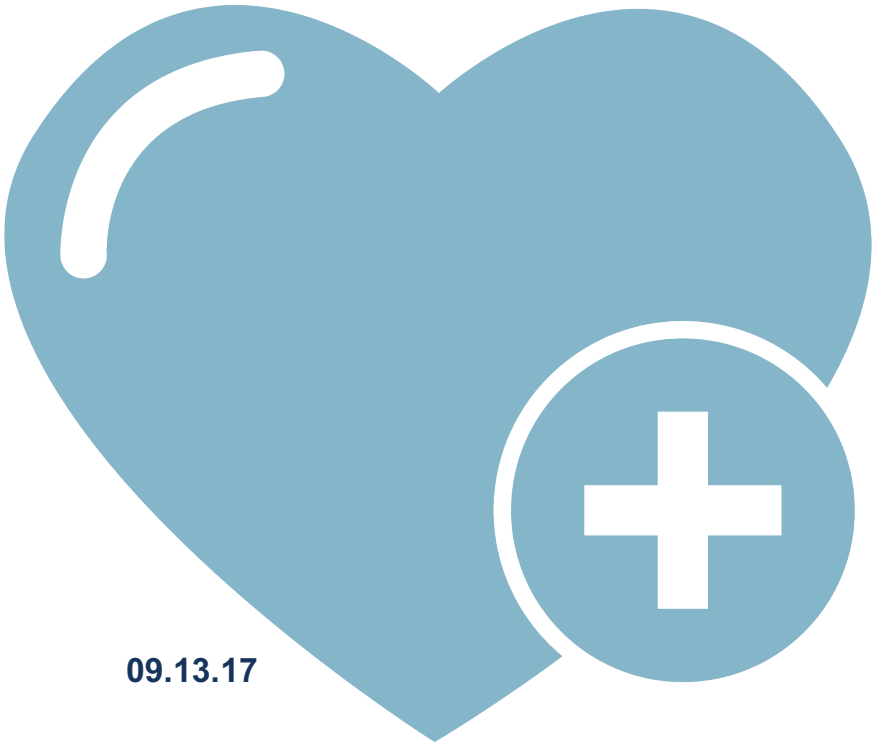
CLINICAL

Grants Working Group Public Review Summary

A Phase 2 Open-Label, Multi-Center, Randomized, Controlled, Optimal Dose-Finding Study of DCC-UCB in Adults Receiving High Dose Chemotherapy for AML

Application Number: CLIN2-09574 (Revised Application)	Review Date: 29 August 2017

Clinical Trial Stage Project Proposal (CLIN2)



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CALIFORNIA'S STEM CELL AGENCY

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A Phase 2 Open-Label, Multi-Center, Randomized, Controlled, Optimal Dose-Finding Study of DCC-UCB in Adults Receiving High Dose Chemotherapy for AML

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Cryopreserved, universal donor hematopoietic stem cell therapy that restores blood cell function and protects against infection after chemotherapy

Indication

Neutropenia arising from high-dose chemotherapy for treatment of Acute Myeloid Leukemia

Therapeutic Mechanism

The primary treatment for patients with AML is chemotherapy. Most chemotherapy results in a period of neutropenia (very low white blood cell counts) when patients are at significant risk of developing life threatening infections, sepsis and related complications. The intended cell therapy provides a source of functional early blood cells that can generate mature and functionally intact white blood cells in the patient for the prevention of infections and sepsis following chemotherapy.

Unmet Medical Need

There are an estimated 500,000 courses of high dose chemotherapy administered globally each year and despite improved antimicrobials for patients who experience febrile neutropenia or documented infections, 15%-20% of patients will go on to have uncontrolled, severe infections.

Project Objective

Phase 2 trial completed, CSR generated

Major Proposed Activities

Prepation for scale-up of DCC-UCB GMP manufacturing

GMP manufacturing of DCC-UCB for clinical use

DCC-UCB Phase II study for the treatment of chemotherapy induced neutropenia in AML patients.

Funds Requested

$6,922,109 ($16,852,313 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 12 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.

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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 reviewers thought that the DCC-UCB product had strong potential for reducing infections in chemotherapy treated AML patients. Reviewers thought that the preclinical and clinical results on DCC-UCB to date supported continued clinical development but had several concerns with the proposed phase 2 study. The reviewers had concerns about the statistical design, potential for bias in infection reporting and feasibility of study implementation. In the revised application, the applicant substantially modified the study design and implementation strategy to address all of the reviewers' major concerns. Reviewers recommended the application 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.

- This application addresses the clear unmet need to prevent serious infections that may result from myeloablative therapy in AML patients.

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

- There are no effective treatments for decreasing the rate of serious infection and this would represent the first viable treatment option.

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

- If successful, the decrease in serious infection rates would be meaningful for both patients and healthcare 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.

- There is sound scientific and clinical rationale for the proposed treatment and it is supported by the applicant's *in vitro*, preclinical and phase 1 clinical studies.
- The applicant provided additional preclinical and clinical data in the revised application that further supported their approach.

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

- Compared to the historical infection rate during treatment of AML, the data from the applicant's phase 1 study support proceeding to a phase 2 study.

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.

- In the initial review of the application, reviewers were concerned that the study design had a potential for bias in infection rate reporting. Reviewers thought that the applicant adequately addressed these concerns by modifying the primary endpoint to be event driven and incorporating a blinded committee review of infectious events.
- In the initial review of the application, reviewers were concerned that the objective for studying multiple doses was unclear and that the clinical study would be underpowered. Reviewers thought that the applicant adequately addressed these concerns by engaging an experienced statistician and clarifying the study objectives.

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

- Manufacturing, drug supply and clinical quality assurance programs are all in place. Primary endpoint and data monitoring committees are appropriately designed.

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.

Is the project feasible?

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

- In the initial review of the application, reviewers thought that timely enrollment of patients could be a concern given competing trials in this indication. The applicant adequately addressed these concerns by adding study team members and revising the study implementation strategy.

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.

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- The team is qualified to conduct the manufacturing and clinical trial activities.

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

- The applicant identified manufacturing, patient recruitment and patient safety risks and provided a detailed contingency plan.

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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).