is appropriate for CIRM's mission.

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Is the project feasible?

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

- The IND enabling studies are feasible.
- Development of potency assays will be challenging but will not preclude the submission of the IND.
- The GMP manufacturing timeline is not feasible as presented.

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.

- One of the key personnel is TBD, but it shouldn't hinder the outcomes. The rest of the team has appropriate qualifications.

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

- Contingency plans are in place with some funding for delays if they should occur.

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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: Do Not Fund and Do Not Allow Reapplication for 6 months (CIRM concurs with the GWG recommendation).