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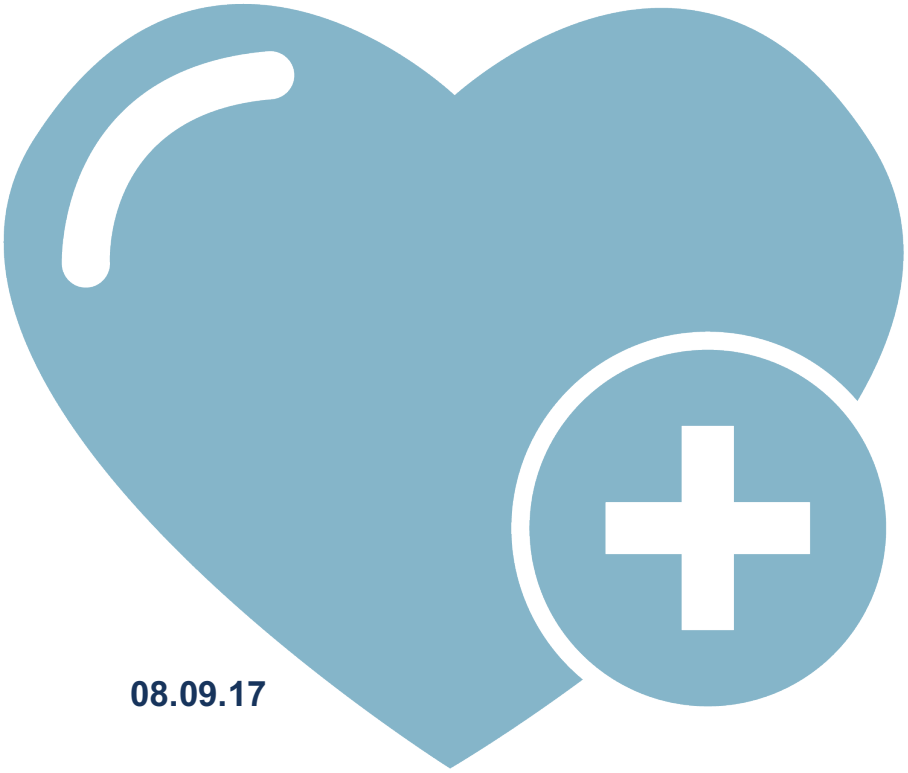
Grants Working Group Public Review Summary

AB-110-001 Phase 1b Trial and Related Activities to Support Clinical Development of AB-110

Application Number: CLIN2-10386 (Revised Application)	Review Date: 25 July 2017

Clinical Trial Stage Project Proposal (CLIN2)



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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

AB-110 consists of cord blood derived hematopoietic stem and progenitor cells co-cultured and expanded with E-CEL UVEC cells.

Indication

Hematologic and immune reconstitution in patients who have received myeloablation conditioning.

Therapeutic Mechanism

Stem and progenitor cells (active ingredient) of AB-110 engraft into the bone marrow of patients, rebuilding a new blood and immune system after appropriate preparation called myeloablation. The E-CEL UVEC cells are thought to aid the engraftment of the stem and progenitor cells into the bone marrow via secretion of angiocrine factors. The remainder of the cord blood cells in AB-110 also aid in the engraftment as well as provide anti-viral and anti-bacterial effects after transplantation.

Unmet Medical Need

Unmet medical need is for a safer, more tolerable and effective stem cell transplantation. AB-110 aims to fullfil this need and provide patients greater access to this potentially curative treatment.

Project Objective

The objective is to complete the Phase 1b trial.

Major Proposed Activities

Initiation of patient recruitment and submission of Interim Analyses Report of initial cohort to the FDA.

Submission of 180 Day Subject Data to FDA.

Completion of Phase 1b trial and submission of Final Study Report to FDA.

Funds Requested

$5,000,000 ($2,667,776 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 13 GWG members

Votes for Score 2 = 0 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

Hematologic and immune reconstitution is an unmet medical need for patients who've undergone myeloablative conditioning and lack HLA-matched donors. The AB-110 product has the potential to address this unmet medical need by providing a safe and effective population of expanded stem cells from umbilical cord blood. Reviewers expressed concerns about AB-110 manufacturing feasibility and inadequate characterization of its endothelial cell component. However, they thought that the preclinical data supported clinical testing of AB-110 and that the Phase 1 study was appropriately designed to demonstrate product safety in humans. The reviewers unanimously recommended the study for 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.

- Unrelated umbilical cord blood transplantation (UCBT) has been used to treat patients with malignant and non-malignant blood disorders who do not have HLA-matched related or unrelated donors.
- A cord blood unit (CBU) contains a limited source of stem cells and this has proven to be a problem in providing sufficiently sized grafts for adult patients.

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

- Expanding the number of CD34+ stem cells, as proposed by the applicants, has the potential to improve UCBT access and outcomes in adult patients.

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

- If the proposed co-culture with allogeneic engineered human umbilical vein endothelial cells truly expands pluripotent CD34+/CD38– stem cells, this would constitute an advance that would be adapted by patients and health care providers.
- *Ex vivo* expansion of stem cells in the UCB promises an end to this restriction and many methods have been described. All will add cost to the transplant and ultimately the decision to use expanded cells will depend on the clinical outcomes achieved using these sources. This proposal should lead to the generation of data of this type.
- Other methods have been developed for expansion of cord blood stem/progenitor cells. The proposal does not address these from a competition perspective.

d) If a phase 3 trial is proposed, is the proposed therapy for a pediatric or rare indication (i.e. FDA orphan drug designation) or, if not, is the project unlikely to receive funding from other sources?

- N/A

Is the rationale sound?

a) Consider whether the proposed project is based on a sound scientific

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and/or clinical rationale, and whether it is supported by the body of available data.

- The application is based on the premise that UCB endothelial cells will support the expansion of UCB derived HSCs while preserving stemness and this is supported by data from the literature.
- The applicants have tested function of expanded cord blood-derived CD34+ cells co-cultured on engineered human umbilical vein endothelial cells in xenogeneic mouse models. The results showed long-term engraftment of these cells. The limitations of the mouse model don't give a definitive answer on the potential for efficiency and longevity of engraftment in human patients.

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

- The available data merit testing in a human trial.
- Co-transplantation of an expanded and an unmodified CBU in this first in-human trial appears to be safe and may provide a definitive answer to the question of longevity of the expanded cells.

Is the project well-planned and designed?

a) Consider whether the project is appropriately planned and designed to meet the objective of the CLIN2 PA and to achieve meaningful outcomes that will support further development of the therapeutic candidate.

- The clinical protocol is well-developed.
- Co-transplantation of one expanded and one unmodified CBU avoids added risk to the patient.
- Characterization and testing of the endothelial cells was not adequately described in the proposal. It is likely that patients will receive different quantities of endothelial cells.
- Under "approval efficacy endpoint" in the TPP, the applicant proposes non-relapse mortality, however a product such as this could conceivably result in greater relapse rates. So this important clinical variable should be captured in any future pivotal study.
- Reviewers questioned the lack of annual replication competent retrovirus testing in patients but noted that the endothelial cells in the product are not detectable 30 days after administration.

b) Consider whether the experiments proposed in the project plan are essential and whether they create value that advances CIRM's mission.

- The proposed clinical trial design has been commonly implemented by the FDA when evaluating the safety of expanded cells.
- The proposed studies will provide essential safety data to support future trials that will evaluate the clinical efficacy of the approach.

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

- The investigators have demonstrated timeliness and productivity in their previous CIRM project. The timeline in this proposal also indicates an appropriate sense of urgency.

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Is the project feasible?

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

- This is a modest 6-patient phase 1 study and, thus, it should be feasible.
- The proposal has inconsistencies in the description of the timelines for manufacturing and product shipment to clinical sites. This raises concerns about the feasibility of the manufacturing processes to supply the clinical trial.

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.

- This is an experienced team that has adequately managed the pre-clinical project to date.
- A minor concern is that the clinical team is not clearly defined at this point but the potential personnel are well-qualified.

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

- There is adequate discussion of the potential risks, especially those concern manufacturing, and the proposed contingency plans are adequate.

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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).